Prognosis of Early-stage Part-solid and Pure-solid Lung Adenocarcinomas

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Abstract. *Background/Aim:* In the new TNM classification (8th edition) of lung cancer, T category is defined based on the solid component size; therefore, part solid type (PST) with and solid type (ST) without ground glass opacity (GGO) are categorized as same T value according to their solid component sizes. However, differences between these tumors have not been clarified. *Patients and Methods* The study included 274 pStage I lung adenocarcinoma patients who had undergone surgery at our Institution from 2003 to 2012. Their tumors were classified as pure GGO, PST, and ST. After propensity score matching for solid component size, we compared prognoses between PST and ST. *Results:* The same percentage was noted for PST and ST tumors (119/274; 43.4%). After propensity score matching, the disease-free survival (DFS) was significantly worse in ST than PST (5-year DFS: 69.2% versus 88.7%; $p=0.0241$). *Conclusion:* Prognoses of PST and ST adenocarcinomas differ even when their solid component sizes are the same.

The TNM classification of lung cancer was revised in January 2017 (8th edition) (1). In this version, the T category was subdivided into 1 cm increments and was defined by the size of the solid component, excluding ground glass opacity (GGO).

In lung adenocarcinomas, radiological GGO is associated with histologically non-invasive or minimally invasive characteristics (2), while higher ratios of solid component to total tumor diameter (consolidation/tumor; C/T ratio) are

reportedly associated with histological evidence of invasiveness (3). Because solid component size is a better prognostic factor than whole tumor size in Stage IA lung adenocarcinomas (4), the TNM classification was revised mainly according to the size of the solid component of the tumor. Thus, part solid type (PST) with GGO and solid type (ST) without GGO are categorized as of the same T category when their solid components are the same size (Figure 1).

However, differences in clinicopathological characteristics and prognoses between PST and ST have not been fully investigated. Although it has been shown by propensity score matching that prognoses of PST and ST were similar for Stage IA non-small cell lung cancer (5), other studies revealed differences in clinicopathological characteristics and prognoses between PST and ST (6-8). Therefore, in the present study we investigated whether the clinicopathological characteristics and prognoses of PST and ST tumors are the same or not. We used propensity score matching to investigate differences in clinicopathological characteristics and prognoses between patients with pathological Stage I PST versus ST lung adenocarcinoma who had undergone surgery.

Patients and Methods

Patients. This retrospective study included a cohort of 274 patients with pathological Stage I (7th TNM classification) primary lung adenocarcinoma who had undergone surgery between January 2003 and December 2012 at the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University. After surgery, routine follow-up, including physical examination, blood tests (including serum tumor markers), and chest radiographs was performed at 3 month intervals for the first 3 years, and 6 monthly thereafter. The patients were divided into the following three groups, according to the tumor C/T ratios as estimated on computed tomography (CT) images obtained within one month before surgery: pure GGO type (C/T=0), PST ($0 < C/T < 1$), and ST (C/T=1). Clinicopathological characteristics, disease-free survival (DFS), and overall survival (OS) were retrospectively analyzed in the PST and ST subgroups. Clinicopathological characteristics

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Figure 1. Computed tomography images of part solid type tumor (A) and solid type tumor (B).

assessed included age, sex, smoking (pack year index), radiological tumor size, radiological solid component size, maximum standardized uptake value (SUV-max), pleural invasion (pl), lymphatic invasion (ly), vascular invasion (v), predominant histological component, epidermal growth factor receptor (*EGFR*) mutation, and programmed cell death ligand-1 (PD-L1) expression. *EGFR* mutation had been assessed in tumor tissue using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (LSI Medience Corporation, Tokyo, Japan). PD-L1 expression had been investigated by immunohistochemical staining with antibody against PD-L1 (rabbit monoclonal, clone SP142, Spring Bioscience, Ventana, Tucson, AZ, USA) as described previously (9). In the present study, more than 5% tumor membrane staining was considered as positive PD-L1 staining (10).

Statistical analysis. Fisher's exact test was used to analyze patient characteristics. DFS was defined as the period between surgery and the date of the last follow-up, recurrence or death, and OS as the period between surgery and the date of last follow-up or death. Survival curves were estimated by using the Kaplan-Meier method with the log-rank test. All results were considered statistically significant at $p < 0.05$. JMP pro 13.0 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Propensity score matching. Propensity score matching for solid component size was performed to eliminate differences in solid component size. A propensity score difference of 0.05 was adopted as the maximum caliper width for matching PST and ST groups. After propensity score matching, 48 matched patients per group were included in the analysis.

Results

Patient characteristics. The study cohort comprised 276 patients with Stage I lung adenocarcinoma who had undergone surgical resection (Table I). Thirty-six (13.1%), 119 (43.4%), and 119 patients (43.4%) were classified as having pure GGO, PST, and ST adenocarcinomas, respectively. The median age was 69 years (range=34-85), and 134 patients (48.6%) were men. The radiological median size of total tumor and solid component were 19.2 mm (range=2.7-106.5) and 12.6 mm (range=0.0-70.3), respectively. As to surgical procedures, bilobectomy, lobectomy, segmentectomy, and partial resection were performed on 2 (0.7%), 183 (66.8%), 35 (12.8%), and 54 patients (19.7%), respectively. On histological examination of resected tumors, 55 patients (20.1%) had tumors of lepidic pattern [adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIS), or lepidic adenocarcinoma] and 219 invasive adenocarcinomas (79.9%). The clinicopathological characteristics according to study group before propensity score matching are shown in Table II. There were significant differences between the PST and ST groups in radiological solid size ($p < 0.0001$), SUV-max ($p < 0.0001$), pl ($p < 0.0001$), ly ($p = 0.0031$), v ($p < 0.0001$), predominant histological component ($p < 0.0001$), presence of *EGFR* mutation ($p < 0.0001$), and PD-L1 expression ($p = 0.0013$). After

Table I. Clinicopathological characteristics of patients with resected pathological Stage I (according to 7th TNM classification) adenocarcinoma.

Characteristic	N=274
Age (years)	
Median	69
Range	34-85
Gender	
Male	134 (48.9%)
Female	140 (51.1%)
Smoking (pack year index)	
<30	188 (68.6%)
≥30	86 (31.4%)
Radiological tumor type	
Pure GGO	36 (13.1%)
Part solid	119 (43.4%)
Pure solid	119 (43.4%)
Radiological size of solid component (mm)	
Median	12.2
Range	0.0-47.5
Radiological tumor size (mm)	
Median	19.0
Range	2.7-48.7
SUV-max*	
<2.5	84 (51.2%)
≥2.5	80 (48.8%)
Surgical procedure	
Bilobectomy	2 (0.7%)
Lobectomy	183 (66.8%)
Segmentectomy	35 (12.8%)
Partial resection	54 (19.7%)
pl*	
Negative	240 (87.9%)
Positive	33 (12.1%)
ly	
Negative	255 (93.1%)
Positive	19 (6.9%)
v	
Negative	227 (82.8%)
Positive	47 (17.2%)
Predominant histological component	
AIS	34 (12.4%)
MIA	1 (0.4%)
Lepidic	20 (7.3%)
Papillary	197 (71.9%)
Acinar	3 (1.1%)
Micropapillary	1 (0.4%)
Solid	14 (5.1%)
Variants	4 (1.5%)
EGFR mutation*	
Negative	89 (52.0%)
Positive	82 (48.0%)
PD-L1 expression	
<5%	227 (82.8%)
≥5%	47 (17.2%)

*Available data were counted, excluding unknown data. AIS, Adenocarcinoma *in situ*; EGFR, epidermal growth factor receptor; GGO, ground glass opacity; ly, lymphatic invasion; MIA, minimally-invasive adenocarcinoma; PD-L1, programmed cell death ligand-1; pl, pleural invasion; SUV, maximum standardized uptake value; v, vascular invasion.

Table II. Clinicopathological characteristics of patients according to adenocarcinoma type.

Characteristics	Part solid (119)	Pure solid (119)	p-Value
Age (years)			0.6456
Median	69	68	
Range	34-84	37-85	
Gender			0.1537
Male	54 (45.4%)	66 (55.5%)	
Female	65 (54.6%)	53 (44.5%)	
Smoking (pack year index)			0.1587
<30	89 (74.8%)	69 (58.0%)	
≥30	30 (25.2%)	50 (42.0%)	
Radiological tumor size (mm)			0.2687
Median	18.9	20.9	
Range	6.5-48.7	2.7-47.5	
Radiological solid size (mm)			<0.0001
Median	9.2	20.9	
Range	1.9-36.7	2.7-47.5	
SUV-max*			<0.0001
<2.5	58 (70.7%)	14 (20.0%)	
≥2.5	24 (29.3%)	56 (80.0%)	
Surgical procedures			0.0279
Bilobectomy	1 (0.8%)	1 (0.8%)	
Lobectomy	81 (68.1%)	89 (74.8%)	
Segmentectomy	7 (5.9%)	15 (12.6%)	
Partial resection	30 (25.2%)	14 (11.7%)	
pl*			<0.0001
Negative	118 (99.2%)	88 (74.6%)	
Positive	1 (0.8%)	30 (25.4%)	
ly			0.0031
Negative	116 (97.5%)	103 (86.5%)	
Positive	3 (2.5%)	16 (13.5%)	
v			<0.0001
Negative	111 (93.3%)	82 (68.9%)	
Positive	8 (6.7%)	37 (31.1%)	
Predominant histological component			<0.0001
AIS	19 (16.0%)	3 (2.5%)	
MIA	1 (0.8%)	0 (0.0%)	
Lepidic	13 (10.9%)	2 (1.7%)	
Papillary	83 (69.8%)	95 (79.8%)	
Acinar	3 (2.5%)	0 (0.0%)	
Micropapillary	0 (0.0%)	1 (0.8%)	
Solid	0 (0.0%)	14 (11.8%)	
Variants	0 (0.0%)	4 (3.3%)	
EGFR mutation*			<0.0001
Negative	36 (40.9%)	48 (75.0%)	
Positive	52 (59.1%)	16 (25.0%)	
PD-L1 expression*			0.0013
<5%	107 (89.9%)	87 (73.1%)	
≥5%	12 (10.1%)	32 (26.9%)	

*Available data were counted, excluding unknown data. AIS, Adenocarcinoma *in situ*; EGFR, epidermal growth factor receptor; GGO, ground glass opacity; ly, lymphatic invasion; MIA, minimally-invasive adenocarcinoma; PD-L1, programmed cell death ligand-1; pl, pleural invasion; SUV, maximum standardized uptake value; v, vascular invasion.

Table III. Clinicopathological characteristics of part and pure solid adenocarcinomas after propensity score matching for size of solid component.

Characteristics	Part solid (n=48)	Pure solid (n=48)	p-Value
Age (years)			0.2415
Median	71	68	
Range	45-84	38-85	
Gender			0.3058
Male	23 (47.9%)	29 (60.4%)	
Female	25 (52.1%)	19 (39.6%)	
Smoking (pack year index)			0.0094
<30	38 (79.2%)	25 (52.1%)	
≥30	10 (20.8%)	23 (47.9%)	
Radiological tumor size (mm)			<0.0001
Median	24.6	14.2	
Range	10.7-48.7	2.7-36.5	
Radiological size of solid component (mm)			0.9766
Median	13.9	14.2	
Range	2.4-36.7	2.7-36.5	
SUV-max*			0.2081
<2.5	18 (56.3%)	11 (39.3%)	
≥2.5	14 (43.7%)	17 (60.7%)	
Surgical procedure			0.1456
Bilobectomy	0 (0.0%)	0 (0.0%)	
Lobectomy	40 (83.3%)	32 (66.7%)	
Segmentectomy	3 (6.3%)	8 (16.7%)	
Partial resection	5 (10.4%)	8 (16.7%)	
pl*			0.0008
Negative	47 (97.9%)	35 (74.5%)	
Positive	1 (2.1%)	12 (25.5%)	
ly			0.1112
Negative	47 (97.9%)	42 (87.5%)	
Positive	1 (2.1%)	6 (12.5%)	
v			0.2083
Negative	41 (85.4%)	35 (72.9%)	
Positive	7 (14.6%)	13 (27.1%)	
Predominant histological component			0.0373
AIS	2 (4.2%)	1 (2.1%)	
MIA	0 (0.0%)	0 (0.0%)	
Lepidic	4 (8.3%)	0 (0.0%)	
Papillary	41 (85.4%)	39 (81.3%)	
Acinar	1 (2.1%)	0 (0.0%)	
Micropapillary	0 (0.0%)	1 (2.1%)	
Solid	0 (0.0%)	5 (10.4%)	
Variants	0 (0.0%)	2 (2.1%)	
EGFR mutation*			0.0148
Negative	13 (41.9%)	19 (76.0%)	
Positive	18 (58.1%)	6 (24.0%)	
PD-L1 expression			0.2243
<5%	40 (83.3%)	34 (70.8%)	
≥5%	8 (16.7%)	14 (29.2%)	

*Available data were counted, excluding unknown data. AIS, Adenocarcinoma in situ; EGFR, epidermal growth factor receptor; ly, lymphatic invasion; MIA, minimally-invasive adenocarcinoma; PD-L1, programmed cell death ligand-1; pl, pleural invasion; SUV-max, maximum standardized uptake value; v, vascular invasion.

Figure 2. Disease-free survival of part solid type (PST) and solid type (ST) groups before propensity score matching for solid component size showing that the prognosis is worse for the ST than PST group (5 year DFS: 64.1% versus 93.0%; $p<0.0001$).

Figure 3. Disease-free survival of part solid type (PST) and solid type (ST) groups after propensity score matching for solid component size shows that the prognosis of ST group is worse than that of the PST group, even when their solid component sizes are the same (5 year DFS: 69.2% versus 88.7%; $p=0.0241$).

propensity score matching for radiological size of the solid component, smoking history ($p=0.0094$), pl positivity ($p=0.0008$), and EGFR mutation negativity ($p=0.0148$) were found to occur more frequently in the ST than PST group (Table III). In addition, the frequency of lepidic pattern (AIS, MIA, and lepidic adenocarcinoma) was higher in the PST than ST group (14.3% versus 2.1%; $p=0.0373$).

Postoperative survival. The DFS was significantly worse in the ST than the PST group (5-year DFS: 64.1% *versus* 93.0%; $p < 0.0001$; Figure 2); the OS was also worse in the ST than PST group (5-year OS: 86.2% *versus* 93.6%; $p = 0.0193$). Additionally, 5-year DFS and OS were both 97.2% in the GGO group. Even after propensity score matching for the size of the solid component, the DFS was significantly worse in the ST than the PST group (5-year DFS: 69.2% *versus* 88.7%; $p = 0.0329$; Figure 3). However, there was no significant difference between the PST and ST groups in OS (5-year OS: 88.4% *versus* 90.8%; $p = 0.6468$).

Discussion

In the present study, we demonstrated a difference in clinicopathological characteristics and prognoses between PST and ST by using propensity score matching in patients with Stage I lung adenocarcinoma. To more accurately determine any discrepancies between PST and ST, the only clinicopathological characteristic matched in propensity score matching was radiological size of solid component. After propensity score matching for solid component size, the DFS was still significantly worse in the ST than PST group. As to clinicopathological characteristics, smoking history, pl positivity, *EGFR* mutation negativity, and invasive predominance were more frequent in the ST than PST group after propensity score matching for solid component size. Taken together, these differences indicate that the prognosis is worse for patients with ST than PST lung adenocarcinomas.

The relationship between radiological GGO and pathological non-invasiveness in lung adenocarcinoma has recently been receiving increased attention, as indicated by the changes in the 8th TNM classification. The JCOG0804 study showed that curative limited resection for lung adenocarcinoma with tumor diameter < 2 cm and C/T ratio < 0.25 is not inferior to lobectomy (11). Therefore, it is reasonable to prioritize solid component size over whole tumor diameter including GGO. However, the changes in the 8th TNM classification may lead to confusion since differences in clinicopathological characteristics and prognoses between ST and PST tumors have not been fully investigated. According to the 8th TNM classification, ST and PST tumors are equally treated according to the sizes of their solid components.

A previous study that incorporated propensity score matching revealed the validity of treating PST and ST tumors equally according to the sizes of their solid components (5). However, another study in patients with stage IA lung carcinoma showed that SUV-max was higher for ST than PST tumors and that the DFS of patients with ST tumor was worse than that of those with PST tumors (6). Furthermore, even when the GGO component of a PST tumor is small ($0.75 \leq \text{C/T ratio} < 1$), the DFS of patients with PST tumors is better than that of those with ST tumors (7).

In early stage non-small cell lung cancer, both DFS and OS of ST tumors are reportedly worse than those of PST tumors in the same clinical T category (8). By considering these evidences, we suggest that the 8th TNM classification can be further improved.

Biologically, there are two pathways for progression of lung adenocarcinoma: linear and non-linear (12). In linear progression, a premalignant lesion, known as atypical adenomatous hyperplasia, progresses to a pre-invasive adenocarcinoma *in situ*, which is followed by invasive adenocarcinoma (12). Linear progression is common in women and non-smokers and is associated with genetic changes such as v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog or *EGFR* mutation (12). In contrast, non-linear progression refers to a *de novo* pathway in which malignant change is not preceded clinically and pathologically by a premalignant or preinvasive lesion (12); details of this type of pathogenesis remain unclear. In the current study, the pack year index was lower and the frequency of *EGFR* mutation higher in the PST than ST group. These findings suggest that non-linear and linear progression may be related to differences between PST and ST tumors. This possible difference in the pathogenesis of PST and ST tumors may, at least in part, explain the results obtained in this study.

One limitation of our study is that the study cohort was relatively small to allow use of univariate and multivariate analysis. Furthermore, the design of this study was retrospective. We consider that the large-scale prospective studies are warranted to further elucidate the difference of the clinicopathological characteristics and prognoses between PST and ST tumors.

In conclusion, the clinicopathological characteristics and prognoses of PST and ST tumors may differ despite the fact that the sizes of their solid component are the same. Further research could elucidate the impact of GGO on lung cancer prognosis and contribute to the selection of the most appropriate treatment.

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Authors' Contributions

FK, GT and TT designed the study. FK and GT wrote the manuscript. TM, YK, TH, ST, TA and FH contributed to data collection and interpretation, and critically reviewed the manuscript. TT and YM performed total organization of writing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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