



Clinicopathologic features and lymph node metastatic characteristics in patients with adenocarcinoma manifesting as part-solid nodule exceeding 3 cm in diameter



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ABSTRACT

Purpose: The purpose of this study was to elucidate the clinicopathologic and lymph node metastatic characteristics in patients with adenocarcinoma manifested as persistent ground glass mass (GGM, ground glass opacity [GGO] exceeding 3 cm in diameter).

Materials and Methods: 304 patients with adenocarcinoma manifested as persistent GGM > 3 cm, who underwent complete surgical resection between November 2013 and December 2017 were included in this study. We elucidated the lymph node metastatic incidence and characteristics according to the primary tumor lobe location and extracted the associated clinicopathological factors, especially thin-section computed tomographic findings, with lymph node involvement.

Results: All of the GGMs were invasive adenocarcinoma in histopathology. The total incidence of lymph node metastasis was 2.0% (6/304). All of the 6 cases with hilar or mediastinal lymph node metastasis were manifested as solid-predominant GGM > 3 cm and no cases with lymph node metastasis were identified in GGO-predominant GGM > 3 cm. Lymph node metastases were more likely to present in younger patients ($p = 0.032$), tumors with solid size > 2.0 cm ($p = 0.000$), more advanced clinical T stage ($p = 0.000$), radiological solid-predominant tumors ($p = 0.002$) and acinar-predominant or papillary-predominant adenocarcinoma ($p = 0.002$). As for solid-predominant GGMs > 3 cm, lymph node metastases were more likely to be found in tumors with solid size > 2.0 cm ($p = 0.026$), more advanced clinical T stage ($p = 0.026$), acinar-predominant or papillary-predominant adenocarcinoma ($p = 0.029$). Whole tumor size was not associated with the presence of lymph node metastases. There were 2 right upper-lobe cases with upper mediastinal lymph nodes skip metastasis without intrapulmonary, interlobar, and hilar lymph node metastasis.

Conclusion: All of the GGMs > 3 cm were invasive adenocarcinoma. The incidence of lymph node metastasis in GGO-predominant GGMs > 3 cm was extremely low. Solid size would be a better predictor of lymph node metastasis than whole tumor size in solid-predominant GGMs > 3 cm.

Abbreviations: GGO, ground glass opacity; GGN, ground glass nodule; GGM, ground glass mass; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IA, invasive adenocarcinoma; NSCLC, non-small cell lung cancer; SqCC, squamous cell carcinoma; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene; ALK, anaplasticlymphoma kinase; ROS1, c-ros oncogene 1 receptor kinase; C/T ratio, consolidation-to-tumor ratio; UMLN, upper mediastinal lymph nodes; SCLN, subcarinal lymph nodes; LMLN, lower mediastinal lymph nodes; LND, lymph node dissection; ASLC/ATS/ERS, International Association for the Study of Lung Cancer/American Thoracic Society /European Respiratory Society; TSCT, thin-section computed tomography

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1. Introduction

Ground glass nodule (GGN) is defined as a hazy increased opacity of the lung, with preservation of the bronchial and vascular margins, and the diameter is less than 3 cm [1]. With the wide spread of computed tomography (CT) screening, more and more lung nodules with a ground glass opacity (GGO) component have been identified [2–4]. And we will meet some GGN cases more than 3 cm occasionally. To our knowledge, few previous studies as of yet had focused on the GGO exceeding 3 cm. Our study dedicatedly included GGO more than 3 cm, and we named it ground glass mass (GGM) > 3 cm firstly.

The persistent presence of GGN on CT usually suggests the presence of lung adenocarcinoma or precancerous lesion [5]. Since tumor presented as GGN is considered to have a lepidic pattern, which is non-invasive in many cases, patients with tumors presented with more GGO content generally have a better prognosis [6–8]. Adenocarcinoma with GGO features may have a variety of prognosis due to amount of heterogeneity, options for surgical treatment is often selected depending on the degree of GGN.

On pathological examination, the GGO and solid part on CT findings were correlated with the lepidic growth and invasive component, respectively [9,10]. Previous studies found that the size of the solid part or the invasive component could better predict the prognosis of lung adenocarcinoma manifesting as GGNs [11,12]. Solitary GGNs (≤ 3 cm) treated with curative resection had a low rate of lymph node metastases and a good long-term survival rate, especially for those whose solid part was less than 80% of the whole lesion in diameter [13]. And many authors have reported that clinical stage IA(T1N0M0) non-small cell lung cancer (NSCLC) spreads to the hilar and mediastinal lymph nodes related to the primary tumor location, and lobe-specific lymph drainage has been advocated [14,15]. However, there are few reports regarding the clinicopathologic features and lymph node metastatic characteristics in patients with adenocarcinoma manifested as persistent GGMs > 3 cm.

In this retrospective study, we aimed to elucidate the clinicopathologic features and lymph node metastatic characteristics in patients with adenocarcinoma manifested as GGM > 3 cm, and to clarify the correlation between lymph node metastasis and clinicopathologic features.

2. Materials and methods

2.1. Study population

In the present study, between November 2013 and December 2017, 7463 GGNs were screened, and 307 were identified as GGM > 3.0 cm at Shanghai pulmonary hospital in China were diagnosed with NSCLC and underwent surgical resection. Patients who presented as pure solid tumor or the tumor diameter is less than 3 cm were excluded. Therefore, the relative frequency of GGM > 3.0 cm was 4.1%. Patients who underwent limited resections and incomplete resection were also excluded. Patients who diagnosed as invasive mucinous adenocarcinoma were excluded. 3 patients with other types of carcinoma rather than adenocarcinoma, including squamous cell carcinoma (SqCC), sarcomatoid carcinoma, and lymphoma were excluded. Overall, we included 304 patients who were diagnosed adenocarcinoma manifested as GGM and underwent complete surgical resection by lobectomy or grater and systematic lymph node dissection (LND) in this study. Medical records of each patient for clinicopathological information were reviewed as follows: age, sex, smoking status (never or ever smoker), preoperative serum carcinoembryonic antigen (CEA) level (cutoff at the normal upper limit of 5.0 ng/ml), tumor laterality (right or left side), tumor location (right upper lobe [RUL], right middle lobe [RML], right lower lobe [RLL], left upper lobe [LUL], or left lower lobe [LLL]), radiological findings (as described below), solid part size, clinical T stage, whole tumor size, histology, lymphatic permeation (negative or positive),

vascular invasion (negative or positive), pleural invasion (negative or positive), and distribution of lymph node metastasis. Data collection and analyses were approved by ethics committee of Shanghai Pulmonary Hospital.

2.2. Preoperative staging

Lymph nodes larger than 10 mm in the short axis on chest CT were clinically defined as metastasis-positive. Mediastinoscopy or positron emission tomography (PET) scan was not routinely performed preoperatively during the period of this study. All patients except for those with early lung cancer underwent a systemic work-up: either contrast-enhanced brain CT or magnetic resonance imaging (MRI) of the brain, bone scintigraphy, and contrast-enhanced whole-abdominal CT scan or contrast-enhanced MRI of the upper-abdominal. If patients underwent PET-CT scan of the whole body, bone scintigraphy and enhanced whole-abdominal CT scan were often skipped. All patients preoperatively underwent an electrocardiogram and respiratory function test for cardiopulmonary work up. For this study, we restaged all cases according to the 8th edition Tumor–Node–Metastasis classification.

2.3. Radiologic evaluation

We evaluated primary tumors on chest CT, and their size was determined based on the findings of thin-section CT (TSCT) scan. GGO was defined as a misty increase in lung attenuation that did not obscure the underlying vascular markings. The solid component was defined as an area of increased opacification, which completely obscured underlying vascular markings [16]. For all tumors, we obtained the maximum dimension of the tumor (tumor) and solid component (consolidation) using a lung window level setting from the TSCT scan images, and estimated the consolidation-to-tumor ratio (C/T ratio) for each tumor. We defined tumors with C/T ratios less than or equal to 0.5 as GGO-predominant tumors, and tumors with C/T ratios greater than 0.5 as solid-predominant tumors. Each lung mass on preoperative TSCT scans was reviewed by three radiologists (L.Z, J.Y. S and W.L.) and one oncologist (F.Z).

2.4. Pathological evaluation

All clinical specimens were examined by pathologists whose observations were recorded. Tumor studies included histologic characteristics like tumor size, location, differentiation, lymph node status, pleural invasion, lymphatic invasion, and vascular invasion. In this series of study, genetic analysis were performed in 76.6% (236/304) patients, including epidermal growth factor receptor (EGFR) mutation, kirsten rat sarcoma viral oncogene (KRAS) mutation, anaplastic lymphoma kinase (ALK) or c-ros oncogene 1 receptor kinase (ROS1) rearrangement et al. The detailed procedures have been described in our previous study [17].

2.5. Classification of Lymph Node stations

We categorized and defined lymph nodes according to the 8th edition Tumor–Node–Metastasis Classification. Hilar node stations (N1) were classified as follows: hilar (#10), interlobar (#11), lobar (#12 u), segmental (#13) and subsegmental (#14) node stations. Mediastinal node stations (N2) were classified as follows: upper paratracheal (left) (#2L), prevascular (#3a), retrotracheal (#3p), lower paratracheal (left) (4L), subaortic (#5), para-aortic (#6), subcarinal (#7), paraoesophageal (#8) and pulmonary ligament (#9) node stations. The sites of mediastinal lymph nodes were grouped based on the International Association for the Study of Lung Cancer (IASLC) staging as follows: upper mediastinal lymph nodes (UMLN) included 2R and 4R lymph nodes in cases of right lung cancer. UMLN included 4L, 5, and 6 lymph nodes in cases of left lung cancer. In both sides, subcarinal lymph nodes

(SCLN) were the 7 lymph node and lower mediastinal lymph nodes (LMLN) included the 8 and 9 lymph nodes. Skip metastasis was generally defined as mediastinal lymph node metastasis without intrapulmonary, interlobar, and hilar lymph node metastasis. We analyzed the association of lymph node metastasis with clinical factors: age, sex, smoking status, preoperative serum CEA level, tumor location, solid component size, whole tumor size, clinical T stage, radiological findings and pathological characteristics.

2.6. Statistical analysis

Two-category comparison was performed by Pearson’s χ^2 test, Fisher’s exact test and Kruskal-Wallis H test for quantitative data, and continuous data were analyzed by independent-samples *t* test. *p* value less than 0.05 was considered to be significant in statistical analyses. All statistical analyses were performed by using SPSS, version 20.0 software.

3. Results

3.1. Clinicopathological characteristics of patients

Of a total of 304 patients, 132 were men and 172 were women, with a median age of 62 years old (range: 35–89). There were 257 never smokers and 47 ever smokers. Regarding tumor location, 145 cases were located at RUL, 13 cases at RML, 39 cases at RLL, 85 cases at LUL and 22 cases at LLL. 130 patients were classified as having clinical stage T1aNOM0 tumors, 104 patients were classified as having clinical stage T1bNOM0 tumors, 56 patients were classified as having clinical stage T1cNOM0 tumors, 12 patients were classified as having clinical stage T2aNOM0 tumors, and 2 patients were classified as having clinical stage T2bNOM0 tumors. The median whole tumor size was 3.8 cm (range: 3.1–7.0 cm). 196 (64.5%) cases had GGO-predominant tumors and 108 (35.5%) had solid-predominant tumors. All the GGMs > 3 cm were invasive adenocarcinoma. Among the invasive adenocarcinoma, 152 were lepidic-predominant adenocarcinoma, 125 cases were acinar-predominant adenocarcinoma, 26 were papillary-predominant adenocarcinoma, and 1 was micropapillary-predominant adenocarcinoma. Regarding the molecular alteration status. EGFR mutations were found in the majority of patients(72.5%, 171/236).

3.2. Distribution and incidence of lymph node metastasis based on the tumor location

Table 1 shows the distribution and incidence of lymph node metastasis based on the primary tumor location.

Table 1
Distribution and Incidence of Lymph Node Metastasis based on the Tumor Location.

| Tumor location | Number of lymph node metastasis | Distribution of lymph node metastasis | | Incidence of lymph node metastasis(%) |
|----------------|---------------------------------|---------------------------------------|----|---------------------------------------|
| | | N1 | N2 | |
| RUL(n = 145) | 3 | 1 | 2 | 2.1 |
| RML(n = 13) | 0 | 0 | 0 | 0 |
| RLL(n = 39) | 1 | 1 | 0 | 2.5 |
| LUL(n = 85) | 2 | 2 | 0 | 2.3 |
| LLL(n = 22) | 0 | 0 | 0 | 0 |

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

Table 2
Associated Clinical and Pathological Factors of Lymph Node Metastasis in Adenocarcinoma manifested as GGMs.

| | Total N = 304 | Lymph Node Metastasis | | P value |
|--------------------------------------|------------------|-----------------------|---------------------|--------------------|
| | | Positive N = 6 | Negative N = 298 | |
| Age (years old) | | | | 0.032 ^a |
| Median 62 (range: 30-85) | | | | |
| Sex | | | | 1.000 |
| Men | 132 | 3 | 129 | |
| Women | 172 | 3 | 169 | |
| Smoking status | | | | 0.233 |
| Never smoker | 257 | 4 | 253 | |
| Ever smoker | 47 | 2 | 45 | |
| Preoperative serum CEA level (ng/ml) | | | | 0.554 |
| < 5 | 266 | 5 | 261 | |
| ≥ 5.0 | 38 | 1 | 37 | |
| Tumor location | | | | 0.848 ^b |
| RUL | 145 | 3 | 142 | |
| RML | 13 | 0 | 13 | |
| RLL | 39 | 1 | 38 | |
| LUL | 85 | 2 | 83 | |
| LLL | 22 | 0 | 22 | |
| Total size(cm) | | | | 0.352 |
| 3 < TS ≤ 5 | 283 | 5 | 278 | |
| 5 < TS ≤ 7 | 21 | 1 | 20 | |
| Solid size(cm) | | | | 0.000 ^b |
| 0 | 22 | 0 | 22 | |
| ≤ 0.5 | 66 | 0 | 66 | |
| 0.6-1.0 | 42 | 0 | 42 | |
| 1.1-2.0 | 104 | 0 | 104 | |
| 2.1-3.0 | 56 | 4 | 52 | |
| 3.1-4.0 | 12 | 1 | 11 | |
| 4.1-5.0 | 2 | 1 | 1 | |
| Clinical T stage | | | | 0.000 ^b |
| c-T1a | 130 | 0 | 130 | |
| c-T1b | 104 | 0 | 104 | |
| c-T1c | 56 | 4 | 52 | |
| c-T2a | 12 | 1 | 11 | |
| c-T2b | 2 | 1 | 1 | |
| Radiographic findings | | | | 0.002 |
| GGO-predominant | 196 | 0 | 196 | |
| Solid-predominant | 108 | 6 | 102 | |
| Pathological Characteristics | | | | 0.002 ^b |
| Lepidic -predominant AD | 152 | 0 | 152 | |
| Acinar- predominant AD | 125 | 3 | 122 | |
| Papillary -predominant AD | 26 | 3 | 23 | |
| Micropapillary -predominant AD | 1 | 0 | 1 | |
| Solid- predominant AD | 0 | 0 | 0 | |
| Molecular alteration (Total) | 236 | 4 | 232 | 0.057 ^b |
| EGFR(+) | 171 | 1 | 170 | |
| KRAS (+) | 2 | 0 | 2 | |
| ALK(+) | 1 | 1 | 0 | |
| ROS1(+) | 3 | 0 | 3 | |
| wild type | 59 | 2 | 57 | |

CEA, carcinoembryonic antigen; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; TS, total size; GGO, ground glass opacity; AD, adenocarcinoma; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene; ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1 receptor kinase.

^a Independent-samples *t*-test.

^b Kruskal-Wallis H test.

3.3. Associated clinical and pathological factors of lymph node metastasis in adenocarcinoma manifested as GGMs > 3 cm

Table 2 shows the associated clinical and pathological factors for lymph node metastasis in adenocarcinoma manifested as GGMs > 3 cm. Lymph node metastases were more likely to present in younger patients (*p* = 0.032), tumors with solid size > 2.0 cm (*p* = 0.000), more advanced clinical T stage (*p* = 0.000), radiological solid-predominant

Table 3
Associated Clinical and Pathological Factors of Lymph Node Metastasis in Adenocarcinoma manifested as solid-predominant GGMs.

| | Lymph Node Metastasis | | | P value |
|--------------------------------------|-----------------------|-------------------|---------------------|--------------------|
| | Total N = 108 | Positive N = 6 | Negative N = 102 | |
| Age (years old) | | | | 0.081 ^a |
| Median63 (range: 30-82) | | | | |
| Sex | | | | 1.000 |
| Men | 54 | 3 | 51 | |
| Women | 54 | 3 | 51 | |
| Smoking status | | | | 0.284 |
| Never smoker | 89 | 4 | 85 | |
| Ever smoker | 19 | 2 | 17 | |
| Preoperative serum CEA level (ng/ml) | | | | 1.000 |
| < 5 | 89 | 5 | 84 | |
| ≥ 5.0 | 19 | 1 | 18 | |
| Tumor location | | | | 0.584 ^b |
| RUL | 46 | 3 | 43 | |
| RML | 4 | 0 | 4 | |
| RLL | 13 | 1 | 12 | |
| LUL | 34 | 2 | 32 | |
| LLL | 11 | 0 | 11 | |
| Total size(cm) | | | | 0.575 |
| 3 < TS ≤ 5 | 94 | 5 | 89 | |
| 5 < TS ≤ 7 | 14 | 1 | 13 | |
| Solid size(cm) | | | | 0.026 ^b |
| 1.1-2.0 | 40 | 0 | 40 | |
| 2.1-3.0 | 54 | 4 | 50 | |
| 3.1-4.0 | 12 | 1 | 11 | |
| 4.1-5.0 | 2 | 1 | 1 | |
| Clinical T stage | | | | 0.026 ^b |
| T1b | 40 | 0 | 40 | |
| T1c | 54 | 4 | 50 | |
| T2a | 12 | 1 | 11 | |
| T2b | 2 | 1 | 1 | |
| Pathological Characteristics | | | | 0.029 ^b |
| Lepidic -predominant AD | 2 | 0 | 2 | |
| Acinar- predominant AD | 88 | 3 | 85 | |
| Papillary -predominant AD | 17 | 3 | 14 | |
| Micropapillary -predominant AD | 1 | 0 | 1 | |
| Solid- predominant AD | 0 | 0 | 0 | |
| Molecular alteration (Total) | 83 | 4 | 79 | 0.057 ^b |
| EGFR(+) | 59 | 1 | 58 | |
| KRAS(+) | 2 | 0 | 2 | |
| ALK(+) | 1 | 1 | 0 | |
| ROS1(+) | 1 | 0 | 1 | |
| wild type | 20 | 2 | 18 | |

CEA, carcinoembryonic antigen; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; TS, total size; AD, adenocarcinoma; EGFR, epidermal growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene; ALK, anaplasticlymphoma kinase; ROS1, c-ros oncogene 1 receptor kinase.

^a Independent-samples *t*-test.

^b Kruskal-Wallis H test.

tumors ($p = 0.002$) and acinar-predominant or papillary-predominant adenocarcinoma ($p = 0.002$). Remarkably, there were no lymph node metastases in GGO-predominant tumors. Patients' sex, smoking status, preoperative serum CEA level, tumor location, whole total size and molecular alteration were not associated with lymph node metastasis ($p > 0.05$).

3.4. Associated Clinical and Pathological Factors of Lymph Node Metastasis in Adenocarcinoma manifested as solid-predominant GGMs > 3 cm

Table 3 shows the associated clinical and pathological factors for lymph node metastasis in adenocarcinoma manifested as solid-predominant GGMs > 3 cm. As for solid-predominant GGMs > 3 cm, lymph node metastases were more likely to be found in tumors with

solid size > 2.0 cm ($p = 0.026$), more advanced clinical T stage ($p = 0.026$), acinar-predominant or papillary-predominant adenocarcinoma ($p = 0.029$). Patients' age, sex, smoking status, preoperative serum CEA level, tumor location, whole tumor size and molecular alteration were not associated with lymph node metastasis ($p > 0.05$).

3.5. CT/MRI findings, histopathological characteristics, postoperative survival situation

Fig. 1 reveals the CT findings and histopathological characteristics of patients manifested as GGO-predominant GGM > 3 cm. Fig. 2 shows the CT/MRI findings and histopathological characteristics of patients manifested as solid-predominant GGM > 3 cm. Table 4 details the clinicopathological characteristics, CT parameter and postoperative survival situation of patients with lymph node metastasis manifested as GGMs > 3 cm.

3.6. Distributions and incidences of Skip Metastasis in Adenocarcinoma manifested as GGMs > 3 cm

There were 2(0.7%) right upper-lobe case with UMLN skip metastasis without intrapulmonary, interlobar, and hilar lymph node metastasis.

4. Discussion

The present study is the first large study to elucidate the incidence and characteristics of lymph node metastasis in patients with adenocarcinoma manifested as GGM > 3 cm. In our study, we found that almost all the GGMs > 3 cm were adenocarcinoma, only 1% of cases (3/307) had other pathologic types, including 1 with SqCC, 1 with sarcomatoid carcinoma and 1 with lymphoma. According to the 2015 WHO classification of lung tumors, adenocarcinoma was classified into various subtypes such as adenocarcinoma in situ(AIS), minimally invasive adenocarcinoma(MIA) or invasive adenocarcinoma(IA) [9,18]. AIS and MIA, in which a lepidic pattern is a major component, show a very good prognosis [19]. Unlike the malignant solid nodule or mass, the nodule or mass consisting of GGO can be easily given a relatively better prognosis. That suggests an interpretation of low risk of lymph node metastasis in our study (2.0%), for even in GGMs > 3 cm, the majority cases (64.4%, 196/304) had GGO-predominant tumors.

In our research, 7.2% cases (22/304) were presenting as GGM > 3 cm composed of pure GGO without lymph node metastasis (N1, N2), vascular invasion, and intrapulmonary metastasis. Among the 22 cases, 8 cases had no invasive component or adenocarcinoma with a predominant lepidic component. Based on the new IASLC/ATS/ERS international multidisciplinary lung adenocarcinoma classification [9,20], even if after pathologic examination of the entire tumor, the tumor shows a pure lepidic pattern without any invasive component, these tumors are classified as lepidic predominant adenocarcinoma rather than a very large AIS. So in our research, all the GGMs > 3 cm were invasive adenocarcinoma. With the solid consolidation(C/T ratio) increased, the percentage of lepidic components will decrease, and acinar, papillary, micropapillary and solid predominant adenocarcinoma will be presented. Prior studies had demonstrated that micropapillary and solid tumor components have a higher malignant potential than acinar, papillary, and lepidic components [21,22]. In addition, some studies reported that tumor prognosis changes when a small amount of micropapillary components(micropapillary > = 5%) is present [21,23,24]. Coincidentally, in our study, as for the invasive adenocarcinoma manifesting as solid-predominant GGMs > 3 cm, 6 cases had lymph node metastasis(N1 or N2), and 3 cases had micropapillary components, which the percentage of micropapillary components was more than 10%.

In previous studies, the incidence of mediastinal lymph node metastasis was extremely low in c-stage I NSCLC cases with GGO-

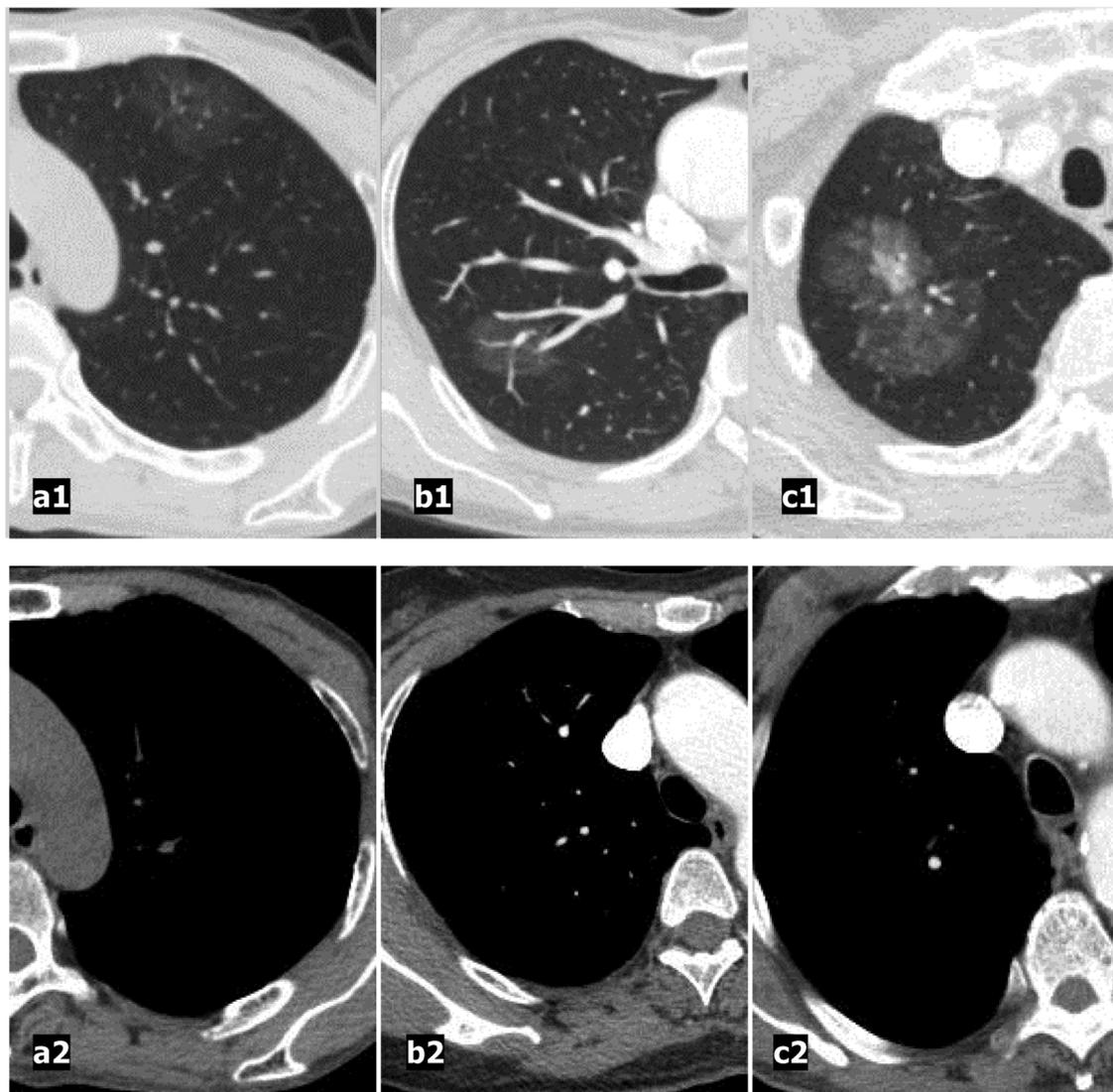


Fig. 1. CT findings and histopathological Characteristics of Patients manifested as GGO-predominant GGM. (a1,a2) A 3.2 cm GGM composed of pure GGO in the left upper lobe in a 60-year-old woman. This patient was classified as having clinical stage T1aN0M0. Postoperative histopathology was confirmed as lepidic predominant adenocarcinoma, and had no stromal, vascular or pleural invasion, also had no hilar or mediastinal lymph node metastasis. (b1,b2) A 3.3 cm GGM composed of pure GGO in the right upper lobe in a 54-year-old woman. This patient was classified as having clinical stage T1aN0M0. Postoperative histopathology was confirmed as adenocarcinoma with a predominant lepidic component, and had no hilar or mediastinal lymph node metastasis. (c1,c2) A 5.4 cm mixture GGM in the right upper lobe in a 71-year-old man. The maximum dimension of the solid component was 1.1 cm, the C/T ratio was 20.4%. This patient was classified as having clinical stage T1bN0M0. Postoperative histopathology was confirmed as lepidic-predominant adenocarcinoma (with acinar components), and had no hilar or mediastinal lymph node metastasis.

predominant tumor [16,25,26]. Suzuki et al [27] first reported the clinical features of GGNs exceeding 3 cm in diameter in 160 patients who underwent complete resection from 2002 to 2012. The lesions were categorized into 3 groups according to the C/T ratio: < 0.25 (type A), 0.25 to 0.5 (type B) and > 0.5 (type C). Type A and type B tumors showed no lymph node metastases. In our research, of the 196 GGO-predominant tumors, 99.0% (194/196) patients' solid component size was less than 2.0 cm, other 2 patients solid part size was 2.1 cm. 66.3% (130/196) patients' solid part size was less than 1.0 cm, 11.2% (22/196) patients had no solid component and manifested GGM > 3 cm composed of pure GGO (C/T = 0). Based on the IASLC proposed that the solid size rather than the whole size of GGNs be used for the clinical T category in the 8th edition staging system for non-mucinous lung adenocarcinomas [28]. 130 patients were classified as having clinical stage T1aN0M0 lung cancer, 64 patients were classified as having clinical stage T1bN0M0, 2 patients were classified as having clinical stage T1cN0M0, and all of the patients were classified as having

clinical stage I NSCLC. In addition, our study also revealed that there was no lymph node metastasis in GGO-predominant tumors manifesting as GGMs > 3 cm. The results in our study correlated well with the previous studies.

In the case of solid-predominant tumor, there have been cases in which tumors previously diagnosed as clinical N0 were diagnosed with mediastinal lymph node metastasis after surgery [26]. In our present study, lymph node metastasis was found in 6 patients (4 had N1 metastasis; 2 had N2 metastasis). All 6 patients had solid-predominant tumors, and all had non-lepidic predominant adenocarcinoma, including acinar, papillary, micropapillary components, especially 3 patients had micropapillary contents. Of the 6 patients with lymph node metastasis, 4 patients were classified as having clinical stage T1cN0M0 lung cancer, 1 patient was classified as having clinical stage T2aN0M0, 1 patient was classified as having clinical stage T2bN0M0, and the 6 patients' solid component size was more than 2.2 cm. As primary whole tumor size was similar between metastasis and non-metastasis group,

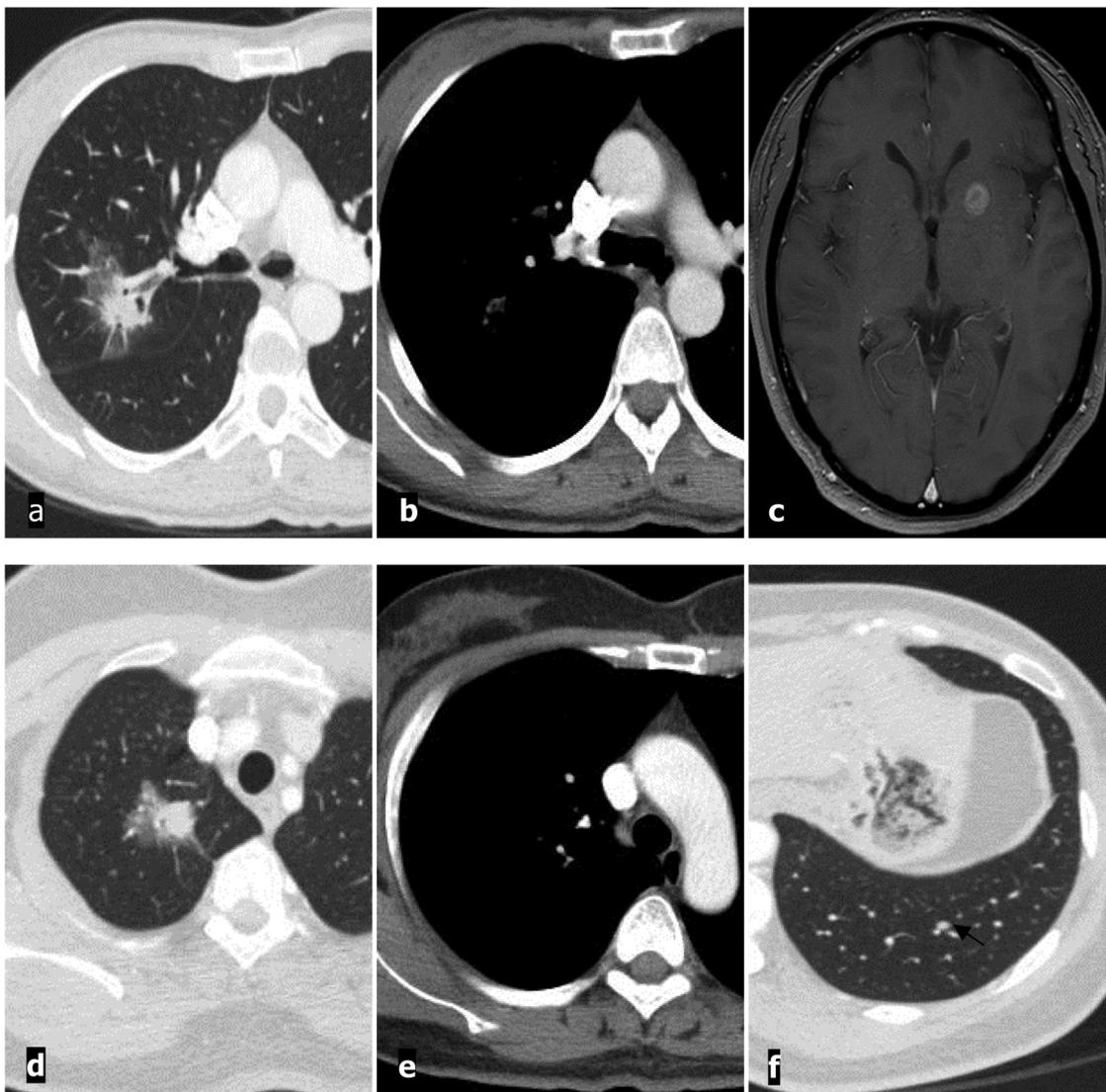


Fig. 2. CT/MR findings and histopathological Characteristics of Patients manifested as Solid-predominant GGM. (a–c) A 4.6 cm mixture GGM in the right upper lobe in a 45-year-old woman. The maximum dimension of the solid component was 2.7 cm, the C/T ratio was 58.7%. This patient was classified as having clinical stage T1cN0M0. Postoperative histopathology was confirmed as papillary-predominant adenocarcinoma (micropapillary components 10%), 11 stations lymph node was positive. Genetic analysis was not performed in this patient. After receiving adjuvant chemotherapy, brain metastasis was appeared 16 months later. (c) Axial contrast-enhanced T1-weighted image show that a ring of enhanced nodule appears at the left basal ganglia region. (d–f) A 3.3 cm mixture GGM in the right upper lobe in a 46-year-old woman. The maximum dimension of the solid component was 2.2 cm, the C/T ratio was 66.7%. This patient was classified as having clinical stage T1cN0M0. Postoperative histopathology was confirmed as papillary-predominant adenocarcinoma (acinar components 25%, micropapillary components 15%), 2, 4 stations lymph node were positive. Gene examination indicated that there were no gene mutation (such as EGFR, KRAS, ALK, or ROS1). After receiving adjuvant chemotherapy, lung metastasis was appeared 18 months later. (f) Axial CT image reveal that the left basal segment appear a few new nodules.

the results showed that the probability of lymph nodes metastasis was more likely to depend on the solid size rather than the overall size of the tumors.

During postoperative follow-up, although all the 6 patients received adjuvant therapy, 5 patients still had developed brain or lung metastases, 1 patient had no vascular metastasis. The median first postoperative recurrence duration (from the date of surgery to the first recurrence) was 18 months (range 14–34 months). All the 6 patients had no local recurrence. In our study, the metastasis occurred mainly in the lungs and brain, whether there was metastasis of other organs required more cases data to support.

From the perspective of lobe-specific selective LND, there was no SCLN metastasis, and there would be some possibility to omit SCLN dissection because the incidence of SCLN metastasis was extremely low, even in solid-predominant GGM > 3 cm. On the other hand, in our study, 5 patients had lymph node metastasis in both upper-lobe (3 were

RUL; 2 were LUL); 1 patient had lymph node metastasis in right lower-lobe (RLL). 2 patients had UMLN (2, 4 stations) metastasis in right upper-lobe (RUL), however, these 2 patients had no intrapulmonary, interlobar, and hilar lymph node metastasis.

We should also pay careful attention to the possibility of skip lymph node metastasis. There were 2 right upper-lobe cases with UMLN skip metastasis without intrapulmonary, interlobar, and hilar lymph node metastasis. It is well known that there are pulmonary lymphatic pathways directly to the mediastinum. Gorai et al suggested that the incidence of skip N2 was significantly associated with pleural involvement in patients with clinical IA NSCLC and in those with nodal metastasis, and assumed an involvement of the subpleural lymphatic drainage [29]. The data from their study would lead to our good understanding of lymphatic drainage pathways of each lobe and segment to the mediastinum.

This study has several limitations that should be considered. The

Table 4
Clinicopathological Characteristics, CT parameter and postoperative survival outcomes of patients with lymph node metastasis manifested as solid-predominant GGM.

| Patient | Age | Sex | Smoking | Preoperative serum CEA level (ng/ml) | Total Size (cm) | C/T ratio | Location | Histopathology | Lymph node metastasis | Number of dissected lymph nodes | Adjuvant therapy | Postoperative metastasis | Interval time (month) | Survival | Follow-up period (month) |
|-----------|-----|-----|---------|--------------------------------------|-----------------|-----------|----------|---|---|---------------------------------|------------------|--------------------------|-----------------------|----------|--------------------------|
| Patient 1 | 55 | M | yes | 11.28 | 4.2 | 83.3% | RUL | acinar-predominant adenocarcinoma(papillary components30%) | 2,4 stations(+);7,810,111,213 stations(-) | 13 | yes | lung | 14 | alive | 19 |
| Patient 2 | 68 | M | yes | 1.56 | 5.5 | 81.8% | LUL | acinar-predominant adenocarcinoma(lepoidic components15%) | 13 stations(+);5,671,011 stations(-) | 13 | yes | lung | 34 | alive | 37 |
| Patient 3 | 71 | F | no | 4.65 | 4.1 | 68.3% | LUL | acinar-predominant adenocarcinoma (micropapillary components15%) | 10 stations(+);4,56,711 stations(-) | 11 | yes | none | / | alive | 38 |
| Patient 4 | 46 | F | no | 4.17 | 3.3 | 66.7% | RUL | papillary-predominant adenocarcinoma(acinar25%, micropapillary components15%) | 2,4 stations(+);710,111,213 stations(-) | 13 | yes | lung | 18 | alive | 46 |
| Patient 5 | 45 | F | no | 1.1 | 4.6 | 58.7% | RUL | papillary-predominant adenocarcinoma (micropapillary components10%) | 11 stations(+);2,47,810 stations(-) | 12 | yes | brain | 16 | alive | 49 |
| Patient 6 | 43 | M | no | 2.16 | 3.2 | 87.5% | RLL | papillary-predominant adenocarcinoma(acinar components35%) | 10 stations(+);2,34,711 stations(-) | 15 | yes | lung | 29 | alive | 60 |

first limitation of this study is that the presented data are derived from a single institution, and there were not a sufficient number of cases, to reach a definitive conclusion. Second, the calculation of volume ratio is more accurate than the maximum dimension ration between the solid component and tumor. In addition, PET/CT can serve as a useful non-invasive tool to predict lymph node metastasis before operation. However, high medical expense hampers the application of PET/CT as a routine examination in China. Finally, the survival cannot be known due to insufficient postoperative follow-up time, a integrated post-operative follow-up data for all patients is necessary to validate our results in the future.

In conclusion, all of the GGMs > 3 cm were invasive adenocarcinoma. The incidence of lymph node metastasis was extremely low in GGO-predominant GGM > 3 cm or GGM > 3 cm composed of pure GGN (0 ≤ C/T < 0.5). Solid size would be a better predictor of lymph node metastasis than whole tumor size in sold-predominant tumor manifested as GGM > 3 cm (0.5 ≤ C/T < 1).

Declaration of Competing Interest

No authors report any conflict of interest

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