Original Article

Different nodal upstaging rates and prognoses for patients with clinical T1N0M0 lung adenocarcinoma classified according to the presence of solid components in the lung and mediastinal windows

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Background: Little is known about the correlation between nodal upstaging and pulmonary nodules classified according to the presence of solid components in the lung and mediastinal windows. This study thus aimed to analyze the risk factors of nodal upstaging and prognosis based on different imaging features, clinical characteristics, and pathological results from patients with clinical stage T1N0M0 lung adenocarcinoma.

Methods: A total of 340 patients between January 2016 and June 2017 were selected from the Affiliated Hospital of Qingdao University database. Imaging features, clinical characteristics, and pathological results were collected for survival and analysis of nodal upstaging risk factors. We used logistic regression models to identify important metastatic risk factors for nodal upstaging. Survival rates were calculated using Kaplan-Meier (KM) survival curves and compared with the log-rank test. Significant prognostic risk factors were identified using the Cox proportional hazards model.

Results: A total of 340 patients, with an average age of 64.89 (±8.775) years, were enrolled. Among them, nonnodal upstaging occurred both in 77 (22.6%) patients with pure ground-glass nodules (pGGNs) and in 30 (8.8%) patients with heterogenous ground-glass nodules (hGGNs). Compared to the 92 (27.1%) patients with real part-solid nodules (rPSNs), the 141 (41.5%) patients with solid nodules were significantly different in terms of in nodal upstaging (P<0.001). Moreover, preoperative carcinoembryonic antigen (CEA) level >3.4 μg/L [odds ratio (OR): 2.931; 95% confidence interval (CI): 1.511–5.688; P=0.001], imaging tumor size >18.3 mm (OR, 3.482; 95% CI: 1.609–7.535; P=0.002), and consolidation tumor ratio (CTR) >0.788 (OR 8.791; 95% CI: 3.570–21.651; P<0.001) were independent risk factors for nodal upstaging. The KM survival curve results showed that patients with pGGNs and those with hGGNs had a much better 5-year disease-free survival (DFS) and 5-year overall survival (OS) than did those with rPSNs and those with solid nodules (DFS: 98.7% *vs.* 100% *vs.* 81.4% *vs.* 73.7%, P<0.001; OS: 97.4% *vs.* 100% *vs.* 90.2% *vs.* 83.7%, P=0.003). In the multivariate Cox regression analysis of patients with rPSNs and solid nodules, tumor location and pathological lymph node grade were found to be independent risk factors for DFS and OS.

Conclusions: Patients with pGGNs and those with hGGNs were more likely to be free of nodal upstaging and had better prognosis than did those with clinical stage IA rPSNs and solid nodules. The patients with pGGNs or hGGNs with preoperative CEA level <3.4 μg/L, imaging tumor size <18.3 mm, and CTR <0.788 can choose systematic lymph node sampling (SLNS) or decline lymph node dissection to avoid postoperative complications.

Keywords: Lung adenocarcinoma; nodal upstaging; ground-glass nodule (GGN); heterogenous ground-glass nodule (hGGN); prognosis

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Introduction

Lung cancer, which has long endangered human health, is a malignant tumor with the highest morbidity and mortality in the world. The incidence of lung adenocarcinoma (LUAD) has gradually increased to become the most common histological type of lung cancer. With the widespread application of the early screening of lung cancer, an increasing number of nodules with a diameter of less than 3 cm and ground-glass nodules (GGNs) are being detected and treated early, which has greatly improved the prognosis of patients with lung cancer. However, even in early-stage lung cancer, lymph node metastasis (LNM) remains a possibility, and mediastinal lymph node metastasis is an independent risk factor for poor prognosis in patients with non–small cell lung cancer (NSCLC) (1).

Small nodules with spiculation sign, pleural indentation sign, lobulation sign or, solid components in early imaging screening are usually associated with a significant increase in the degree of malignancy (2). Pulmonary nodules can be divided into solid and subsolid nodules. According to the presence or absence of ground-glass components, subsolid nodules can include pure ground-glass nodules (pGGNs) and mixed ground-glass nodules (mGGNs) (3). Some studies have suggested that subsolid nodules can be divided into pGGNs with no solid component in both computed tomography (CT) lung and mediastinal windows, heterogenous ground-glass nodules (hGGNs) with solid components only in the lung window but not in the mediastinal window, and real part-solid ground-glass nodules (rPSNs) with solid components in both CT lung and mediastinal windows. They further speculate that these 3 stages represent continuous progression, with an increasing degree of malignancy and invasion (4,5). Among the various histological subtypes, the presence of micropapillary and solid (MPSOL) components is associated with lymph node metastasis and poor prognosis (6-9). Thus far, no research has been conducted on the correlation between nodal upstaging due to lymph node metastasis and the classification of pulmonary nodules according to the presence of solid components in the lung and mediastinal windows. Therefore, in this study, we aimed to investigate the risk factors of nodal upstaging and the prognostic impact of lung cancer based on different imaging features, clinical characteristics, and pathological results in patients with clinical T1N0M0 LUAD. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-18/rc).

Highlight box

Key findings

- The new classification system based on the presence of solid components in lung and mediastinal windows of cT1N0M0 lung adenocarcinoma (LUAD) may be associated with different nodal upstaging rates and prognoses.

What is known and what is new?

- Subsolid nodules are typically divided into pure ground-glass nodules (pGGNs) and mixed ground-glass nodules (mGGNs). Recent studies have classified subsolid nodules, according to the presence or lack of solid components on computed tomography (CT) lung and mediastinal windows, into 3 categories: pGGNs, heterogenous ground-glass nodules (hGGNs), and real part-solid nodules (rPSNs). It has been speculated that these 3 categories represent 3 stages of continuous progression, with an increasing degree of malignancy and invasion.
- Patients with clinical T1N0M0 pGGNs or hGGNs and preoperative carcinoembryonic antigen (CEA) level <3.4 μg/L, imaging tumor size <18.3 mm, and consolidation tumor ratio (CTR) <0.788 can be advised to undergo systematic lymph node sampling (SLNS) or decline lymph node dissection to avoid postoperative complications.

What is the implication, and what should change now?

- Our study shows pGGNs and hGGNs patients with cIA LUAD can select more appropriate method of lymph node dissection. And it helps to avoid postoperative complications and provide the same prognosis as SLNS.

Methods

Study population

The complete medical records of 582 patients with LUAD

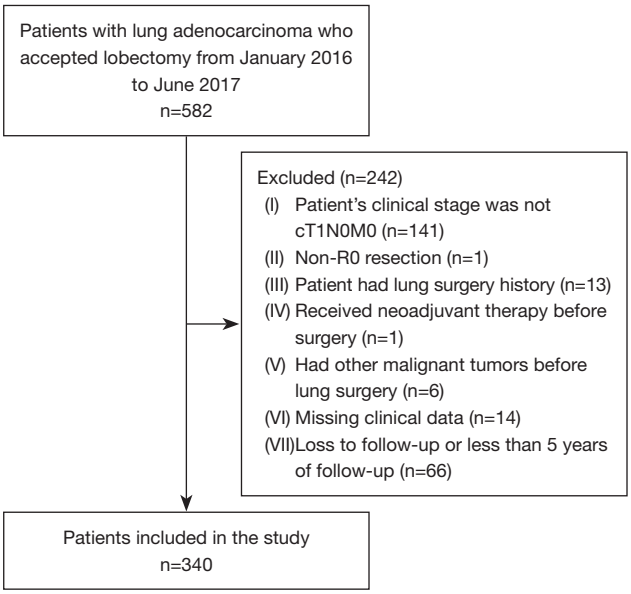

Figure 1 Study flow chart.

who accepted lobectomy in the Affiliated Hospital of Qingdao University from January 2016 to June 2017 were retrospectively retrieved. Data from a total of 427 patients were gathered based on the following inclusion criteria: (I) cT1N0M0 clinical stage according to the eighth edition of the TNM classification, (II) R0 resection, and (III) no history of lung surgery. Subsequently, data from 87 patients were excluded according the following exclusion criteria: (I) patients who received neoadjuvant therapy before surgery, (II) patients with other malignant tumors before lung surgery, (III) patients with missing clinical data, and (IV) patients lost to follow-up or with less than 5 years of follow-up. Finally, a total of 340 patients with cT1N0M0 LUAD were included for further analysis (*Figure 1*).

Radiologic assessment

Preoperative CT images were reviewed by 2 radiologists. Tumor size was measured at the level showing the largest tumor diameter in the CT lung window as was the largest solid component diameter in the presence of a solid component. GGNS were classified into pGGNs, hGGNs, or rPSNs according to the presence or absence of solid components in the pulmonary and mediastinal windows and were ranked alongside solid nodules as grade variables. Consolidation tumor ratio (CTR) was defined as the ratio of the largest solid component diameter to the largest tumor diameter in the CT lung window (5,10). In hGGNs and rPSNs, CTR can be measured if there are both ground glass and solid components in the lung windows (0< CTR <1). However, in pGGNs, as there are no solid components in the lung windows, the CTR is 0. Similarly, as solid nodules have no ground-glass components, the CTR is 1. Clinical lymph node negative was defined as hilar or mediastinal lymph nodes with a maximum diameter of less than 1.0 cm on CT or a maximum standardized uptake value of less than 2.5 on positron emission tomography (PET). Tumor size, CTR, morphology, air bronchogram sign, vacuolar sign or cavity, pleural indentation sign, lobulation sign, and spiculation sign information were recorded. Any disagreements were resolved through discussion between the 2 radiologists until a consensus was reached.

Pathological evaluation

Surgical specimens from each patient were formalin-fixed and embedded in paraffin, and stained sections of the largest surface area tumor specimen were examined and evaluated under microscopy. The pathological specimens were evaluated by 2 pathologists independently according to the new classification criteria of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory International Multidisciplinary Classification of Lung Adenocarcinoma (IASLC/ATS/ERS). Tumor size, histological type, pathologic lymph node involvement, visceral pleural invasion (VPI), and lymphatic/vascular invasion (LVI) were recorded. Any disagreements were resolved through discussion between the 2 radiologists until a consensus was reached.

Patient follow-up protocol

Follow-up assessments were performed every 3 months in the first year, every 6 months in years 2 to 3, and then annually until 5 years after surgery. Follow-up assessments included physical examination, CT, and blood tests. When any symptoms and signs of recurrence or metastasis were detected, the patient was evaluated for further examination and confirmed recurrence or metastasis according to the examination results. Local recurrence was defined as the presence of a tumor in the same lobe or in the ipsilateral thoracic cavity and in the hilar or mediastinal lymph nodes. Distant recurrence was defined as the presence of a tumor in another lobe, pleural space, or other site.

Statistical analysis

An independent samples *t* test was used to compare continuous data that fit a normal distribution, and the chi-squared test and Fisher exact test were used to compare the frequencies of categorical data between 2 groups. Logistic regression models were used to identify important metastatic risk factors for nodal upstaging, and baseline variables that were considered clinically relevant or whose outcome showed a univariate relationship were included in the multivariate model. The disease-free survival (DFS) was considered to be the interval between the date of surgical resection and the date of detection of recurrence and metastasis, while the overall survival (OS), was considered to be the time from surgical resection to the date of death or the last follow-up. Survival rates were calculated using Kaplan-Meier (KM) survival curves and compared using the log-rank test. Significant prognostic risk factors associated with survival outcomes were identified with Cox proportional hazards modeling, and baseline variables considered clinically relevant or with outcomes showing a univariate relationship were included in the multivariate model. The predictive efficiency associated with imaging tumor size and nodal upstaging of CTR value was quantified using the area under the curve (AUC) of receiver operating characteristic (ROC) analysis. A statistically significant difference was set at a P value <0.05. All analyses were performed using SPSS software version 26 (IBM Corporation) and GraphPad Prism software version 9.4.1 (GraphPad Software).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Approval No. QYFY WZLL 27494). Individual consent for this retrospective analysis was waived.

Results

Patient characteristics

The clinical, imaging, and pathological characteristics of the patients are summarized in *Table 1*. Among 340 patients, 125 were male patients, 215 were female patients, the average age was 64.89 (±8.775) years, and 89 patients had a history of smoking. The nodal upstaging status of the patients was as follows: postoperative pathology showed that 285 (83.8) patients had nonnodal upstaging, 55 (16.2) patients had nodal upstaging, and the highest lymph node pathological stage was pN2. Among the 2 groups, significant differences were observed in age (P=0.044), preoperative carcinoembryonic antigen (CEA) level (P<0.001), tumor location (P=0.040), and imaging tumor size (P<0.001). The ROC curve showed that the critical value of tumor size on imaging was 18.3 mm; the sensitivity and specificity of nodal upstaging were 81.8% and 53.7%, respectively; and the AUC was 0.715 (95% CI: 0.646–0.783) (*Figure 2A*).

Imaging results showed that there were 77 (22.6%) patients with pGGNs and 30 (8.8%) with hGGNs; both patients with pGGNs and those with hGGNs experienced nonnodal upstaging. There were 92 (27.1%) patients with rPSNs and 141 (41.5%) with solid nodules. The proportion of patients with rPSN was similar in the two groups, while the proportion of patients with solid nodules had significantly different (P<0.001). In addition, there were significant differences in pleural indentation sign (P=0.025), lobulation sign (P<0.001), spiculation sign (P=0.001), and CTR (P<0.001) between the 2 groups. The ROC curve showed that the critical value of CTR was 0.788; the sensitivity and specificity of nodal upstaging were 89.1% and 59.3%, respectively; and the AUC was 0.753 (95% CI: 0.699–0.807) (*Figure 2B*).

The pathological results showed that 307 (90.3%) cases were invasive carcinoma, 32 (9.4%) were microinvasive carcinoma, and only 1 was carcinoma in situ. All cases in the nodal-upstaged group were invasive carcinoma, and there was a statistically significant difference in infiltration degree between the upstaged and nonupstaged groups (P=0.007). Among these 2 groups, significant differences were observed in the anatomical structure (P=0.006), major pathological type (P<0.001), micropapillary and solid (MPSOL) components ≥1% (P<0.001), visceral pleural invasion (VPI) (P<0.001), lymphatic vessel invasion (LVI) (P<0.001), pathological T stage (P<0.001), pathological N stage (P<0.001), and pathological TNM stage (P<0.001).

Independent risk factors for nodal upstaging

Univariate and multivariate logistic regression were used to analyze the risk factors for nodal upstaging. The results are shown in *Table 2*. Univariate logistic regression showed that age, preoperative CEA level >3.4 μg/L, tumor location, imaging tumor size >18.3 mm, pleural indentation sign,

Table 1 Baseline characteristics of the enrolled patients

Characteristics	Nonupstaged (n=285)	Upstaged (n=55)	P value
Age (years), mean ± SD	64.47±8.618	67.07±9.327	0.044[a]
Sex, n (%)			0.248[b]
Male	101 (35.4)	24 (43.6)	
Female	184 (64.6)	31 (56.4)	
Smoking history, n (%)	77 (27.0)	12 (21.8)	0.422[b]
Preoperative CEA level (>3.4 μg/L), n (%)	64 (22.5)	31 (56.4)	<0.001[b]
Tumor location, n (%)			0.040[c]
LUL	59 (20.7)	18 (32.7)	
LLL	47 (16.5)	14 (25.5)	
RUL	103 (36.1)	10 (18.2)	
RML	25 (8.8)	4 (7.3)	
RLL	51 (17.9)	9 (16.4)	
Imaging tumor size (>18.3 mm), n (%)	132 (46.3)	45 (81.8)	<0.001[b]
Classification, n (%)			<0.001[c]
pGGN	77 (27.0)	0 (0.0)	
hGGN	30 (10.5)	0 (0.0)	
rPSN	77 (27.0)	15 (27.3)	
Solid	101 (35.4)	40 (72.7)	
Air bronchogram sign, n (%)	14 (4.9)	3 (5.5)	0.539[c]
Vacuolar sign or cavity, n (%)	31 (10.9)	6 (10.9)	1[b]
Pleural indentation sign, n (%)	124 (43.5)	33 (60.0)	0.025[b]
Lobulation sign, n (%)	94 (33.0)	33 (60.0)	<0.001[b]
Spiculation sign, n (%)	122 (42.8)	37 (67.3)	0.001[b]
Multiple nodules, n (%)	93 (32.6)	23 (41.8)	0.188[b]
CTR, n (%)			<0.001[b]
>0.788	117 (41.1)	49 (89.1)	
≤0.788	168 (58.9)	6 (10.9)	
Clinical T stage, n (%)			<0.001[c]
T1a	34 (11.9)	0 (0.0)	
T1b	151 (53.0)	17 (30.9)	
T1c	100 (35.1)	38 (69.1)	
Anatomical structure, n (%)			0.006[c]
Central type	6 (2.1)	6 (10.9)	
Peripheral type	279 (97.9)	49 (89.1)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Nonupstaged (n=285)	Upstaged (n=55)	P value
Infiltration degree, n (%)			0.007[c]
AIS	1 (0.4)	0 (0.0)	
MIA	32 (11.2)	0 (0.0)	
IAC	252 (88.4)	55 (100.0)	
Major pathological type, n (%)			<0.001[c]
Acinar	159 (55.8)	33 (60.0)	
Lepidic	66 (23.2)	2 (3.6)	
Papillary	43 (15.1)	6 (10.9)	
Micropapillary	0 (0.0)	3 (5.5)	
Solid	9 (3.2)	10 (18.2)	
Mucinous	8 (2.8)	1 (1.8)	
MPSOL ≥1%, n (%)	38 (13.3)	26 (47.3)	<0.001[b]
VPI, n (%)	44 (15.4)	29 (52.7)	<0.001[b]
LVI, n (%)	9 (3.2)	16 (29.1)	<0.001[c]
Pathologic T stage, n (%)			<0.001[b]
T1a	64 (22.5)	1 (1.8)	
T1b	133 (46.7)	17 (30.9)	
T1c	41 (14.4)	9 (16.4)	
T2a	47 (16.5)	28 (50.9)	
Pathologic N stage, n (%)			<0.001[c]
N0	285 (100.0)	0 (0.0)	
N1	0 (0.0)	21 (38.2)	
N2	0 (0.0)	34 (61.8)	
Pathologic TNM stage, n (%)			<0.001[c]
IA1	64 (22.5)	0 (0.0)	
IA2	134 (47.0)	0 (0.0)	
IA3	40 (14.0)	0 (0.0)	
IB	47 (16.5)	0 (0.0)	
IIB	0 (0.0)	21 (38.2)	
IIIA	0 (0.0)	34 (61.8)	

[a], independent samples *t*-test; [b], chi-squared test; [c], Fisher exact test. SD, standard deviation; CEA, carcinoembryonic antigen; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; pGGN, pure ground-glass nodule; hGGN, heterogenous ground-glass nodule; rPSN, real part-solid ground-glass nodule; CTR, consolidation tumor ratio; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IAC, invasive adenocarcinoma cancer; MPSOL, micropapillary and solid; VPI, visceral pleural invasion; LVI, lymphatic vessel invasion.

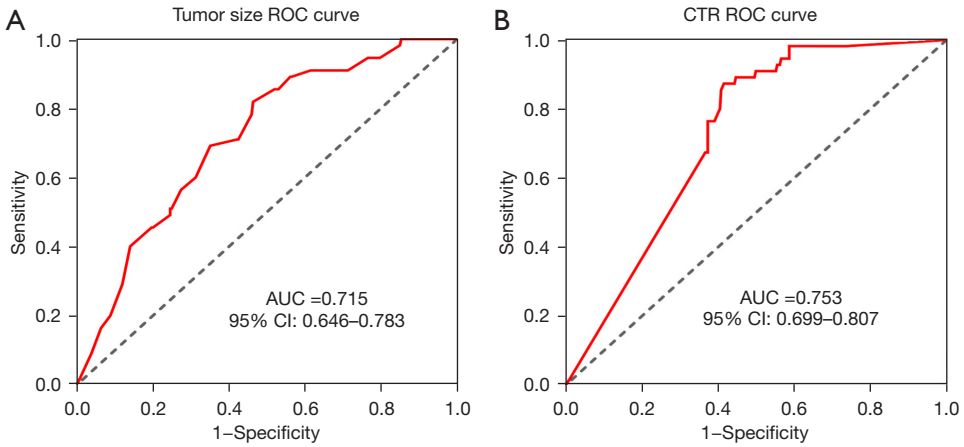

Figure 2 ROC curve of imaging tumor size and CTR in predict nodal upstaging. (A) Imaging tumor size. (B) CTR. ROC, receiver operating characteristic; CTR, consolidation tumor ratio; CI, confidence interval; AUC, area under the curve.

Table 2 Univariable and multivariable logistic regression analysis of nodal upstaging

Variables	Univariable analysis			Multivariable analysis		
	OR	P value	95% CI	OR	P value	95% CI
Age	1.036	0.045	1.001, 1.073			
Preoperative CEA level (>3.4 μg/L)	4.460	<0.001	2.445, 8.137	2.931	0.001	1.511, 5.688
Tumor location		0.057				
LUL						
LLL	0.976	0.953	0.440, 2.166			
RUL	0.318	0.007	0.138, 0.735			
RML	0.524	0.284	0.161, 1.707			
RLL	0.578	0.225	0.239, 1.400			
Imaging tumor size (>18.3 mm)	5.216	<0.001	2.530, 10.755	3.482	0.002	1.609, 7.535
Pleural indentation sign (presence)	1.948	0.026	1.082, 3.507			
Lobulation sign (presence)	3.048	<0.001	1.684, 5.516			
Spiculation sign (presence)	2.746	0.001	1.492, 5.055			
CTR (>0.788)	11.726	<0.001	4.864, 28.270	8.791	<0.001	3.570, 21.651

OR, odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; CTR, consolidation tumor ratio.

lobulation sign, spiculation sign, and CTR >0.788 were risk factors for nodal upstaging. Subsequently, we used multivariate logistic regression to analyze the meaningful results, and the results showed that preoperative CEA level >3.4 μg/L (P=0.001), imaging tumor size >18.3 mm (P=0.002), and CTR >0.788 (P<0.001) were independent risk factors for nodal upstaging.

Frequency and distribution of nodal upstaging

A total of 6,052 lymph nodes were removed from 2,274 lymph node groups in 340 patients, with an average of 17.8 lymph nodes removed from 6.69 lymph node groups per patient. A total of 285 (83.8%) patients had nonnodal upstaging, and 55 (16.2%) patients had nodal upstaging,

Table 3 The distribution of lymph node metastasis according to tumor location in the right lung

Location	2R	3	4R	5	6	7	8	9	10	11	12
RUL (n=10)	4	0	6	0	0	1	0	0	5	3	4
RML (n=4)	1	0	3	1	0	2	0	0	2	3	0
RLL (n=9)	2	0	3	0	0	3	0	0	4	4	4

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe.

Table 4 The distribution of lymph node metastasis according to tumor location in the left lung

Location	2L	3	4L	5	6	7	8	9	10	11	12
LUL (n=18)	1	1	1	9	6	2	0	0	9	4	8
LLL (n=14)	1	0	0	1	1	4	0	2	3	7	8

LUL, left upper lobe; LLL, left lower lobe.

with an average of 4.4 pathologically positive lymph nodes per patient. Furthermore, 21 (6.2%) patients had only N1 lymph node metastasis, 11 (3.2%) patients had skip metastasis, and 23 patients (6.8%) had N1 + N2 metastasis. All 107 patients with pGGNs and hGGNs had nonnodal upstaging, while 15 (16.3%) patients with rPSNs and 40 (28.4%) with solid nodules had nodal upstaging. All positive patients had invasive adenocarcinoma. The distribution of lymph node transfer stations of 55 patients is shown in *Tables 3*,*4*.

Prognosis

During 60 months of follow-up, a total of 55 (16.2%) patients who were observed had recurrence and metastasis, including 20 (7%) pN0 patients and 35 (63.6%) pN1-2 patients. The median follow-up time was 60 months. The details of recurrence patterns are shown in *Table 5*. There were 34 patients who died (10%), with 3 of the 13 (4.6%) pN0 deaths due to accident and 1 of the 21 (38.2%) pN1-2 deaths due to accident. The remaining deaths were all related to lung cancer. The 5-year OS rate and 5-year DFS rate respectively were 95.4% and 93% in the pN0 group, and 61.8% and 36.1% in the N1-2 group. The 5-year OS rate and 5-year DFS rate in the pN0 group were significantly higher than those in the pN1-2 group (both P values <0.001) (*Figure 3A*,*3B*).

By evaluating the pGGN, hGGN, rPSN, and solid nodules groups, we found that the rPSN and solid nodule groups had significantly worse 5-year OS (83.7% *vs.* 90.2% *vs.* 100% *vs.* 97.4%; P=0.003) and 5-year DFS (73.7% *vs.* 81.4% *vs.* 100% *vs.* 98.7%; P<0.001) than did the pGGN and hGGN groups, which is basically consistent with the results of a previous study (5) (*Figure 4A*,*4B*). A Cox proportional risk model was used to analyze the risk factors of OS and DFS in patients with rPSNs and those with solid nodules. Univariate and multivariate analysis showed that tumor location and pathological lymph node grade were independent risk factors related to DFS and OS (*Table 6*).

Discussion

Most of the previous related studies have divided pulmonary nodules into pGGNs, mGGNs, and solid nodules, while few studies have divided pulmonary nodules into pGGNs, hGGNs, rPSNs, and solid nodules. To our knowledge, our study is the first to classify pulmonary nodules according to this classification to explore nodal upstaging. In contrast to dividing subsolid nodules into pGGNs and mGGNs, the new grouping focuses more on the comparison of different stages of tumor progression. The genomics study of Li *et al.* showed that hGGNs are a genetic intermediate form of pGGNs and rPSNs (11). Previous studies have shown that the probability of lymph node metastasis in pGGNs is 0, so lymph node dissection is not required, while the probability of lymph node metastasis in solid component-predominant mGGNs is higher (12). In our study, nodal upstaging only occurred in patients with rPSNs or solid nodules, patients with pGGNs and patients with hGGNs were free of nodal upstaging, and the prognosis of patients with hGGNs was basically the same as that for those with pGGNs. We speculate that compare to rPSNs, hGGNs with solid

Table 5 The details of recurrence and metastasis patterns

Characteristics	Nonupstaged (n=285)	Upstaged (n=55)	P value
Overall recurrence, n (%)	20 (7.0)	35 (63.6)	<0.001[a]
Locoregional recurrence, n (%)	5 (1.8)	3 (5.5)	0.123[b]
Hilar or/and mediastinal lymph node metastasis	2	1	
Ipsilateral pulmonary metastasis	3	2	
Distant recurrence, n (%)	15 (5.3)	31 (56.4)	<0.001[a]
Contralateral pulmonary metastasis	1	6	
Brain metastasis	2	7	
Bone metastasis	5	7	
Cervical lymph node metastasis	1	2	
Pleural metastasis	2	1	
Supraclavicular lymph node metastasis	0	1	
Larynx metastasis	0	1	
Malignant pleural effusion	0	1	
Contralateral pulmonary and bone metastasis	1	0	
Contralateral pulmonary and brain metastasis	0	1	
Bone and liver metastasis	1	0	
Bone and supraclavicular lymph node metastasis	0	1	
Brain and supraclavicular lymph node metastasis	0	2	
Brain and cervical lymph node metastasis	0	1	
Contralateral pulmonary, pleural, brain, and bone metastasis	1	0	
Brain, bone, liver, and supraclavicular lymph node metastasis	1	0	
Both local and distant recurrence, n (%)	0 (0.0)	1 (1.8)	0.162[b]
Mediastinal and cervical lymph node metastasis	0	1	
Cancer death, n (%)	10 (3.5)	20 (36.4)	<0.001[b]

[a], chi-squared test; [b], Fisher exact test.

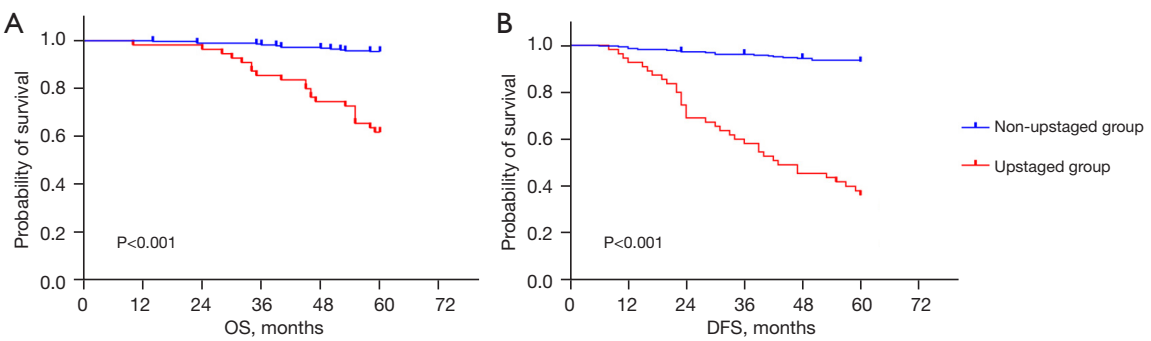

Figure 3 Survival curves of OS and DFS for the nonupstaged group and upstaged group. (A) OS. (B) DFS. OS, overall survival; DFS, disease-free survival.

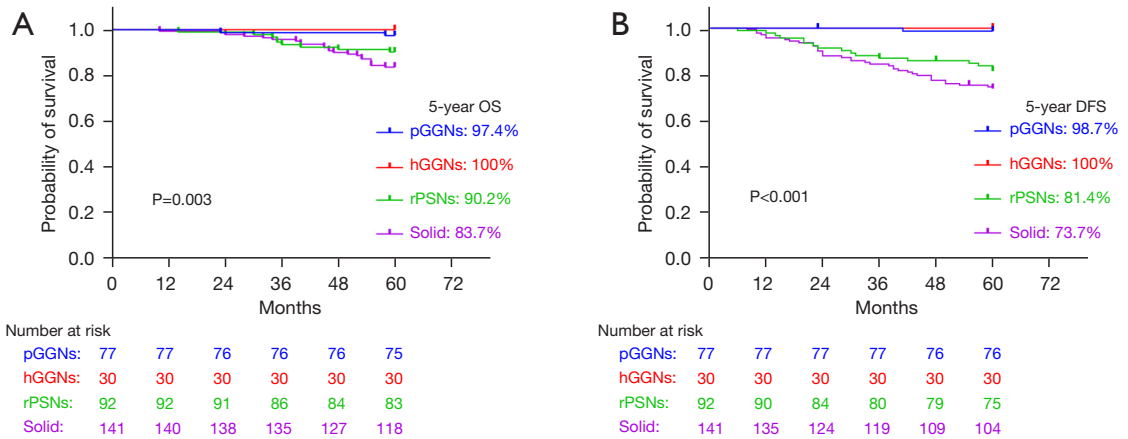

Figure 4 Survival curves of OS and DFS for patients with pGGNs, hGGNs, rPSNs, and solid nodules. (A) OS. (B) DFS. OS, overall survival; DFS, disease-free survival; pGGN, pure ground-glass nodule; hGGN, heterogenous ground-glass nodule; rPSN, real part-solid ground-glass nodule.

Table 6 Univariable and multivariable Cox regression analysis of risk factors associated with disease-free survival and overall survival for patients with rPSNs and patients with solid nodules

Variables	Univariable analysis			Multivariable analysis		
	HR	P value	95% CI	HR	P value	95% CI
Disease-free survival						
Smoking history (presence)	0.595	0.124	0.307, 1.154			
Preoperative CEA level (>3.4 μg/L)	2.098	0.006	1.231, 3.578			
Tumor location		0.035			0.001	
LUL						
LLL	1.116	0.78	0.517, 2.407	1.239	0.594	0.564, 2.720
RUL	0.653	0.311	0.286, 1.489	0.885	0.774	0.385, 2.036
RML	2.576	0.025	1.129, 5.877	5.187	<0.001	2.163, 12.438
RLL	0.912	0.838	0.378, 2.201	1.151	0.758	0.471, 2.811
Classification						
rPSN						
Solid	1.471	0.188	0.828, 2.612			
Pleural indentation sign (presence)	1.496	0.158	0.856, 2.615			
CTR	6.389	0.017	1.395, 29.269			
Anatomical structure (Peripheral type)	0.44	0.081	0.175, 1.106			
MPSOL ≥1% (presence)	2.922	<0.001	1.710, 4.993			
VPI (presence)	2.777	<0.001	1.628, 4.738			
LVI (presence)	4.397	<0.001	2.417, 7.998			
Pathological tumor size	1.245	0.223	0.875, 1.773			

Table 6 *(continued)*

Table 6 *(continued)*

Variables	Univariable analysis			Multivariable analysis		
	HR	P value	95% CI	HR	P value	95% CI
Pathologic N stage		<0.001			<0.001	
N0						
N1	7.679	<0.001	3.778, 15.611	8.406	<0.001	4.079, 17.322
N2	9.27	<0.001	4.995, 17.205	11.691	<0.001	6.086, 22.458
Overall survival						
Smoking history (presence)	0.439	0.091	0.169, 1.141			
Preoperative CEA level (>3.4 μg/L)	2.072	0.039	1.036, 4.143			
Tumor location		0.113			0.053	
LUL						
LLL	0.59	0.299	0.218, 1.596	0.604	0.33	0.219, 1.666
RUL	0.311	0.046	0.099, 0.977	0.436	0.161	0.137, 1.390
RML	1.545	0.391	0.571, 4.179	2.503	0.08	0.896, 6.989
RLL	0.656	0.434	0.228, 1.887	0.756	0.609	0.259, 2.209
Classification						
rPSN						
Solid	1.692	0.181	0.783, 3.657			
Pleural indentation (presence)	1.75	0.142	0.829, 3.697			
Lobulation sign (presence)	1.588	0.199	0.784, 3.216			
CTR	9.147	0.044	1.064, 78.643			
MPSOL ≥1% (presence)	2.843	0.003	1.420, 5.694			
VPI (presence)	2.646	0.006	1.323, 5.292			
LVI (presence)	3.279	0.004	1.472, 7.302			
Pathological tumor size	1.331	0.212	0.849, 2.086			
Pathologic N stage		<0.001			<0.001	
N0						
N1	5.961	<0.001	2.309, 15.384	6.659	<0.001	2.544, 17.427
N2	8.146	<0.001	3.695, 17.960	8.421	<0.001	3.722, 19.049

rPSNs, real part-solid nodules; HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; rPSN, real part-solid ground-glass nodule; CTR, consolidation tumor ratio; MPSOL, micropapillary and solid; VPI, visceral pleural invasion; LVI, lymphatic vessel invasion.

components in the lung window may be more similar to pGGNs in oncologic behavior and malignant degree.

In this study, we found that the nodal upstaging incidence was 16.2%, which was relatively higher than that of the patients with clinical N0 lung cancer in previous studies. Some studies indicated the incidence of nodal upstaging in patients with cT1N0 NSCLC to be generally about 10% (8.6–13%) (13-16). However, some studies reported a higher nodal upstaging incidence in early-stage NSCLC which is similar to that in our study (16.9–18.6%) (17,18). We believe

that the difference may be due to a number of reasons. First, our study was a single center study, the sample size was small, and only LUAD was examined; thus, bias was inevitable. In the future, we need a larger sample size for further studies to verify our findings. Second, larger tumor diameters and higher CTR ratios lead to a higher incidence of nodal upstaging (13,16). The number of pulmonary nodules with large diameters (tumor size ≤10 mm, n=34) and high CTR ratios (CTR >0.50, n=202) was relatively high in our study. Finally, the number of lymph nodes removed in our study was higher compared with that in previous studies, and thus the reason for the relatively high nodal upstaging incidence may be related to the extensiveness and thoroughness of intraoperative lymph node dissection (16). The nodal upstaging incidence in the clinical stage IA LUAD study by Ye *et al.* was 10.6%, and the median number of lymph nodes removed in the overall patient population was 10.3, while in our study, this number was 17.0 (19).

In our study, univariate logistic analysis showed that nodal upstaging was statistically different for age, preoperative CEA level >3.4 μg/L, tumor location, imaging tumor size >18.3 mm, lobulation sign, spiculation sign, pleural indentation sign, and CTR >0.788. Multivariate logistic analysis showed that preoperative CEA level >3.4 μg/L, imaging tumor size >18.3 mm, and CTR >0.788 were independent risk factors for nodal upstaging. Previous studies have shown that CEA, CTR, and tumor size can affect lymph node metastasis. A retrospective study which involved 3,042 patients showed that a high expression of serum CEA, cytokeratin 19 fragment (CYFRA 21-1) was an independent risk factor for mediastinal lymph node metastasis and could be used to predict metastasis (20). In our study, 3.4 μg/L was the upper limit of normal serum CEA level on the instrument which is used in our hospital; therefore, we classified patients with this level. A retrospective study by Haruki *et al.* showed an association between larger tumor size and unexpected lymph node metastasis (21). In our study, the AUC of the CTR model was 0.715 (95% CI: 0.646–0.783), and an optimal cutoff value with best-combined sensitivity and specificity for predicting postoperative recurrence was 18.3 mm. Therefore, for patients with pulmonary nodules, especially rPSNs and solid nodules, systematic lymph nodes dissection (SLND) should be strictly performed for patients with a maximum diameter greater than 18.3 mm. In a retrospective study of 2504 patients, lymph node metastasis was independently associated with CTR >0.61 (22). This conclusion is consistent with our study in that mGGNs with predominantly solid components were more likely to have nodal upstaging.

In addition to being used to predict lymph node metastasis, CEA also has other roles in lung cancer. CEA is a cell surface glycoprotein with a complex structure, which can be upregulated in a variety of malignant tumors, such as lung cancer, colorectal cancer, gastric cancer, and pancreatic cancer. It is one of the commonly used serum tumor markers of lung cancer in clinical practice (23). However, the sensitivity and specificity in lung cancer of a single detection of serum CEA is not sufficiently high, and thus CEA is often combined with other tumor markers to improve the diagnosis of lung cancer (24), for example, the combination of CEA and CRYFRA21-1. The study by Ando *et al.* suggested that the combination of CEA and CT can improve the effect of lung cancer screening (25). CEA can also be used to evaluate the therapeutic effect, recurrence monitoring, and prognosis of lung cancer (26-32). A number of previous studies have found a high serum CEA level to be associated with the poor prognosis of patients with early lung cancer (26,28,29).

Whether or not tumor location has an effect on the survival of patients with lung cancer remains controversial, and some studies suggest that tumor location has no effect on survival (33,34). However, other research indicates that patients with upper lobe NSCLC have a better prognosis (35,36). Some earlier studies concluded that lung cancers in the right middle lobe are associated with a worse prognosis compared to those located in other lobes, but a study on the prognosis and survival of 922,317 American patients with lung cancer in the Surveillance, Epidemiology, and End Results (SEER) database in 2021 showed that primary lung cancer in the right middle lobe has the best prognosis (37-39). Therefore, this issue remains unresolved. In our survival analysis, we first included all available variables. We then found that the variable of tumor location was significant in the univariate Cox regression analysis of DFS, so we included it in the multivariate Cox regression analysis. Finally, the P value of tumor location in DFS was significant, and it was borderline positive in OS. However, the number of patients with right middle-lobe LUAD in this study was too small (8.5%), and thus the possibility of bias could not be excluded. Nonetheless, we decided to present the results in this paper, although the number of patients should be expanded in future research.

Lymph node dissection is an indispensable part of the surgical treatment of lung cancer. As medical technology has advanced, a greater variety of lymph node dissection

methods has been made available to clinicians. According to the European Society of Thoracic Surgeons, lymph node dissection can be divided into 5 types: SLND, systematic lymph nodes sampling (SLNS), selected lymph node biopsy, lobe-specific lymph nodes dissection (L-SLND), and extended lymph node dissection (40). National Comprehensive Cancer Network (NCCN) guidelines recommend lobectomy + SLND as the standard surgical treatment. However, the method of lymph node dissection for patients with clinical stage IA (cT1N0M0) is still controversial. Some studies have suggested that for patients with clinical stage I, the incidence of postoperative complications (alveolar and bronchopleural fistula, recurrent laryngeal nerve injury, esophageal injury, etc.) of SLND is significantly higher than that of SLNS or L-SLND, and the intraoperative blood loss and postoperative drainage volume are also significantly increased. There is no significant difference in postoperative survival rate between SLND and SLNS or L-SLND (41). However, SLND is still the first choice for early-stage NSCLC due to the presence of lymph node micrometastasis and skip metastasis. In this study, we found that the nodal upstaging and prognosis of patients with clinical stage IA hGGNs compared to those with pGGNs were basically similar, and both groups had nonnodal upstaging and excellent prognosis. Therefore, lymph node dissection can be avoided or SLNS favored for these patients. However, patients with rPSNs or solid nodules had a high rate of nodal upstaging and a poor prognosis, so we recommend performing rigorous SLND in these patients.

Our study has several limitations. First, we used a single-center retrospective design, and thus bias was inevitable. In addition, there was a high proportion of females and patients who had never smoked. Second, the selection and dissection method of lymph nodes depends on the experience and habits of the surgeon, which may cause selection bias. Third, the number of patients was small. Therefore, we need a larger number of patients datasets from multiple centers to confirm our findings.

Conclusions

This study found patients with cT1N0M0 pGGNs or hGGNs to be free of nodal upstaging and to have a much better prognosis as compared to those with rPSNs or solid nodules. After further statistical analysis, we found that preoperative CEA level >3.4 μg/L, imaging tumor size >18.3 mm, and CTR >0.788 were independent risk factors for nodal upstaging. Tumor location and pathological lymph node grade were independent risk factors for DFS and OS. If a patient has pGGNs or hGGNs and a preoperative CEA level <3.4 μg/L, imaging tumor size <18.3 mm, and CTR <0.788, then we recommend performing SLNS or not performing lymph node dissection to avoid postoperative complications.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-18/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-18/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Approval No. QYFY WZLL 27494). Individual consent for this retrospective analysis was waived.

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