Original Article

Impact of ground glass opacity in a three-dimensional analysis for pathological findings and prognosis in stage IA pure solid lung cancer

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Background: We investigated whether a three-dimensional (3D) analysis could correct the discrepancy between conventional computed tomography findings and pathological findings and contribute to prognostic stratification in early pure solid lung cancer.

Methods: A total of 370 patients with two-dimensional (2D) pure solid, clinical stage IA non-small cell lung cancer (NSCLC) who underwent complete resection at our hospital between January 2010 and March 2021 were included in the present study. We classified the patients into the 3D solid group and the 3D ground glass opacity (GGO) group according to the consolidation volume/tumor volume ratio (C/T volume ratio) measured using a Synapse Vincent 3D analysis workstation, and compared the pathological findings and prognosis between the two groups.

Results: There were 142 (38.4%) patients in the 3D GGO group. Lepidic lesions were significantly more frequent in the 3D GGO group (27.6% *vs.* 59.2%, P<0.001). Lymphatic invasion, vascular invasion and lymph node metastasis were significantly more frequent in the 3D solid group (52.2% *vs.* 27.5%, P<0.001; 67.5% *vs.* 43.0%, P<0.001; 22.3% *vs.* 11.2%, P=0.04). A Cox proportional hazards multivariate analysis for overall survival (OS) and recurrence-free survival (RFS) showed that 3D solid was an independent poor prognostic factor [hazard ratio (HR): 1.981, P=0.02; HR: 1.815, P=0.02]. Kaplan-Meier curves for 5-year OS (74.1% *vs.* 87.8%, P<0.001) and 5-year RFS (65.6% *vs.* 84.9%, P<0.001) showed significant differences between the two groups.

Conclusions: The C/T volume ratio determined by a 3D analysis detects GGO and reflects the pathological findings, and further prognostic stratification is possible in early 2D pure solid lung cancer.

Keywords: Lung cancer; clinical stage IA; consolidation volume/tumor volume ratio (C/T volume ratio); Synapse Vincent; ground-glass opacity

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Introduction

The consolidation to tumor ratio (C/T ratio) is a preoperative evaluation item that is highly correlated with pathological non-invasive lung cancer (defined as negative for lymph node metastasis, lymphatic and vascular invasion) (1). There are also reports that the C/T ratio can predict pathological N1–2 in clinical N0 cases (2,3). Consensus was obtained by considering reduced surgery for early-stage lung cancer based on this value, and multiple large-scale prospective studies have been conducted in recent years (4-6). Furthermore, with the increase in the use of thin-section computed tomography (CT) due to advances in imaging technology (7), multiple studies in recent years have reported that the prognosis is superior in two-dimensional (2D) CT image evaluations with even a very small ground glass opacity (GGO) component in comparison to pure solid findings (8-11). Therefore, the presence of the GGO component has received increased attention as a reliable prognostic factor in early non-small cell lung cancer (NSCLC) (8,10).

Conventionally, a GGO component observed in adenocarcinoma on CT images is pathologically associated with lepidic growth, which proliferates and spreads by alveolar epithelial replacement while maintaining the existing alveolar structure in the early stage of cancer development. It is considered to be a characteristic of early-stage lung adenocarcinoma, and is associated with a good prognosis (12-14). However, even lesions that are judged to be pure solid on 2D CT images are pathologically accompanied by lepidic growth, and there is a certain percentage of patterns in which lepidic growth is predominant. In other words, there may be a group with a good prognosis among pure solids lesions, which are considered to be associated with a poor prognosis in early-stage lung cancer. We previously reported the usefulness of the consolidation volume/tumor volume ratio (C/T volume ratio), which is the C/T ratio of the lesion volume, determined using a Synapse Vincent three-dimensional (3D) analysis workstation as a preoperative pathological non-invasive lung cancer predictor (15). Similarly, there it is also reported that the volume-based C/T ratio is useful for predicting postoperative upstaging (16). Therefore, in small lung cancer judged to be completely free of GGO on 2D CT (pure solid, C/T ratio =1), the C/T volume ratio calculated by a 3D analysis was significantly different from the above-mentioned imaging findings and pathological findings. We examined whether it could correct the discrepancy and whether it could contribute to prognostic stratification. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-341/rc).

Highlight box

Key findings

- The C/T volume ratio determined by a 3D analysis detects GGO and reflects the pathological findings, and further prognostic stratification is possible in early 2D pure solid lung cancer.

What is known and what is new?

- It has been reported that the C/T volume ratio is useful as a preoperative pathological predictor of non-invasive cancer in peripheral small lung cancer, and that the presence or absence of GGO is a prognostic factor. It was newly found that there are many cases in which GGO is detected by the C/T volume ratio even if judged to be pure solid, and that pathological and prognostic stratification is possible.

What is the implication, and what should change now?

- It was found that mechanical assessment in 3D contributed to prognostic stratification better than gross assessment in 2D. In the future, after performing stratification by 3D analysis, the optimal surgical procedure for peripheral small lung cancer should be examined.

Methods

Study population

Among 1,065 patients with clinical stage IA NSCLC with a maximum tumor diameter of 3 cm who underwent complete resection at our hospital between January 2010 and March 2021, there were 556 patients who were judged to be without GGO on 2D CT. After excluding cases with missing positron emission tomography (PET) data, simultaneous multiple lung cancer, preoperative chemoradiotherapy, or a centrally located tumor (if the tumor is centrally located, the vessels will be close and there is a high possibility of misrecognition by the 3D workstation), and same intralobar pneumonia cases 370 patients were included in the present study. The 8th edition of the American Joint Commission on Cancer TNM classification was used for clinical staging (17,18). With regard to clinical nodal assessment, clinical N0 was defined as non-enlarged lymph nodes (short axis <10 mm) on thin-section CT. Endobronchial ultrasound-guided transbronchial needle aspiration for mediastinal lymph node staging was performed preoperatively to confirm the node-negative status in cases that showed swollen lymph nodes on thin-section CT or uptake on PET. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013). The Institutional Review Board (IRB) of Seirei Mikatahara General Hospital approved the study protocol and publication of data (No. 22-64, Approval date: February 24, 2023). Informed consent was obtained from each patient before examination and the contents of this study were disclosed at our hospital. The medical records of each patient were retrospectively reviewed under a waiver of authorization approved by our IRB.

Two-dimensional image evaluation

Tumor evaluation by 2D CT was performed under lung field conditions (window level: −650 to −700 HU; window depth: 1,400–1,500 HU) using thin-section CT imaged at intervals of <2 mm. In addition, the evaluation of lymph nodes was performed under mediastinal conditions (window level: 30–60 HU; window depth: 300–400 HU). All evaluations by 2D CT were performed by a staff of multiple respiratory surgeons (4 thoracic surgeons with sufficient clinical experience and 2 qualified general surgeons but not thoracic surgeons). All staff members were aware that the lesions were likely primary lung cancers, but were unaware of the detailed pathological findings, including histology. All lesions that were the target of this study had all CT sections checked by the above staff, and were judged to be completely free of GGO.

GGO detection method using 3D analysis workstation

All preoperative 2D thin-section CT images were imported into a 3D analysis workstation Synapse Vincent (Fuji Photo Film Co., Ltd., Japan). Using the "Lung Analysis" application in the workstation, the tumor was recognized by specifying the lesion on CT, and the C/T volume ratio was calculated mechanically. Initially, we planned to define C/T volume ratio =1 as 3D pure solid, but GGO can be detected even in squamous cell carcinoma, which theoretically cannot be accompanied by GGO because it does not have a pathological lepidic component. It was judged that there was some degree of mechanical error, and a C/T volume ratio of 0.9 was adopted as the cutoff value. Therefore, in this study, the 3D solid group was defined by a C/T volume ratio of ≥0.9, and the 3D GGO group was defined by a C/T volume ratio of <0.9.

Statistical analysis

The purpose of this study was to investigate the clinical and pathological significance of the presence of GGO identified by a 3D analysis in clinical stage IA radiologically pure solid NSCLC. The primary endpoint was Overall survival (OS), and the secondary endpoint was recurrence-free survival (RFS) and pathological findings. We used Fisher's exact test for categorical variables and an unpaired *t*-test for continuous variables to compare the two groups. OS or RFS was estimated using the Kaplan-Meier method and compared between different groups using the log-rank test. In addition, a Cox proportional hazards model was used to identify factors that affect the prognosis. Univariate and multivariate analyses including all covariates were performed using Cox proportional hazards models and adjusted for confounding variables for survival and recurrence. For continuous variables, values higher than the median were classified as the high group. In addition, propensity score matching was used to control for confounding factors and reduce prognostic imbalance caused by a selection bias. Patient background variables adjusted by propensity score matching were sex, age, Brinkman index, clinical stage, and surgical procedure. Patients with equivalent propensity scores were selected using a one-to-one greedy matching algorithm using nearest neighbors without replacement, with a caliper width equal to 0.2 standard deviations of the propensity score logit. Follow-up was performed monthly until 3 months, every 3 months until 2 years, and every 6 months until 5 years after surgery. After 5 years postoperatively, follow-up was continued every six months or 1 year as needed. There was no loss to follow-up in this study, and withdrawal was treated as a discontinued case with respect to survival outcome. P values of <0.05 were considered statistically significant, and all statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results

Figure 1 shows a flow chart of this study, and *Table 1* shows the patient background. The median follow-up time was 62.2 months. A total of 370 cases were included, 73.2% were male, and the median age was 69 years. The clinical stage was stage IA1 in 6.2% of cases, IA2 in 54.4%, and IA3 in 39.4%. The surgical procedures included lobectomy in 76.5% of cases, segmentectomy in 14.8%, and wedge resection in 8.7%. At our facility, we basically choose lobectomy for 2D pure solid early lung cancer. Segmentectomy may be performed as aggressive reduction surgery based on SUVmax, tumor growth rate,

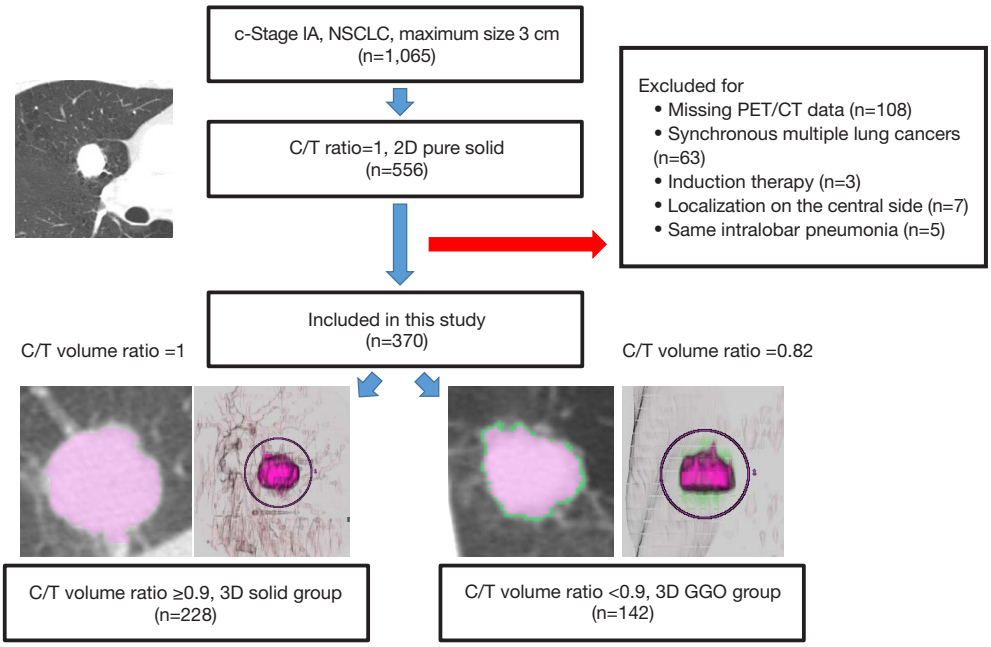

Figure 1 The consort diagram of the current study. A total of 370 patients with clinical stage IA NSCLC who were judged to be pure solid on 2D CT and who did not meet the exclusion criteria were enrolled in this study. After measuring the C/T volume ratio, 228 cases with a C/T volume ratio of ≥0.9 were classified into the 3D solid group, and 142 cases with a C/T volume ratio of <0.9 were classified into the 3D GGO group. In the 3D analysis image, purple indicates the solid component and green indicates the GGO component. NSCLC, non-small cell lung cancer; PET, positron emission tomography; CT, computed tomography; C/T ratio, consolidation to tumor ratio; GGO, ground glass tumor; 2D, two-dimensional; 3D, three-dimensional.

tumor marker values, etc., or as passive reduction surgery considering pulmonary function and complications. Regarding wedge resection, all cases are carried out as passive reduction surgery. The pathological stage was 0–IA3 in 51.9% of cases and IB–IIIB in 48.1%. Adenocarcinoma was the most common histologic type, accounting for 70% of cases, while squamous cell carcinoma accounted for 25.9% of cases. Pathological findings included lymphatic invasion in 42.7% of cases, vascular invasion in 58.1%, lymph node metastasis in 18.1%, lepidic in 39.7%, and lepidic predominant in 10.3%. Since the target period of this study was from 2010, many cases were not evaluated for micropapillary and spread through air spaces (STAS), so they were excluded from the survey items of this time. Two hundred twenty-eight cases (61.6%) in the 3D solid group and 142 cases (38.4%) in the 3D GGO group were classified and compared. Regarding patient background, age, Brinkman index, maximum standardized uptake value (SUVmax), and carcinoembryonic antigen (CEA) were significantly higher in the 3D solid group, the tumor size tended to be larger in the 3D solid group, resulting in less IA1 and more IA3 at the clinical stage. As pathological findings, pathological stage IB–IIIB was significantly more common in the 3D solid group. Squamous cell carcinoma was also more common. The rates of lymphatic invasion, vascular invasion, and lymph node metastasis were also significantly higher in the 3D solid group. In contrast, the rates of lepidic and lepidic predominant pathological findings were significantly higher in the 3D GGO group.

The Kaplan-Meier curves for OS and RFS are shown in *Figure 2*. In comparison to the 3D solid group and the 3D GGO group, the 5-year OS rate was 74.1% and 87.8%, respectively, while the 5-year RFS rate was 65.6% and 84.9%. 3D GGO was associated with a significantly better prognosis for both OS and RFS. Univariate and multivariate analyses using a Cox proportional hazards model for OS also showed that age, squamous cell carcinoma, lymph node metastasis, and 3D solid were independent poor prognostic factors. Lepidic and lepidic predominant pathological findings tended to be associated with a better prognosis, but did not show statistical significance in a univariate analysis (*Table 2*). Similarly, univariate and multivariate analyses

Table 1 Clinicopathological characteristics in clinical stage IA pure solid non-small cell lung cancer

Characteristic	Total (N=370)	3D solid (N=228)	3D GGO (N=142)	P value
Sex, n (%)				0.07
Male	271 (73.2)	175 (76.8)	96 (67.6)	
Female	99 (26.8)	53 (23.2)	46 (32.4)	
Median age, years	69	69	67	0.019
Median Brinkman index	690	750	618	0.037
Median SUVmax	4.95	7.1	4.03	<0.001
Median CEA, ng/mL	3.2	6.87	4.04	0.005
cStage (ver. 8), n (%)				0.002
IA1	23 (6.2)	8 (3.5)	15 (10.6)	
IA2	201 (54.4)	117 (51.3)	84 (59.2)	
IA3	146 (39.4)	103 (45.2)	43 (30.3)	
Surgery, n (%)				0.183
Lobectomy	283 (76.5)	181 (79.4)	102 (71.8)	
Segmentectomy	55 (14.8)	28 (12.3)	27 (19.0)	
Wedge resection	32 (8.7)	19 (8.3)	13 (9.2)	
pStage (ver. 8), n (%)				<0.001
0–IA3	192 (51.9)	97 (42.5)	95 (66.9)	
0	4 (1.0)	1 (0.4)	3 (2.1)	
IA1	36 (9.7)	8 (3.5)	28 (19.7)	
IA2	99 (26.7)	52 (22.8)	47 (33.1)	
IA3	53 (14.3)	36 (15.8)	17 (12.0)	
IB–IIIB	178 (48.1)	131 (57.5)	47 (33.1)	
IB	95 (25.6)	70 (30.7)	25 (17.6)	
IIA	2 (0.5)	1 (0.4)	1 (0.7)	
IIB	47 (12.7)	34 (14.9)	13 (9.2)	
IIIA	28 (7.5)	22 (9.6)	6 (4.2)	
IIIB	6 (1.5)	4 (1.7)	2 (1.4)	
Histology, n (%)				0.001
Adenocarcinoma	259 (70.0)	143 (62.7)	116 (81.7)	
Squamous cell carcinoma	96 (25.9)	75 (32.9)	21 (14.8)	
Others	15 (4.1)	10 (4.4)	5 (3.5)	
Pathological findings, n (%)				
Ly (+)	158 (42.7)	119 (52.2)	39 (27.5)	<0.001
V (+)	215 (58.1)	154 (67.5)	61 (43.0)	<0.001
LN meta (+)	67 (18.1)	51 (22.4)	16 (11.2)	0.044
Lepidic (+)	147 (39.7)	63 (27.6)	84 (59.2)	<0.001
Lepidic predominant (+)	38 (10.3)	12 (5.3)	26 (18.3)	<0.001

3D, three-dimensional; GGO, ground glass opacity; SUVmax, maximum standardized uptake value; CEA, carcinoembryonic antigen; Ly, lymphatic invasion; V, vascular invasion; LN meta, lymph node metastasis.

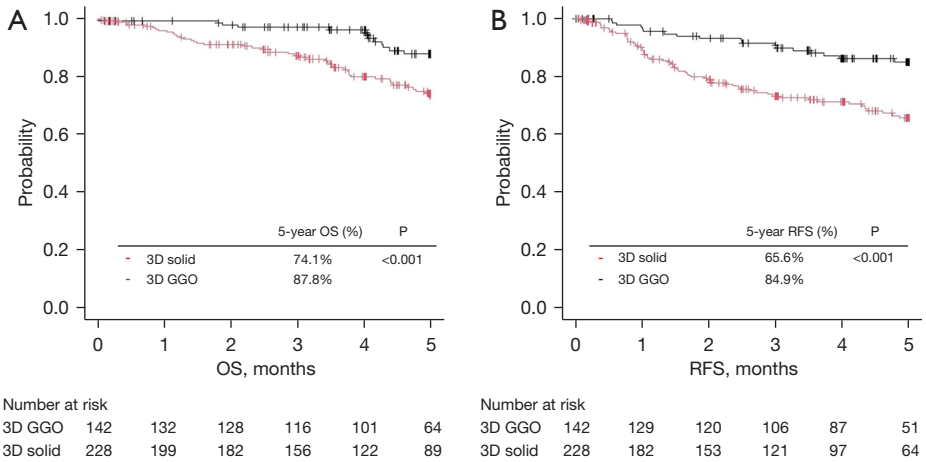

Figure 2 Kaplan-Meier curves showing the survival outcomes of the two groups. The significant differences in OS (A) and RFS (B) were observed between the two groups. OS, overall survival; RFS, recurrence-free survival; GGO, ground glass tumor.

Table 2 Cox proportional hazards model for overall survival in clinical stage IA pure solid non-small cell lung cancer

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Male	1.827	1.002–3.329	0.049	1.667	0.894–3.107	0.107
Age high	2.879	1.717–4.827	<0.001	2.543	1.488–4.348	<0.001
Brinkman index high	1.305	0.82–2.077	0.26			
3D solid	2.782	1.576–4.91	<0.001	1.981	1.107–3.544	0.021
SUVmax high	1.475	0.929–2.34	0.098			
Squamous cell carcinoma	2.772	1.747–4.397	<0.001	2.351	1.433–3.858	<0.001
Ly	1.694	1.069–2.686	0.024	1.266	0.785–2.042	0.332
V	1.037	0.65–1.655	0.877			
LN meta	1.851	1.096–3.125	0.021	2.535	1.447–4.441	0.001
Lepidic	0.75	0.458–1.229	0.253			
Lepidic predominant	0.747	0.323–1.725	0.494			

3D, three-dimensional; SUVmax, maximum standardized uptake value; Ly, lymphatic invasion; V, vascular invasion; LN meta, lymph node metastasis; HR, hazard ratio; CI, confidence interval.

using a Cox proportional hazards model for RFS revealed that age, lymphatic invasion, and lymph node metastasis as well as 3D solid, were also independent poor prognostic factors. Similarly, in RFS, lepidic predominant pathology tended to be associated with a favorable prognosis, but there was no significant difference in univariate (*Table 3*).

In addition, propensity score matching was performed to control for confounding factors and reduce prognostic imbalance caused by selection bias. Patient background factors and the number of cases other than the pathological stage and pathological findings were arranged (*Table 4*). As a result, there were 117 cases in both the 3D solid and 3D GGO groups, and a comparison between the two groups was performed again. As before propensity score matching, pathological stage IB–IIIB, lymphatic invasion, vascular invasion, and lymph node metastasis were significantly more frequent in the 3D solid group, and lepidic and lepidic predominant pathological findings were significantly more frequent in the 3D GGO group. In addition, *Figure 3* shows the Kaplan-Meier curves of the two groups for OS and RFS

Table 3 Cox proportional hazards model for recurrence-free survival in clinical stage IA pure solid non-small cell lung cancer

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Male	0.783	0.5–1.228	0.287			
Age high	1.607	1.044–2.473	0.031	2.015	1.29–3.147	0.002
Brinkman index high	0.721	0.472–1.101	0.129			
3D pure solid	2.605	1.581–4.291	<0.001	1.815	1.094–3.012	0.021
SUVmax high	2.379	1.54–3.676	<0.001	1.374	0.862–2.19	0.181
Squamous cell carcinoma	0.98	0.595–1.615	0.938			
Ly	3.734	2.383–5.852	<0.001	2.548	1.595–4.072	<0.001
V	2.449	1.511–3.969	<0.001	1.299	0.768–2.197	0.328
LN meta	4.961	3.245–7.585	<0.001	3.989	2.531–6.286	<0.001
Lepidic	1.286	0.844–1.958	0.24			
Lepidic predominant	0.457	0.185–1.129	0.08			

3D, three-dimensional; SUVmax, maximum standardized uptake value; Ly, lymphatic invasion; V, vascular invasion; LN meta, lymph node metastasis; HR, hazard ratio; CI, confidence interval.

after propensity score matching. Similar to the analysis before propensity score matching, 3D GGO was associated with a significantly better prognosis (5-year OS: 78.1% *vs.* 87.7%, P=0.001; 5-year RFS: 62.8% *vs.* 86.9%, P<0.001). Univariate and multivariate analyzes for OS and RFS also showed that 3D solid was an independent poor prognostic factor as before propensity score matching (Tables S1,S2).

Discussion

This study shows that the C/T volume ratio calculated using the 3D analysis workstation can predict the presence of GGO more accurately than the 2D image. GGO was present in 3D even if it was purely solid in 2D, and it was shown that GGO lesions in 3D had a good prognosis. Previous studies suggest that the maximum size of the solid part is better than the whole tumor size in conventional CT to predict its invasiveness and prognosis in part solid nodules (19-21). The maximum size of the solid part is incorporated as the clinical T-factor for lung cancer in the 8th edition of the International Union for Control of Cancer TNM classification. In recent years, with the spread of 3D analysis workstations, there are reports that the 3D parameters calculated by such workstations can more accurately evaluate pathological invasiveness and lymph node metastasis (22). We previously compared various parameters calculated by a 3D analysis with other factors, including the C/T ratio, and showed a better correlation of the C/T volume ratio in early-stage lung cancer with pathological non-invasive cancer. We reported on its usefulness (15).

Lung cancer is classified as pure solid or part solid based on CT findings, and solid lung cancer is said to have a worse prognosis than part solid because of its rapid growth and rapid metastasis (23-25). According to our analysis in the present study, even in 2D pure solid cases, a good prognosis was observed in the 3D GGO group when it was judged, based on the C/T volume ratio determined by a 3D analysis, to contain GGO. Therefore, our findings—which were based on 3D analysis—were in line with previous studies reporting that the prognosis of part solid with GGO is better than that of pure solid without GGO (8-11). We speculate that this is due to the fact that tumors can have distorted shapes in 3D rather than the pure round or oval shapes observed in 2D. Although 3D analysis workstations are gradually becoming popular, they are still not available at all facilities, and it may be difficult to use the C/T volume ratio calculated from them as a universal poor prognostic factor at the present time. Based on the results of recent large-scale prospective studies, it is expected that the number of segmentectomy procedures performed for early-stage lung cancer will increase in the future. However, because of the high local recurrence rate, it is considered important to ensure an accurate surgical margin using a 3D analysis workstation when performing segmentectomy. Along with this, it is assumed that the spread of 3D analysis workstations will continue in the future. Therefore,

Table 4 Propensity score matched clinicopathological characteristics in clinical stage IA pure solid non-small cell lung cancer

Characteristic	Total (N=234)	3D solid (N=117)	3D GGO (N=117)	P value
Sex				1
Male	162 (69.2)	81 (69.2)	81 (69.2)	
Female	72 (30.8)	36 (30.8)	36 (30.8)	
Age, years	69	67	67	0.989
Brinkman index	620	694	637	0.468
SUVmax	5.6	5.72	4.3	0.124
CEA, ng/mL	4.2	4.19	4.11	0.452
cStage (ver. 8)				1
IA1	12 (5.1)	6 (5.1)	6 (5.1)	
IA2	138 (59.0)	69 (59.0)	69 (59.0)	
IA3	84 (35.9)	42 (35.9)	42 (35.9)	
Surgery				1
Lobectomy	182 (77.8)	91 (77.8)	91 (77.8)	
Segmentectomy	32 (13.7)	16 (13.7)	16 (13.7)	
Wedge resection	20 (8.5)	10 (8.5)	10 (8.5)	
pStage (ver. 8)				0.001
0–IA3	125 (53.4)	49 (41.9)	76 (65.0)	
0	3 (1.3)	1 (0.9)	2 (1.7)	
IA1	19 (8.1)	3 (2.6)	16 (13.7)	
IA2	69 (29.5)	28 (23.9)	41 (35.0)	
IA3	34 (14.5)	17 (14.5)	17 (14.5)	
IB–IVA	109 (46.6)	68 (58.1)	41 (35.0)	
IB	54 (23.1)	32 (27.4)	22 (18.8)	
IIA	1 (0.4)	0 (0.0)	1 (0.9)	
IIB	32 (13.7)	20 (17.1)	12 (10.3)	
IIIA	18 (7.7)	14 (12.0)	4 (3.4)	
IIIB	4 (1.7)	2 (1.8)	2 (1.7)	
Histology				0.076
Adenocarcinoma	172 (73.5)	79 (67.5)	93 (79.5)	
Squamous cell carcinoma	53 (22.6)	34 (29.1)	19 (16.2)	
Others	9 (3.8)	4 (3.4)	5 (4.3)	
Pathological findings				
Ly (+)	100 (42.7)	66 (56.4)	34 (29.1)	<0.001
V (+)	136 (58.1)	82 (70.1)	54 (46.2)	<0.001
LN meta (+)	43 (18.4)	30 (25.6)	13 (11.1)	0.006
Lepidic (+)	97 (41.4)	33 (28.2)	64 (54.7)	<0.001
Lepidic predominant (+)	23 (9.8)	4 (3.4)	19 (16.2)	0.002

Data are shown as the median or number (percentage). 3D, three-dimensional; GGO, ground glass opacity; SUVmax, maximum standardized uptake value; CEA, carcinoembryonic antigen; Ly, lymphatic invasion; V, vascular invasion; LN meta, lymph node metastasis.

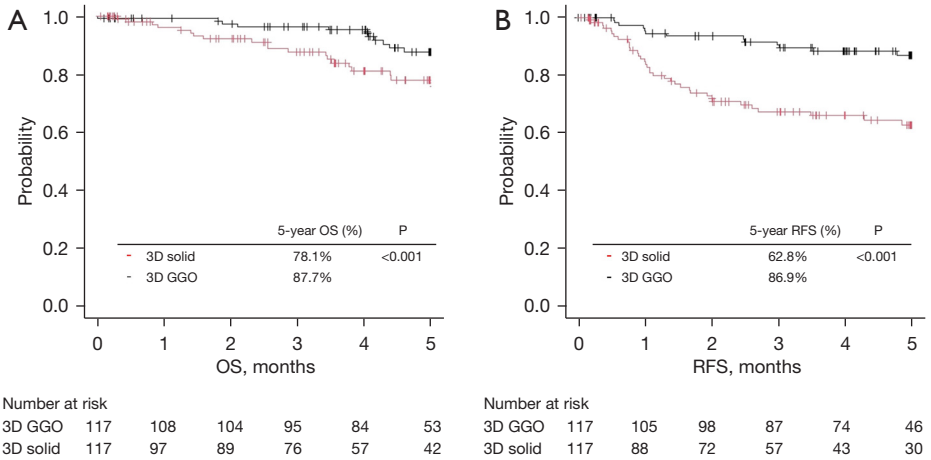

Figure 3 Kaplan-Meier curves showing the survival outcomes of the two propensity score matched groups. Significant differences were observed between the two groups in OS (A) and RFS (B), as was observed before propensity score matching. Consistently, the 3D GGO group showed a better prognosis than the 3D solid group. OS, overall survival; RFS, recurrence-free survival; GGO, ground glass tumor; 3D, three-dimensional.

we believe that the versatility of the C/T volume ratio calculated by 3D analyses will increase in the future.

There are many cases in which there is a large difference between the C/T ratio and the C/T volume ratio. Therefore, these are similar but different indicators, and we believe that the C/T volume ratio can more accurately evaluate pathological findings and the prognosis. As a result of using the C/T ratio, the Japan Clinical Oncology Group (JCOG)0802/West Japan Oncology Group (WJOG)4607L demonstrated the superiority of segmentectomy in terms of the prognosis, in comparison to lobectomy in solid predominantly early lung cancer of ≤2 cm (4). However, it remains possible that different results could be obtained if the pathologic findings and prognosis are better screened using the C/T volume ratio. In other words, there may be a certain number of cases in which lobectomy, which is the conventional standard surgery, should be performed instead of aggressive segmentectomy, even for early-stage lung cancer.

In addition, there are reports that the SUVmax and its visual evaluation obtained from ^{18}F-fluorodeoxyglucose-PET can reflect the prognosis and malignancy as a prognostic stratification factor other than the C/T ratio in early-stage lung cancer (26,27). In our analysis in the present study, SUVmax was significantly higher in the 3D pure solid group. However, in univariate and multivariate analyses for OS and RFS, although a high SUVmax tended to be associated with a poor prognosis, no significant difference was found. Regarding the value of SUVmax, it is said that there is a large error between facilities, measuring instruments, and measurers, and it is possible that this analysis did not show a significant difference due to this. Interesting results may be obtained by visual evaluation using the Deauville score, which was reported by Kagimoto *et al.* (26). The results of JCOG0802/WJOG4607L are of great significance to thoracic surgeons, and there is no objection to expanding the indications for segmentectomy. However, we believe that the expanded range of indications should be studied and examined from various angles in the future.

The present study was associated with some limitations. First, it was a retrospective study conducted in a single center. Second, the correlation with the C/T volume ratio measured by other 3D analysis workstations with similar functions is unknown. However, among the existing 3D analysis workstations used for surgical medicine, the Synapse Vincent system that we used is said to have the highest market share, and the system was as versatile as possible. Third, potential measurement error by Synapse Vincent should be considered. This workstation sometimes recognizes blood vessels running inside the tumor as solid components, and also recognizes the area around the tumor that seems to be an air-filled defective site as GGO. An accurate cut-off value for the C/T volume ratio that includes such errors is an issue for future study. Fourth, we were unable to evaluate the micropapillary and STAS statuses, which are pathological poor prognostic factors. If these items were added to the Cox proportional hazards analysis, it is possible that the analysis would obtain different results. Fifth, this study that as it is an observational study, we could not eliminate the potential effect of the higher clinical

stage in 3D solid group on the poorer outcome in this group. Further prospective clinical trial is recommended to overcome this limitation.

Conclusions

In conclusion, from the results of this study, tumors judged to be pure solid by a 2D analysis could be further classified, based on a 3D analysis, into a solid group with a poorer prognosis and a GGO group with a relatively favorable prognosis. We found that the C/T volume ratio determined using 3D analysis could accurately reflect the pathological findings. Moreover, it was found to be an independent prognostic factor. In the future, we expect that various studies using the C/T volume ratio will be conducted at other facilities and multiple institutions, and it will be necessary to confirm the validity of reduction surgery for patients with 3D solid findings, which are associated with a truly poor prognosis in early lung cancer.

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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-23-341/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-23-341/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). The Institutional Review Board (IRB) of Seirei Mikatahara General Hospital approved the study protocol and publication of data (No. 22-64, Approval date: February 24, 2023). Informed consent was obtained from each patient before examination and the contents of this study were disclosed at our hospital. The medical records of each patient were retrospectively reviewed under a waiver of authorization approved by our IRB.

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Supplementary

Table S1 Propensity score matched cox proportional hazards model for overall survival

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Male	1.713	0.847–3.465	0.134			
Age high	2.32	1.233–4.366	0.009	2.02	1.031–3.959	0.04
Brinkman Index high	1.447	0.799–2.617	0.222			
3D solid	2.642	1.404–4.971	0.002	2.01	1.01–4.367	0.04
SUVmax high	2.132	1.155–3.934	0.015	0.976	0.456–2.087	0.951
Squamous cell carcinoma	2.709	1.504–4.881	<0.001	2.547	1.285–5.049	0.007
Ly	2.043	1.133–3.685	0.017	1.469	0.743–2.901	0.268
V	1.511	0.82–2.782	0.185			
LN meta	2.115	1.108–4.038	0.023	2.705	1.269–5.768	0.009
Lepidic	0.569	0.296–1.094	0.09			
Lepidic predominant	0.668	0.238–1.872	0.443			

3D, three-dimensional; SUVmax, maximum standardized uptake value; Ly, lymphatic invasion; V, vascular invasion; LN meta, lymph node metastasis; HR, hazard ratio; CI, confidence interval.

Table S2 Propensity score matched cox proportional hazards model for recurrence-free survival

Factor	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Male	0.645	0.387–1.078	0.094			
Age high	1.559	0.93–2.614	0.091			
Brinkman index high	0.562	0.331–0.953	0.032	0.756	0.421–1.356	0.348
3D pure solid	2.84	1.65–4.888	<0.001	2.235	1.481–4.032	0.021
SUVmax high	3.28	1.867–5.763	<0.001	1.742	0.904–3.356	0.097
Squamous cell carcinoma	0.817	0.434–1.538	0.532			
Ly	4.114	2.371–7.139	<0.001	2.113	1.12–3.987	0.02
V	3.395	1.838–6.272	<0.001	1.324	0.651–2.692	0.438
LN meta	5.431	3.261–9.044	<0.001	3.03	1.666–5.512	<0.001
Lepidic	1.141	0.687–1.891	0.61			
Lepidic predominant	0.591	0.236–1.478	0.26			

3D, three-dimensional; SUVmax, maximum standardized uptake value; Ly, lymphatic invasion; V, vascular invasion; LN meta, lymph node metastasis; HR, hazard ratio; CI, confidence interval.

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