CLINICAL RESEARCH

Comprehensive Study of Surgical Treated Lung Adenocarcinoma with Ground Glass Nodule Component

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: More and more patients with lung adenocarcinoma were detected with ground glass nodule (GGN) due to the popularity of low-dose spiral computed tomography (LDCT) recently. The clinicopathological characteristics and epidermal growth factor receptor (EGFR) mutation features were unclear.

Material/Methods: This retrospective study enrolled patients with surgical resected primary lung adenocarcinomas with GGN component. The clinicopathological data included age, gender, smoking history, tumor staging, lymph node staging, surgical methods, subtypes, thyroid transcription factor-1 (TTF-1) expression, EGFR gene mutation and follow-up records were investigated.

Results: There were 338 lung adenocarcinoma patients with GGN component eligible for our analysis: 219 patients (64.8%) harbored the EGFR mutation. In addition, the EGFR mutation rate was higher in patients with TTF-1+ than in patients with TTF-1– (72 out of 108 patients, 66.7% versus 147 out of 231 patients, 63.6%). In multivariable analysis, surgical procedure, tumor size, nodal stage, and subtype were still significant factors for relapse-free survival (RFS) while only subtype acted as the significant factor for overall survival (OS). In subgroup analyses, patients with TTF-1- had better prognosis in RFS (log-rank P=0.0142) when compared with those with TTF-1+ but not in OS (log-rank P=0.1113). Furthermore, patients with high-risk subtype had worse outcomes than those with low-risk subtype (RFS: log-rank P<0.0001; OS: log-rank P<0.0001). Patients who underwent limited resection experienced high risk of relapse (log-rank P<0.0001) while there was no statistical significance in OS (log-rank P=0.1644) between patients underwent lobectomy and those underwent limited resection.

Conclusions: The prognosis of lung adenocarcinomas with GGN component depends mainly on the pathological subtype and there is no significant correlation between EGFR mutation and prognosis. Lobectomy should be performed actively in patients whose preoperative puncture biopsy or intraoperative freezing indicates an invasive or worse subtype. For postoperative patients, we should consider follow-up more frequently.

MeSH Keywords: Genes, erbB-1 • Lung Neoplasms • Prognosis

Abbreviations: GGN – ground glass nodule; GGO – ground glass opacity; LDCT – low-dose spiral computed tomography; EGFR – epidermal growth factor receptor; TTF-1 – thyroid transcription factor-1; AAH – atypical adenomatous hyperplasia; AIS – adenocarcinoma *in situ*; MIA – minimally invasive adenocarcinoma; IHC – immunohistochemical; RFS – relapse-free survivals; OS – overall survivals

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Background

Lung cancer is the leading cause of cancer-specific mortality worldwide and adenocarcinoma acts as the most common histologic subtype, accounting for nearly half of all lung cancer patients [1]. The efficacy of thoracic low-dose computed tomography (LDCT) for lung cancer has been verified in recent years [2,3]. LDCT has been extensive utilized for lung cancer screening and therefore more small-sized lung cancer patients with pure ground-glass opacity (GGO) are detected, most of whom with an excellent postoperative outcome [4].

GGO is defined as an area of haziness with increased attenuation of the lung while do not obscure underlying bronchial and vascular margin [5]. Ground glass nodule (GGN) is a nodular shadow with GGO, which might present interstitial or alveolar changes on CT images [6]. Moreover, GGN changes can represent lung edema, lung infections, interstitial diseases and even malignant diseases [6]. Some researches demonstrated that persistent GGN on CT images should be suspected of having pulmonary malignancy and most of these nodules were verified as adenocarcinoma by postoperative pathological analyses [7–9].

Malignant nodules with pure GGN changes are often considered as low-risk neoplasms, including atypical adenomatous hyperplasia (AAH), adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA), and lepidic adenocarcinoma [10]. However, on CT images, GGN changes often act as a kind of component, mixed by solid component. There are still some controversies on the choice of operative approach in these patients. Besides, the clinicopathological characteristics and epidermal growth factor receptor (EGFR) mutation features were also unclear. Therefore, in this study, we investigated the clinicopathological and EGFR mutation features of lung adenocarcinomas with ground glass opacity component, as well as exploring the prognosis in stratified studies.

Material and Methods

Patient cohort

This study was supported by the institutional review board of Shanghai Chest Hospital [KS(Y)1755]. Between October 2011 and June 2017, we retrospectively evaluated surgical resected primary lung adenocarcinomas with GGN component as specimens in the Department of Thoracic Surgery of our hospital. In this article, we used GGN as identical meaning to GGO. All the patients' medical records were reviewed and all the them underwent routine preoperative assessment to exclude tumor distant metastases and confirm the diagnosis of primary lung neoplasms. The inclusive criteria were: 1) primary lung

adenocarcinomas; 2) without distant metastases; and 3) with GGN component on CT images. All the tumor specimens were identified and reviewed by pathologists to confirm the histologic subtypes postoperatively.

A signed consent form was provided by each patient or the legal representatives. The study started after the approval of institutional review board. The clinical records for all the patients were reviewed to gain relevant clinicopathologic data including gender, age, smoking history, tumor location, procedure, tumor stage (according to the 8th AJCC TNM staging system [11]), tumor size, nodal stage, and pleural invasion. AAH, AIS, and MIA are non-invasive lesions and free from LN metastasis. Thus, patients with these lesions were not included in the survival analysis. For invasive lung adenocarcinomas, high-risk patients were defined as lung adenocarcinoma patients with solid or micropapillary subtype while low-risk patients were defined as patients with invasive adenocarcinoma like lepidic, papillary, acinar, and invasive mucinous subtypes.

Immunohistochemical (IHC) staining and EGFR mutation analysis

The 4 μm formalin fixed paraffin embedded tissue samples were stained by immunohistochemical (IHC). The slide first removed affinity, and then pretreated with 3% hydrogen peroxide and ethylenediaminetetraacetic acid in turn. Thyroid transcription factor-1 (TTF-1, 8G7G3/1) was utilized at a 1: 200 dilution. After pretreatment, the slices were washed with Tris-HCl, and then the anti-rabbit EnVision+kit (DAKO) was coupled with horseradish peroxidase. Hematoxylin was used to counterstain all the slides. TTF-1+ is defined as sole nuclear staining. The mutation status of EGFR (exons 18–21) was determined using direct dideoxynucleotide sequencing and verified by DNA sequencing analysis.

Statistical analyses

All the clinical pathologic data were analyzed using SPSS 22.0 software package (SPSS Inc., Chicago, IL, USA). The distributions of relapse-free survival (RFS) and overall survival (OS) were calculated by Prism 5 (Graph Pad Software Inc., La Jolla, CA, USA), with the Kaplan-Meier method, while the comparisons between 2 categories was explored by the log-rank test. A *P* value <0.05 was considered statistically significant.

Results

Clinicopathologic characteristics

A total of 338 lung adenocarcinoma patients with GGO component were eligible for our analysis. The demographic and

Table 1. Baseline characteristics of lung adenocarcinoma patients with GGO component.

Characteristics	N (%)	Characteristics	N (%)
Gender		Stage	
Male	114 (33.7)	Tis	32 (9.5)
Female	224 (66.3)	Ia	209 (61.8)
Age		1b	2 (0.6)
≤60	190 (56.2)	2a	74 (21.9)
>60	148 (43.8)	2b	3 (0.9)
Smoking history		3a	18 (5.3)
Never	277 (82)	T size	1.68 ± 0.86
Ever	61 (18)	N stage	
Tumor location		0	320 (94.7)
Right upper lobe	119 (35.2)	1	6 (1.8)
Right middle lobe	31 (9.2)	2	11 (3.3)
Right lower lobe	58 (17.2)	Pleural invasion	
Left upper lobe	89 (26.3)	Yes	79 (23.4)
Left lower lobe	41 (12.1)	No	259 (76.6)
Procedure		EGFR mutation	
Lobectomy	242 (71.6)	Yes	219 (64.8)
Limited resection	96 (28.4)	No	119 (35.2)
Pathology		TTF-1	
AAH/AIS/MIA	109 (32.2)	Positive	108 (32)
Invasive	229 (67.8)	Negative	230 (68)

GGO – ground-glass opacity; AAH/AIS/MIA – adenomatous hyperplasia/adenocarcinoma *in situ*/minimally invasive adenocarcinoma; EGFR – epidermal growth factor receptor; TTF-1 – thyroid transcription factor-1.

clinicopathologic characteristics of these patients were listed in Table 1. There were more female patients (224 patients, 66.3%) and young patients (190 patients, 56.2%) in our study. Non-smokers accounted for the majority of patients (270 patients, 82%), and most of the tumors were located in the right upper lobe (119 tumors, 35.2%). Postoperative pathology confirmed 229 patients (67.8%) with invasive adenocarcinoma while another 109 patients (32.2%) with non-invasive. The mean tumor size was 1.68±0.86 cm. Moreover, there were 320 patients (94.7%), 6 patients (1.8%), and 11 patients (3.3%) were stage N0, N1, and N2 diseases, respectively. In postoperative pathological analyses, 79 patients (23.4%) had pleural invasion while 108 patients (32%) had positive TTF-1 expression. As for EGFR mutation, 219 patients (64.8%) harbored EGFR mutation, including 111 L858R mutation patients, 92 19del mutation patients, 10 20ins mutation patients, 4 G719A mutation patients, 2 L861Q mutation patients, and 1 mutation

T790M patient, respectively (Figure 1). In addition, the EGFR mutation rate was higher in patients with TTF-1+ than in patients with TTF-1– (72 out of 108 patients, 66.7% versus 147 out of 231 patients, 63.6%).

Survival analyses

Univariable analysis indicated that gender, surgical procedure, tumor size, nodal stage, pleural invasion, EGFR mutation, tumor stage, subtype, and TTF-1+ were significant factors for relapse-free survival (RFS) while age, gender, tumor size, nodal stage, pleural invasion, tumor stage, and subtype were significant factors for overall survival (OS) (Table 2). In multivariable analysis, surgical procedure, tumor size, nodal stage and subtype were still significant factors for RFS while only subtype acted as the significant factor for OS (Table 3).
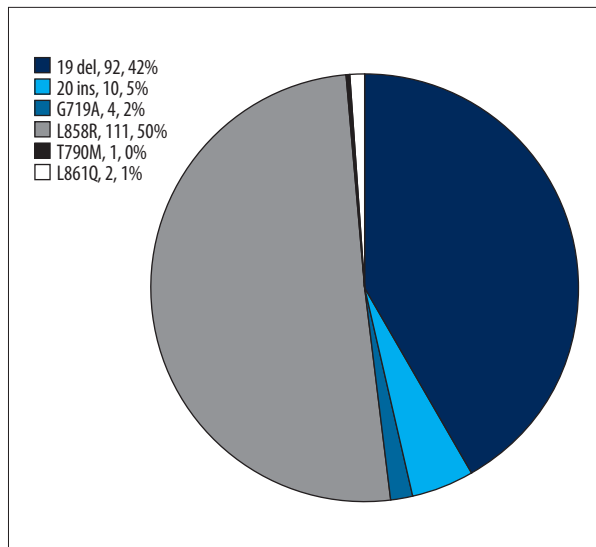
Figure 1. Distribution of gene mutation.

In subgroup analyses, patients with TTF-1- had better prognosis in RFS (log-rank *P*=0.0142) when compared with those with TTF-1+, but not in OS (log-rank *P*=0.1113) (Figure 2). Furthermore, patients with high-risk subtype had worse outcomes than those with low-risk subtype (RFS: log-rank *P*<0.0001; OS: log-rank *P*<0.0001) (Figure 3). Patients who underwent limited resection experienced high risk of relapse (log-rank *P*<0.0001) while there was no statistical significance in OS (log-rank *P*=0.1644) between patients underwent lobectomy and those underwent limited resection (Figure 4).

Discussion

Although some existing controversies focus on the management of primary lung adenocarcinoma with GGN component, scarce literature discusses the prognosis in stratified groups and the EGFR mutation status of these patients. Besides, previous studies often investigated patients with early-staged lung adenocarcinoma. In the current study of primary lung adenocarcinomas with GGN component, with tumor stage ranging from Tis to IIIA, we assessed the clinicopathological and EGFR mutation features of these patients, as well as explored their outcomes in subgroup analyses. Our findings suggested that lung adenocarcinomas with GGN component have relatively better outcome and display more frequent EGFR mutation.

Previous research has indicated that patients with GGO featured lung adenocarcinoma had excellent long-term outcomes [12,13]. Sawada et al. [14] assessed the long-term prognosis of 124 early-staged patients with GGO lesions after surgery and found only 2 patients experienced recurrences and died of lung cancer (median follow-up time: 119.0 months). Hattori et al. [15] evaluated the clinical significance of GGO component in clinical stage IA radiologic invasive non-small cell lung cancer (NSCLC) and found the 5-year OS of GGO-predominant cohort was 95.3% while that of solid-predominant cohort reached 96.8%, the presence of GGO component might predict a favorable outcome in such patients. In the Hattori et al. study, the radiologic invasive NSCLC was defined as a tumor showing a consolidation tumor ratio of 0.5 or more on the CT scan. Patients with AAH,

Table 2. Univariable analyses for RFS and OS.

Variable	RFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, years	0.991	0.550 to 1.784	0.975	0.123	0.016 to 0.962	0.046
Gender	0.536	0.298 to 0.964	0.037	0.270	0.079 to 0.924	0.037
Smoking history	1.843	0.949 to 3.578	0.071	1.868	0.495 to 7.057	0.357
Procedure2	1.945	1.218 to 3.105	<0.001	1.004	0.314 to 3.205	0.164
Tumor location	0.968	0.793 to 1.182	0.752	0.787	0.512 to 1.209	0.274
T size	2.435	1.818 to 3.262	<0.001	2.243	1.188 to 4.234	0.013
N stage	3.350	2.248 to 4.993	<0.001	5.336	2.847 to 10.002	<0.001
Pleural invasion	3.307	1.842 to 5.937	<0.001	4.007	1.221 to 13.147	0.022
EGFR mutation	0.863	0.746 to 0.999	0.048	0.837	0.620 to 1.130	0.246
Stage	1.801	1.489 to 2.178	<0.001	2.408	1.617 to 3.585	<0.001
Subtype2	9.395	4.698 to 18.789	<0.001	11.697	3.412 to 40.099	<0.001
TTF-1 positive	2.518	1.395 to 4.544	0.014	3.419	0.989 to 11.826	0.111

RFS – recurrence-free survival; OS – overall survival; HR – hazard ratio; CI – confidence interval; EGFR – epidermal growth factor receptor; TTF-1 – thyroid transcription factor-1.

Table 3. Multivariable analyses for RFS and OS.

Variable	RFS			OS		
	HR	95% CI	P	HR	95% CI	P
Age, years				0.167	0.020 to 1.374	0.096
Gender	0.629	0.333 to 1.191	0.155	0.446	0.111 to 1.794	0.255
Procedure2	3.082	2.003 to 4.743	<0.001			
T size	1.820	1.210 to 2.737	0.004	0.653	0.258 to 1.651	0.368
N stage	2.043	0.986 to 4.237	0.055	3.155	0.516 to 19.279	0.213
Pleural invasion	1.151	0.482 to 2.744	0.752	1.535	0.276 to 8.548	0.625
EGFR mutation	0.907	0.778 to 1.057	0.211			
Stage	1.326	0.857 to 2.052	0.205	1.553	0.562 to 4.290	0.396
Subtype2	8.173	3.770 to 17.714	<0.001	12.802	2.928 to 55.975	0.001
TTF-1 positive	1.724	0.892 to 3.329	0.105			

RFS – recurrence-free survival; OS – overall survival; HR – hazard ratio; CI – confidence interval; EGFR – epidermal growth factor receptor; TTF-1 – thyroid transcription factor-1.
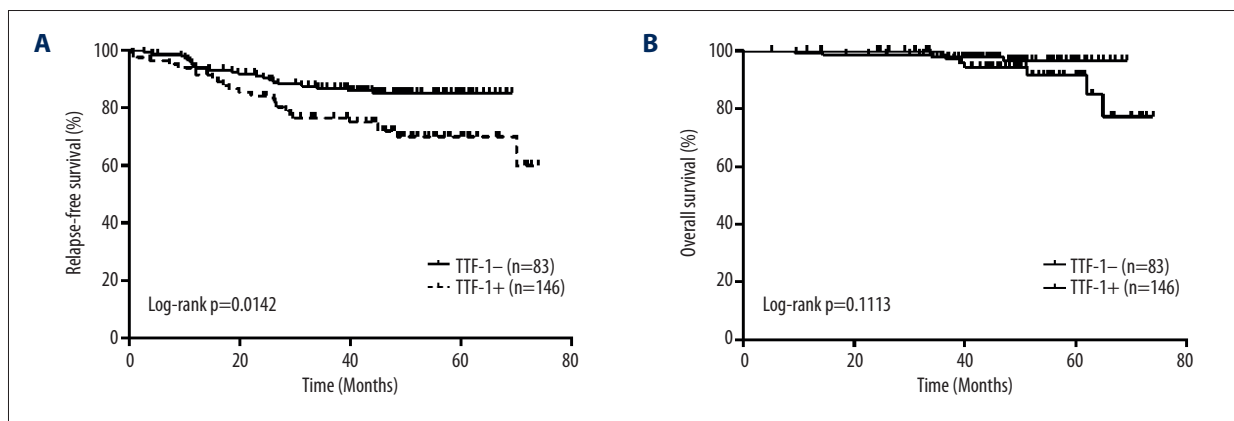

Figure 2. Kaplan-Meier survival curves for relapse-free survival (**A**) and overall survival (**B**) according to TTF-1 status. TTF-1 – thyroid transcription factor-1.
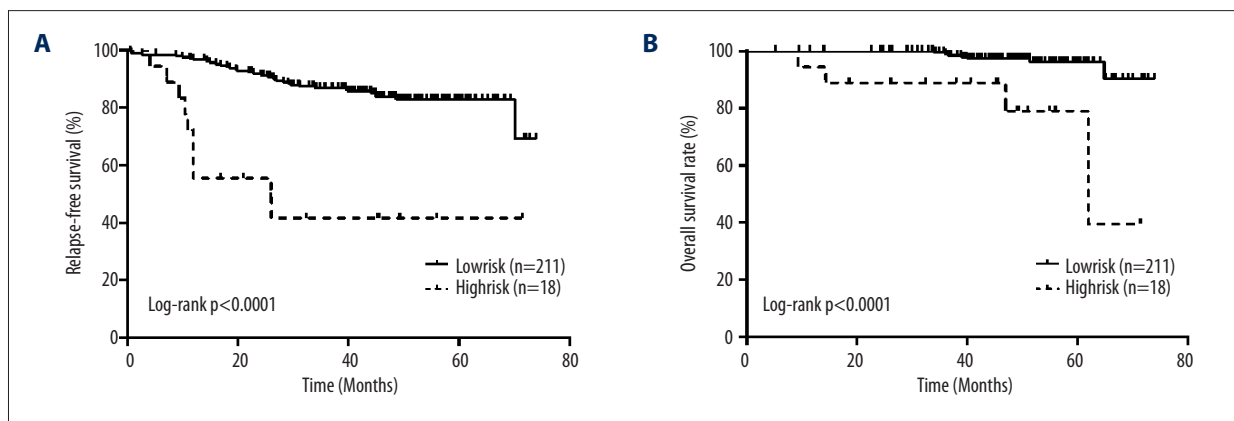

Figure 3. Kaplan-Meier survival curves for relapse-free survival (**A**) and overall survival (**B**) according to histological risk groups.
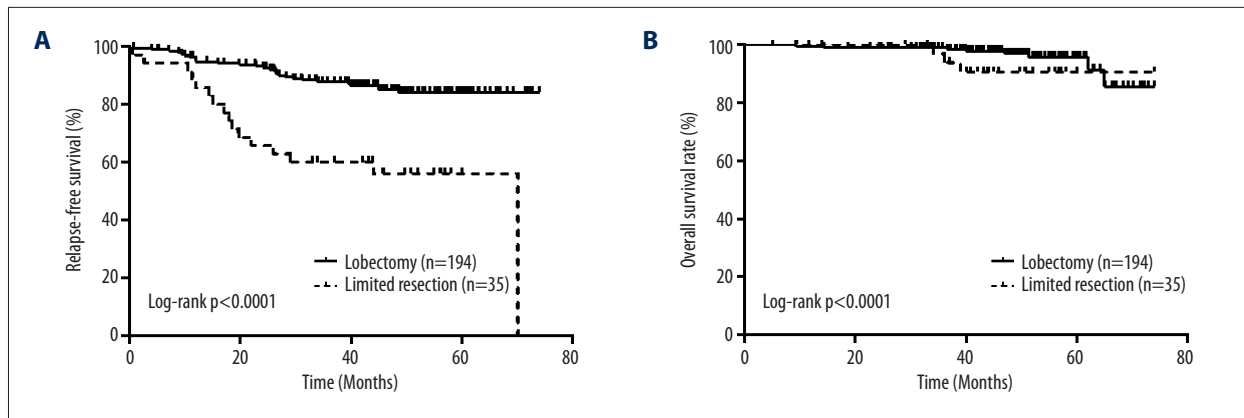
Figure 4. Kaplan-Meier survival curves for relapse-free survival (**A**) and overall survival (**B**) according to surgical procedure.

AIS, or MIA would have excellent prognosis after surgical resection [16]. Similarly, in our study, patients with AAH, AIS, or MIA all achieved 100% survival during the follow-up period. Besides, in multivariable analysis, only subtype acted as the significant factor for OS (hazard ratio [HR]: 12.802; 95% confidence interval [CI]: 2.928 to 55.975; $P=0.001$). Patients with high-risk subtype had worse outcomes than those with low-risk subtype (RFS: log-rank $P<0.0001$; OS: log-rank $P<0.0001$).

TTF-1 plays a role in the differentiation and development of bronchioloalveolar cells [17]. Previous studies revealed that TTF-1+ is associated with better prognosis in primary lung adenocarcinoma [18,19]. Zhang et al. [20] revealed the relationship between gene mutation status and TTF-1 expression that TTF-1+ adenocarcinomas would have a higher EGFR mutation rate. However, in current study, we found a negative correlation between patient prognosis and TTF-1 expression in RFS. Univariate Cox regression analysis indicated that EGFR mutation was an independent risk factor for RFS. The reason would be that a higher EGFR mutation rate exists in patients with TTF-1+ when compared with those with TTF-1– (72 out of 108 patients, 66.7% versus 147 out of 231 patients, 63.6%).

Recently, sublobectomy, including segmental resection and wedge resection, has been considered a compromise operation for high-risk patients, especially elderly patients with poor lung function, because of the benefit of preserving more lung tissue [21]. For stage IA NSCLC patients, the equivalence of limited resection and lobectomy has already been confirmed by many researchers [22,23]. And the application of limited resection in higher staged lung cancer remains controversial. In our study, the tumor stage of patients who underwent limited resection were generally lower than that of patients who received lobectomy. Except those diagnosed as AAH, AIS, and MIA, limited resection was significantly inferior to lobectomy group in OS (log-rank $P<0.0001$). However, there was no significant difference between the lobectomy group and the limited resection group in RFS (log-rank $P=0.1644$). Surgeons should be more cautious about the surgical management of primary lung adenocarcinoma with GGN component, especially for larger tumors.

The limitations of this study are as follows: 1) this was a retrospective study and thus the nature of retrospective analysis could cause some bias; 2) only EGFR mutation status was examined and the information of other gene mutations such as ALK, ROS-1, RAS in the cohort were lacking, which should be further explored in the future.

Conclusions

In summary, the prognosis of lung adenocarcinomas with GGN component depends mainly on the pathological subtype. EGFR mutation had no significant correlation with prognosis, and surgeons should be more cautious about the surgical management of these patients. Lobectomy should be performed actively in patients whose preoperative puncture biopsy or intraoperative freezing indicates an invasive or worse subtype. For postoperative patients, we should consider follow-up more frequently.

Conflict of interest

None.

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