Original Article

Correlation in histological subtypes with high resolution computed tomography signatures of early stage lung adenocarcinoma

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Background: Uncertainty remains on the association between image characteristics of the nodules in computed tomography (CT) scans and lung adenocarcinoma histopathologic subtypes. We aimed to estimate the correlation between preoperative high resolution computed tomography (HRCT) scan and postoperative histopathology of stage IA lung adenocarcinoma in East Asian Chinese population.

Methods: We retrospectively reviewed the clinical records and HRCT images of 190 patients (106 female and 84 male) with resected, preoperatively untreated stage IA adenocarcinomas. The relationship between image characteristics of nodules at preoperative HRCT and their histological subtypes after resection were analyzed. The one-way ANOVA, chi-square test and logistic regression were used for analysis.

Results: In 190 patients with stage IA lung adenocarcinoma, median tumor diameter was significantly lower in lepidic predominant invasive adenocarcinoma (LPA) (15.96±6.95 mm). Univariate analysis revealed that ground-glass opacity (GGO) proportion (P<0.001), margin (P<0.001), border definition (P=0.015), pleural retraction (P<0.001) and enhancement (P<0.001) had statistically significant differences in four histological subtypes. The multivariate analysis referenced for lepidic group which indicated that GGO proportion and pleural retraction were independent associated with acinar group (RR=4.221, 95% CI: 1.770–10.066, P=0.001; RR=0.380, 95% CI: 0.158–0.916, P=0.031, respectively). Male and whose nodule margin with spiculation or lobulation were prone to papillary predominant invasive adenocarcinoma (PPA) (RR=0.288, 95% CI: 0.090–0.920, P=0.036; RR=0.250, 95% CI: 0.070–0.887, P=0.032, respectively). GGO proportion and nodule margin were independent related factors in solid predominant invasive adenocarcinoma (SPA) (RR=13.338, 95% CI: 2.974–59.811, P=0.001; RR=0.097, 95% CI: 0.016–0.606, P=0.013, respectively).

Conclusions: Nodules with spiculation or lobulation and less GGO proportion are determinants of histological subtypes with poor prognosis in stage IA lung adenocarcinoma patients according to the 2011 histologic IASLC/ATS/ERS classification.

Keywords: High resolution computed tomography (HRCT); lung adenocarcinoma; histopathology; ground-glass opacity (GGO)

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Introduction

Lung cancer is the most frequently diagnosed cancer and remains a leading cause of cancer death worldwide (1). While lung adenocarcinoma is the most common histological subtype (2). In 2011 Feb, International Association for the Study of Lung Cancer (IASLC), American Thoracic Society (ATS), and European Respiratory Society (ERS) jointly published a newly lung adenocarcinoma classification. The classification addresses both resection specimens and small biopsies/cytology. New concepts such as adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) were added. And invasive adenocarcinomas (IA) were classified with lepidic, acinar, papillary, micropapillary, and solid patterns Travis *et al*. (3). According to this new classification, patients who have AIS, MIA, and lepidic predominant adenocarcinomas have shown excellent survival rates after complete resection.

The National Lung Screening Trial (NLST) found a relative reduction in mortality from lung cancer with low-dose computed tomography (CT) screening of 20.0% compared with chest radiography (4). While on CT scans, these indolent and less aggressive tumors of AIS, MIA, and lepidic predominant adenocarcinomas frequently present as pure ground-glass opacity (pGGO) or mixed ground-glass opacity (mGGO) (5). Several other studies confirmed a well correlation between CT findings and histologic prognostic factors in lung adenocarcinomas (5-7). However, when pGGOs are greater than 15 mm in diameter or have high pixel attenuation (>–472 HU), the nodules are more likely to be IA (8). Recently, a similar observation has been documented for early stage tumors about GGO component. They found that in patients with tumors smaller than 3 cm, disease free survival (DFS) was significantly associated with solid tumor size, but not with whole tumor size (9).

GGO proportion is very important for prognosis in lung adenocarcinoma. Previous studies have explored CT features correlating with pathological invasiveness. They reported that tumors with higher solid volume proportion and larger diameter indicated IA rather than non-invasive lesions (AIS and MIA) (10-12). Nevertheless, uncertainty remains on the correlation between image characteristics of the nodules in CT scans and adenocarcinoma histopathologic subtypes.

We performed this retrospective analysis to estimate the correlation between preoperative high resolution computed tomography (HRCT) scan and postoperative histopathology of stage IA lung adenocarcinoma in East Asian Chinese population. In addition, we'd like to find some independent risk factors in HRCT signatures which can help distinguish histological subtypes in early stage lung adenocarcinoma to predict their prognosis.

Methods

Patients

We retrospectively reviewed the clinical records and CT images of 190 patients (106 female and 84 male; age range, 29–81 years; average age, 59 years) with resected, preoperatively untreated pT1N0M0 stage IA adenocarcinomas. These patients underwent lung cancer surgery in Jinling hospital (Jiangsu, China) between July 2008 and March 2015. All cases met the 2011 IASLC/ATS/ERS classification (3) of lung adenocarcinomas and were considered as stage IA according to the 7th Edition Union for International Cancer Control/American Joint Committee on Cancer TNM classification (13). Patients concurrent with other tumors were excluded (*Figure 1*).

Histological evaluation

Histological classification was according to the IASLC/ATS/ERS classification of lung adenocarcinomas (3). Tumors were classified as atypical adenomatous hyperplasia (AAH), AIS, MIA and IA. IA was further divided into lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, solid predominant with mucin, invasive mucinous adenocarcinoma and colloid predominant.

HRCT evaluation

Two radiologists with 3 years of experience retrospectively interpreted the HRCT images independently. If they have different opinions, a third radiologist will confirm it. Margin characteristics of nodules and the internal characteristics within the nodules were all analyzed. These characteristics included diameter, proportion of GGO, margin, border definition, bubble lucency, shape, air bronchogram, vessel convergence sign, pleural retraction, pleural thickening, lymphadenopathy, enhancement and so on. GGO was defined as hazy and amorphous increased lung attenuation without obscuration of the underlying vascular markings and bronchial walls. In regard to evaluated the GGO proportion of the tumor (GGO/tumor ratio; G/T ratio),

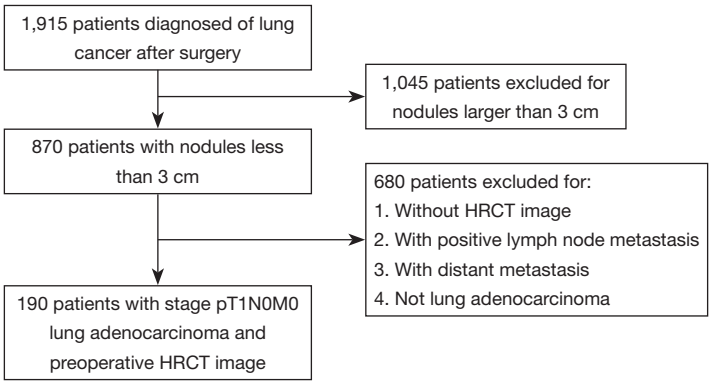

Figure 1 Selection process for stage pT1N0M0 lung adenocarcinoma with high resolution computed tomography (HRCT) image.

the G/T ratio was calculated as (1-DSOL)/ DGGO, where DGGO was the largest area of the tumor, and DSOL was the largest solid area of the tumor (14).

Statistics

Statistical analysis was performed using the one-way ANOVA for continuous variables and chi-square test for categorical variables. To analyze the relationship between HRCT and histological subtypes, we used logistic regression model for multivariate analysis. Values of $P<0.05$ were considered significant. Statistical analysis was conducted using Statistical Product and Service Solutions (SPSS) version 20.0.

Results

Clinical characteristics

Clinical features including sex, age, smoking history, tumor location, surgical procedures, and histological subtype were summarized in *Table 1*. Most patients were female (56%) and never smoking (71%). Median age was 59 years (range, 29–81 years). A large majority of tumors (65%) were located in right lung. Seventy four tumors (39%) were located in right upper lobe (RUL) and 46 tumors (24%) were located in left upper lobe (LUL). One hundred and sixty one patients (85%) underwent lobectomy, 22 patients (12%) underwent wedge resection, and 7 patients (4%) underwent segmentectomy (*Table 1*). No patient received preoperative adjuvant chemotherapy and/or radiation therapy. Among the patients, 55 received *EGFR* mutation detection, 32 (58%) of them were *EGFR* mutation positive (*Table 2*).

Histological characteristics

According to the IASLC/ATS/ERS classification, there were 2 AAH cases (1%), 3 AIS cases (2%), 10 MIA cases (5%) and 175 IA cases (92%) which were mostly acinar predominant adenocarcinoma (44%) (*Table 1*).

Since solid adenocarcinomas have a poor prognosis, papillary and acinar adenocarcinomas have an intermediate prognosis, and lepidic adenocarcinomas have a favorable prognosis (15). In order to better carry out statistics, we classified lung adenocarcinoma in four groups. Lepidic group contains AAH, AIS, MIA and lepidic predominant IA. Acinar group is acinar predominant IA. Papillary group is papillary predominant IA. And solid group is solid predominant invasive adenocarcinoma (SPA).

Univariate analysis

We conducted one-way ANOVA analysis to find the differences among four groups. Median tumor diameter was 19.58±7.33 mm, and it was significantly lower in level 1 group (15.96±6.95 mm), whereas acinar predominant adenocarcinoma and papillary-predominant (21.28±7.18 mm; 19.90±6.85 mm, respectively) were of intermediate size, and level 4 (21.70±6.49 mm) were larger ($P<0.001$). GGO proportion ($P<0.001$), margin ($P<0.001$), border definition ($P=0.015$), pleural retraction ($P<0.001$) and enhancement ($P<0.001$) had statistically significant differences in four histological levels (*Table 2*). There were no significant differences in bubble lucency, shape, air bronchogram, vessel convergence sign, pleural thickening, lymphadenopathy and *EGFR* mutation by chi-square test (*Table 2*).

Table 1 Clinical characteristics of patients with pT1N0M0 lung adenocarcinoma

Characteristics	Overall (n=190, %)
Sex	
Female	106 [56]
Male	84 [44]
Age (years)	
<50	33 [17]
50–59	63 [33]
60–69	65 [34]
≥70	29 [15]
Median [range]	59 [29–81]
Smoking history	
No	135 [71]
Yes	55 [29]
Tumor location	
RUL	74 [39]
RML	10 [5]
RLL	39 [21]
LUL	46 [24]
LLL	21 [11]
Surgical procedures	
Wedge resection	22 [12]
Segmentectomy	7 [4]
Lobectomy	161 [85]
Histological subtype	
AAH	2 [1]
AIS	3 [2]
MIA	10 [5]
LPA	40 [21]
APA	83 [44]
PPA	29 [15]
SPA	23 [12]

RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; APA, acinar predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

Multivariate analysis

To find the association between HRCT characteristics and histological subtypes, we conducted the multivariate analysis referenced for lepidic group which indicated that GGO proportion and pleural retraction were independent associated with acinar group (RR=4.221, 95% CI: 1.770–10.066, P=0.001; RR=0.380, 95% CI: 0.158–0.916, P=0.031, respectively, *Table 3*). Tumors which HRCT characterized without GGO component and with positive pleural retraction were more likely to be acinar predominant IA than lepidic predominant IA. While male and whose nodule margin with spiculation or lobulation were prone to papillary predominant IA (RR=0.288, 95% CI: 0.090–0.920, P=0.036; RR=0.250, 95% CI: 0.070–0.887, P=0.032, respectively, *Table 3*). GGO proportion and nodule margin were independent prediction factors in solid group (RR=13.338, 95% CI: 2.974–59.811, P=0.001; RR=0.097, 95% CI: 0.016–0.606, P=0.013, respectively, *Table 3*). Nodules without GGO component or nodule margin with spiculation or lobulation were risk factors for poor prognosis histological subtypes.

Discussion

In this study, we retrospectively reviewed 190 patients with preoperatively untreated pT1N0M0 stage IA adenocarcinomas in East Asian Chinese population, and investigated a number of prediction factors in clinical and HRCT scan between different histological subtypes.

In univariate analysis, we found that smaller tumor size and larger GGO proportion were significantly associated with indolent and less aggressive tumors. Similarly, there were several studies also found that the size and mass of the nodule are determinants of invasive adenocarcinoma (8,16-18). While, recently an observation found that in patients with tumors smaller than 3 cm, DFS was significantly associated with solid tumor size, but not with whole tumor size in early stage tumors (9). They suggested that nomogram-based T descriptors provide better prediction of survival than conventional T descriptors (9). Our results thus are in concordance with previous findings and support the hypothesis that larger tumor size and smaller GGO proportion are risk factors for poor prognosis histological subtypes in early stage lung adenocarcinomas. In addition, we have shown that tumors with spiculation or lobulation, poorly defined border and positive pleural retraction were more likely to be poor prognosis histological

Table 2 Univariate analysis of HRCT characteristics and lung adenocarcinoma histologic subtypes

HRCT characteristics	Number	Histologic subtype[#]				χ^2/F	P value
		Lepidic	Acinar	Papillary	Solid		
All patients	190	55 (29%)	83 (44%)	29 (15%)	23 (12%)		
Diameter (mm)*	19.58±7.33	15.96±6.95	21.28±7.18	19.90±6.85	21.70±6.49	7.297	<0.001
Proportion of GGO (%)						43.721	<0.001
0	115	16	62	17	20		
1–50	27	9	11	5	2		
51–100	48	30	10	7	1		
Margin						22.805	<0.001
Smooth	49	27	15	5	2		
Spiculation or lobulation	141	28	68	24	21		
Border definition						10.487	0.015
Poorly defined	69	28	30	7	4		
Well defined	121	27	53	22	19		
Bubble lucency						1.643	0.650
–	128	40	52	20	16		
+	62	15	31	9	7		
Shape						7.266	0.064
Round	131	41	49	22	19		
Irregular	59	14	34	7	4		
Air bronchogram						3.081	0.379
–	114	38	45	17	14		
+	76	17	38	12	9		
Vessel convergence sign						2.456	0.483
–	160	47	70	22	21		
+	30	8	13	7	2		
Pleural retraction						20.907	<0.001
–	79	34	20	13	12		
+	111	21	63	16	11		
Pleural thickening						5.259	0.154
–	166	51	70	23	22		
+	24	4	13	6	1		
Lymphadenopathy						1.112	0.774
–	154	44	68	22	20		
+	36	11	15	7	3		
Enhancement						19.044	<0.001
–	36	15	16	5	0		
+	94	11	50	15	18		
EGFR mutation						6.125	0.106
–	23	6	8	4	5		
+	32	8	19	4	1		

[#], lepidic group contains AAH, AIS, MIA and LPA. Acinar group is APA. Papillary group is PPA. Solid group is SPA; *, diameter analysis used the one-way ANOVA analysis, others used chi-square test; HRCT, high resolution computed tomography; GGO, ground-glass opacity; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; APA, acinar predominant invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

Table 3 Multivariate analyses of clinical/HRCT characteristics and lung adenocarcinoma histologic subtype

Histologic subtype[#, *]	P value	RR	95% CI
Acinar			
Sex			
Female	0.089	2.632	0.863–8.029
Male	Reference	–	–
Smoking			
No	0.150	0.399	0.114–1.395
Yes	Reference	–	–
GGO proportion (%)			
0	0.001	4.221	1.770–10.066
1–100	Reference	–	–
Margin			
Smooth	0.370	0.650	0.254–1.666
Spiculation or lobulation	Reference	–	–
Pleural retraction			
No	0.031	0.380	0.158–0.916
Yes	Reference	–	–
Pleural thickening			
No	0.715	0.787	0.218–2.844
Yes	Reference	–	–
Papillary			
Sex			
Female	0.036	0.288	0.090–0.920
Male	Reference	–	–
Smoking			
No	0.380	1.832	0.474–7.076
Yes	Reference	–	–
GGO proportion (%)			
0	0.223	2.008	0.654–6.165
1–100	Reference	–	–
Margin			
Smooth	0.032	0.250	0.070–0.887
Spiculation or lobulation	Reference	–	–
Pleural retraction			
No	0.799	1.149	0.394–3.349
Yes	Reference	–	–
Pleural thickening			
No	0.401	0.522	0.115–2.378
Yes	Reference	–	–
Solid			
Sex			
Female	0.327	0.428	0.079–2.331
Male	Reference	–	–
Smoking			
No	0.207	0.341	0.064–1.816
Yes	Reference	–	–
GGO proportion (%)			
0	0.001	13.338	2.974–59.811
1–100	Reference	–	–
Margin			
Smooth	0.013	0.097	0.016–0.606
Spiculation or lobulation	Reference	–	–
Pleural retraction			
No	0.069	3.298	0.911–11.934
Yes	Reference	–	–
Pleural thickening			
No	0.081	8.982	0.761–106.075
Yes	Reference	–	–

[#], lepidic group contains AAH, AIS, MIA and LPA. Acinar group is APA. Papillary group is PPA. Solid group is SPA; *, the reference category is: lepidic group. HRCT, high resolution computed tomography; RR, relative risk; CI, confidence interval; GGO, ground-glass opacity; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma *in situ*; MIA, minimally invasive adenocarcinoma; LPA, lepidic predominant invasive adenocarcinoma; APA, acinar predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid predominant invasive adenocarcinoma.

subtypes. Not all patients took enhanced CT examination, but tumors with enhancement were significantly relevant with acinar predominant IA.

However, we did not find significant difference in bubble lucency, shape, air bronchogram, vessel convergence sign, pleural thickening, lymphadenopathy in *EGFR* mutation (*Table 2*). While, different observations were found last year (19,20). One of the studies enrolled 35 patients with 72 lesions. Among them, 33 (45.8%) tumor lesions were found harboring *EGFR* mutations, and their founding indicated that there was a high discrepancy of driver mutations in NSCLC patients with ground-glass nodules (GGNs) (19). Another research showed that *EGFR* mutation especially L858R was detected more frequently in invasive solid pattern and significantly less in pure GGO pattern in stage I lung adenocarcinoma (21). In our study, 55 patient conducted EGFR detection, only 9 of them were pGGOs. Although there was no significant difference, a majority of patients with positive *EGFR* mutation were acinar predominant IA (59%) (*Table 2*).

In multivariate analysis, we used lepidic group (histological subtypes with favorable prognosis) as reference for logistic regression model. Tumors which HRCT characterized without GGO component and with positive pleural retraction were more likely to be acinar predominant IA than lepidic predominant IA. Male and whose nodule margins with spiculation or lobulation were prone to papillary predominant IA. Solid nodules without GGO component or nodule margin with spiculation or lobulation were prediction factors for poor prognosis histological subtypes.

Our results suggest that GGO proportion, margin signature and pleural retraction should be focused initial evaluation of histological subtypes in early stage lung adenocarcinomas. Several studies also showed that proportion of GGO remains important for predicting less invasive lung cancer (22-24). In their opinion, small peripheral adenocarcinoma or BAC may present with a high ratio of GGO components on CT scans. Investigators have reported that the solid components in advanced-stage lesions are significantly larger than those in lesions at earlier stage (5,25). Solid component increases the level of suspicion for invasive adenocarcinoma. Our study firstly evaluated the correlation between HRCT image and four histological subtypes.

However, we did not find significant difference in smoking history (*Table 3*). Recent studies have showing that smoking was a significant predictive for unfavorable prognosis in lung adenocarcinoma (26). And it was robustly associated with GGO growth (27). In our study, most patients were female (56%) (*Table 1*). We could not exclude passive smoking and exposure to dust (28) from those without smoking history. Besides, air pollution may be another reason.

This study had some limitations. First, this was a retrospective study and the number of patients was relatively small for our strict inclusion criteria. And some cases were excluded for not available HRCT image in other hospitals. We hope to further validate these results in a prospective study with a large number of cases. Second, since our study reviewed patients between July 2008 and March 2015, we could not get complete prognostic information now. We look forward to confirm these results and find more useful risk factors in early stage lung adenocarcinoma prognosis by follow-up research.

In conclusion, we demonstrated that nodules with spiculation or lobulation and less GGO proportion are determinants of poor prognosis histological subtypes in stage IA lung adenocarcinoma patients according to the 2011 histologic IASLC/ATS/ERS classification. HRCT signatures such as tumor diameter, GGO proportion, margin, border definition and pleural retraction may help infer histological subtypes of lung adenocarcinoma in early stage.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Ethical Committee (approval number: 2016NZHX-005) and written informed consent was obtained from all patients.

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