Original Article

Diagnostic sensitivity of solid volume measurement for pathological invasion in non-solid lung adenocarcinoma

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Background: In the current tumor-node-metastasis (TNM) classification, the clinical T descriptor is defined by solid size (SS) on a computed tomography (CT) slice and the pathological one is done by invasive size (IS) in microscopic evaluations. We sometimes experience discrepancies in diagnosis of both descriptors. A volume analyzing application enables semi-automatic measurement of three-dimensional (3D) parameters in cases where there are discrepancies in diagnosing tumors' solid size and IS. In this study, we aimed to evaluate the association between 3D parameters and pathological invasion in non-solid small-sized lung adenocarcinomas.

Methods: We enrolled 246 consecutive patients who underwent pulmonary resection at Shizuoka Cancer Center. Patients with lung adenocarcinomas that were radiologically non-solid, node-negative and sized ≤3 cm were eligible. We used a volume analyzing application to retrospectively measure 3D parameters of max and mean Hounsfield units (HUs) and solid volume (SV). The cut-off value of these parameters for diagnosing invasive adenocarcinoma (IAD) was set by describing receiver operating characteristic (ROC) curves. The correlation of IAD with these parameters was compared to its correlation with the SS. This study was not registered.

Results: Of 246 patients with adenocarcinoma, 183 (74.4%) had IADs. In multivariate analyses, the total size (TS) and SS were significantly associated with IAD (P=0.006, 0.001, respectively), whereas 3D parameters including SV were not (P=0.80). In radiological adenocarcinoma (2.1–3.0 cm), SV >300 mm^3 diagnosed IAD with a higher sensitivity than that of the SS (0.93 and 0.83, respectively).

Conclusions: TS >20 mm and SS >5 mm were well-correlated with IAD. SV measurement may complement the current computed tomographic diagnosis of IAD based on the SS (2.1–3.0 cm).

Keywords: Lung adenocarcinoma; solid size (SS); total size (TS); solid volume (SV); ground-glass opacity (GGO)

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Introduction

Background

A variety of small-sized lung cancer images can be obtained using the novel innovations of high resolution-computed tomography (HR-CT). Impacts of ground-glass opacity (GGO) lesions on survival outcomes have been evaluated in recent decades. Several factors besides radiological total size (TS), including tumor disappearance rate, consolidation tumor ratio (CTR), and solid size (SS), have been suggested as potential factors that predict lung cancer outcomes (1-4). The Japan Clinical Oncology Group (JCOG) launched

clinical trials of limited resections for early-stage lung cancer using CTR criteria based on a JCOG 0201 study (5). Limited impact of GGO and the corresponding lepidic lesion on survival were widely reported in lung adenocarcinoma; SS has been focused on as one of the promising prognostic factors. Subsequently, the clinical T descriptor has been defined by SS, although it had been defined by TS previously. The current 8th tumor-node-metastasis (TNM) classification defines a lesion with SS greater than 5 mm radiologically diagnosed as invasive adenocarcinoma (IAD) (6).

Rationale and knowledge gap

Although the survival outcomes of patients who are pathologically diagnosed with adenocarcinoma in situ (AIS) or minimally IAD (MIA) are known to be extremely favorable, the discrepancy between SS and pathological invasive size (IS) practically exists in the clinics (7,8). One of the potential reasons for discrepancies is the bias induced by the physicians who measure SS. Although HR-CT slice is advantageous in terms of easy measurement, diagnoses of solid parts depend strongly on the physician's subjectivity unlike for the diagnoses of pathological invasive findings. To predict the biological nature of small-sized adenocarcinomas and explore novel surgical strategies, estimating the pathological invasion appropriately before surgery is crucial.

Highlight box

Key findings

- TS and SS, not 3D parameters were significantly associated with IAD, although sensitivity of SV was higher than that of SS in the diagnosis of IAD with a TS of 2.1–3.0 cm.

What is known and what is new?

- The discrepancy between SS defined by the current TNM classification and IS has existed practically.
- Eleven out of 18 IAD cases (61.1%) with SS ≤5 mm were diagnosed accurately by using SV.

What is the implication, and what should change now?

- SV measurement may compensate for the sensitivity of the current cT diagnosis to diagnose IAD in radiological adenocarcinoma sized 2.1–3.0 cm.

Objective

In the present study, we semi-automatically measured three-dimensional (3D) parameters including the solid volume (SV) using a volume analyzing application, which does not require the specific CT slice, and investigated the association between those parameters and IAD. We also evaluated the ability of 3D parameters to diagnose pathologically invasive small-sized adenocarcinoma and compared this method with SS. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1603/rc).

Methods

Between January 2017 and December 2020, 884 consecutive patients underwent pulmonary resection for lung adenocarcinoma at Shizuoka Cancer Center. Among them, patients with cN0 tumor radiologically sized ≤3 cm and pure or part solid GGO lesion were eligible for the study. Two hundred ninety-four patients with pure solid nodules were excluded due to the potential aggressive characteristics of these nodules for which limited resection was not known to preserve prognosis (9,10). The remaining 246 patients with non-solid nodules were enrolled in this study (*Figure 1*). Of them, 173 (70.3%), 35 (14.2%), and 38 (15.5%) patients underwent lobectomy, segmentectomy, and wedge resection, respectively. Clinicopathological data, such as age, gender, smoking history, pre-operative serum carcinoembryonic antigen (CEA) level, TS, SS, CTR, pathological whole tumor size, IS, pN status, and presence of lymphatic invasion (ly), vascular invasion (v), and pleural invasion (pl) were reviewed from the medical records. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective diagnostic study was approved by the institutional review board of Shizuoka Cancer Center (No. J2020-1-2020-1-3) and was not registered. The need for obtaining written informed consent from patients was waived due to the retrospective nature of this study.

All histologic sections of completely submitted tumor were stained with hematoxylin and eosin and were reviewed by two pathologists. Whole tumor size and IS were determined by direct measurement. In addition, all cases

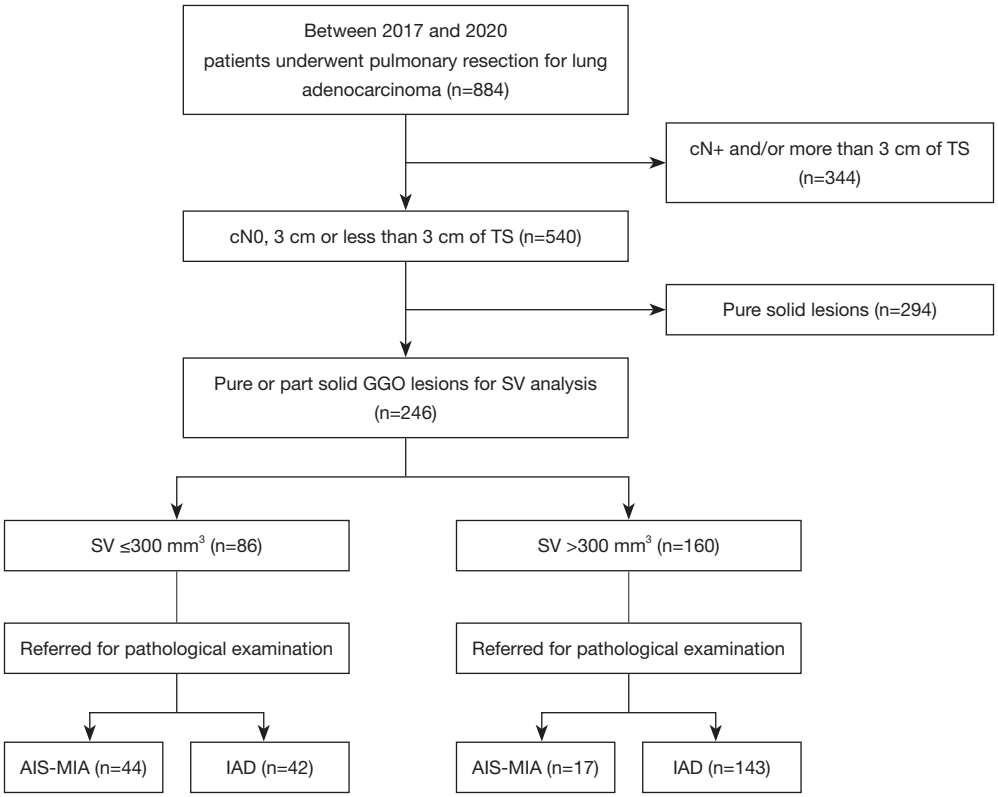

Figure 1 Flow diagram evaluating the accuracy of SV for diagnosis of IAD. TS, total size; GGO, ground-glass opacity; SV, solid volume; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; IAD, invasive adenocarcinoma.

were evaluated for the presence of ly, v, and pl.

CT scan was performed using a multi-detector CT scanner (Aquilion16; Toshiba Medical Systems Corporation, Tochigi, Japan). Images with a slice thickness of 1–2 mm were acquired in the helical mode without intravascular contrast material. SS measurement was performed and confirmed by our surgical cancer board. Digital images were transferred to a teleradiology workstation, and volume-rendered 3D models of the lungs were retrospectively reconstructed using the Synapse Vincent imaging application (FUJIFILM, Tokyo, Japan). This application enabled the measurement of 3D data semi-automatically without selecting a specific slice; 3D data of max Hounsfield unit (HU), mean HU, a total volume of more than –800 HU, and SV of more than –300 HU were measured in the targeted lesion (*Figure 2*). This software algorithm was used in previous reports (11,12). To evaluate the diagnostic ability of 3D parameters in diagnosing IAD, receiver operating characteristic (ROC) curves were plotted for max HU, mean HU, and SV. Cut-off values were set for respective variables and used for further analyses. Diagnostic abilities of SS (>5 mm), which has been defined in the 8th TNM classification, and the set cut-off value for SV were compared. To explore differences of diagnostic abilities by TS, 0–2.0 cm, and 2.1–3.0 cm of the TS tumor was compared, in addition to the whole cohort. Furthermore, investigations for diagnostic ability in IAD with either ly, v, pl or nodal metastases, which is termed aggressive IAD, were carried out.

Statistical analysis

Statistical analyses were performed using SPSS software for Windows, version 12.0 (IBM, Armonk, NY, USA). Comparison of patient categorical variables between the groups and area under ROC curves between respective parameters were performed using the chi-squared test. Continuous variables were compared using Mann-Whitney U test. Univariate and multivariate logistic regression analyses were performed to identify factors predicting IAD, with $P<0.05$ indicating statistical significance. Confounding factors were adjusted by the multivariate analysis.

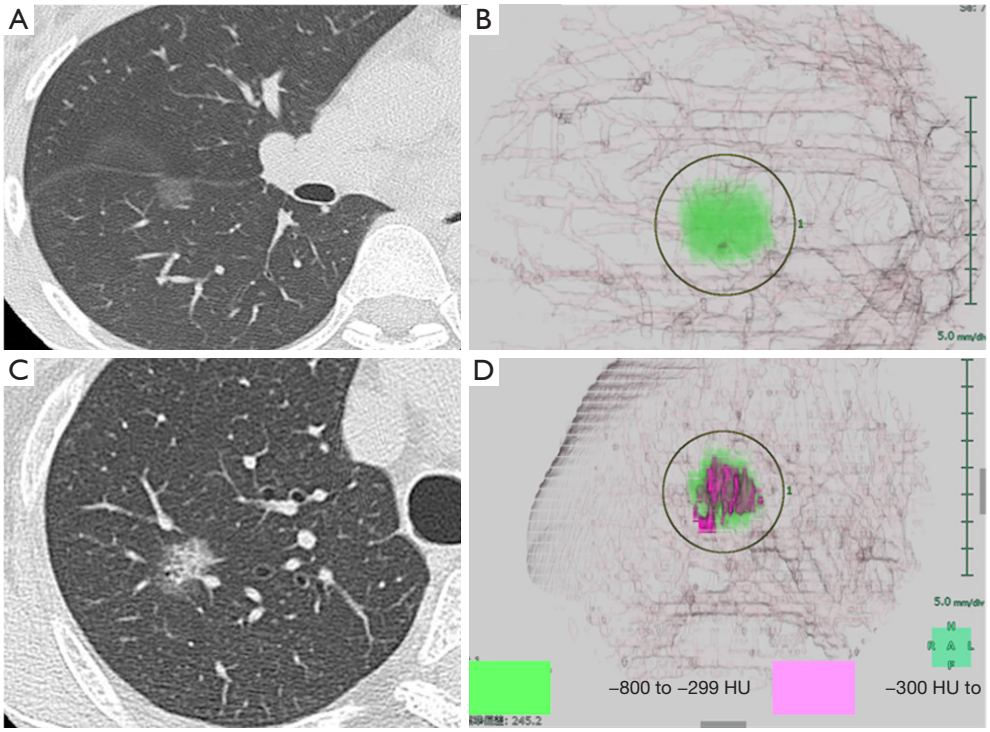

Figure 2 Representative images of axial-specific CT- and 3D-volume analyses. (A) An axial CT image. (B) A 3D image of a cTis/pTis case (TS =12 mm, SS =0 mm, SV =6.5 mm^3, and IS =0 mm). (C) An axial CT image and (D) a 3D image of a cTis/pT1b case (TS =16 mm, SS =0 mm, SV =324 mm^3, and IS =11 mm). HU, Hounsfield unit; CT, computed tomography; 3D, three-dimensional; TS, total size; SS, solid size; SV, solid volume; IS, invasive size.

Results

Demographics of enroled 246 patients are shown in *Table 1*. Approximately 10% of the patients presented with a high serum CEA level ≥5 ng/mL before pulmonary resection. Median TS and SS were 20 mm and 8 mm, respectively. Altogether, 152 patients (61.8%) had nodules with >5 mm of SS. The median pathological whole tumor size and IS were 18 and 10 mm, respectively. Overall, 183 patients (74.4%) had IAD, 51 patients (20.7%) had MIA, and 12 patients (4.9%) had AIS. In larger TS tumor of 2.1–3.0 cm, TS, SS, max HU, and SV were significantly higher compared to those of the smaller tumor. Further, more patients with radiological IAD (SS >5 mm) were included significantly. Other pathological invasive findings, such as ly, v, and pl, were diagnosed in limited numbers of patients. Pathological lymph node metastases were diagnosed in 2 cases (0.8%) (*Table 2*). Twenty-three aggressive IAD cases were identified. Among 246 patients, 4 patients experienced recurrence, 7 patients died of other causes. No patients died of lung cancer.

In 3D data measurement, the median max HU, median HU and median SV were 381, −522, and 514 mm^3, respectively (*Table 1*). ROC curves were generated to evaluate the diagnostic abilities of SS, max HU, mean HU, and SV for IAD. Areas under the curve (AUC) for SS and SV were 0.83 and 0.84, respectively, significantly higher than those of max HU and mean HU. The difference between the AUCs of SS and SV was not significant (P=0.77) (*Figure 3*). Furthermore, according to the ROC curves, the cut-off values were set as 5 mm, 320, −600, and 300 mm^3 for SS, max HU, mean HU, and SV, respectively. Among 160 patients with SV >300 mm^3, 143 patients (89.3%) were diagnosed with IAD, meanwhile 42 patients (48.8%) out of 86 patients with SV ≤300 mm^3 were diagnosed with IAD (*Figure 1*).

In univariate analyses, TS >20 mm, SS >5 mm, CTR >0.5, max HU >320, mean HU >−600, and SV >300 mm^3 were significantly associated with the occurrence of IAD. Multivariate analysis revealed that TS and SS were significantly associated with IAD, whereas variables derived from 3D data were not (*Table 3*).

Table 1 Patient characteristics by TS

Variables	Total (n=246)	0–2.0 cm (n=127)	2.1–3.0 cm (n=119)	P value
Age >75 years old, n (%)	67 (27.2)	35 (27.6)	32 (26.9)	>0.99
Male, n (%)	99 (40.2)	52 (40.9)	47 (39.5)	0.90
Never smoker, n (%)	128 (52.0)	64 (50.4)	64 (53.8)	0.61
Pre.Op CEA ≥5 ng/mL, n (%)	24 (9.8)	12 (9.4)	12 (10.1)	>0.99
TS (mm), median [IQR]	20 [16–25]	17 [14–18]	25 [22–27]	<0.001
SS (mm), median [IQR]	8 [4–13]	5 [3–9]	12 [6–17]	<0.001
SS >5 mm, n (%)	152 (61.8)	63 (49.6)	92 (77.3)	<0.001
CTR >0.5, n (%)	97 (39.4)	43 (33.9)	54 (45.4)	0.07
Max HU, median [IQR]	381 [311–458]	349 [260–405]	415 [352–515]	<0.001
Mean HU, median [IQR]	−522 [−641 to −410]	−538 [−657 to −446]	−505 [−628 to −356]	0.05
SV (mm^3), median [IQR]	514 [217–1,085]	241 [107–463]	983 [593–1,799]	<0.001

P value represent the result of statistical tests of two groups stratified by size. TS, total size; Pre.Op, preoperative; CEA, carcinoembryonic antigen; IQR, interquartile range; SS, solid size; CTR, consolidation tumor ratio; HU, Hounsfield unit; SV, solid volume.

Table 2 Pathological findings by TS

Variables	Total (n=246)	0–2.0 cm (n=127)	2.1–3.0 cm (n=119)	P value
Whole tumor size (mm), median [IQR]	18 [14–22]	15 [12–17]	22 [20–25]	<0.001
IS (mm), median [IQR]	10 [5–15]	7 [4–11]	15 [10–19]	<0.001
IS >5 mm (IAD), n (%)	183 (74.4)	76 (59.8)	107 (89.9)	<0.001
pl+, n (%)	12 (4.8)	0 (0.0)	11 (9.2)	0.004
ly+, n (%)	9 (3.7)	2 (1.6)	7 (5.9)	0.09
v+, n (%)	5 (2.0)	2 (1.6)	3 (2.5)	0.67
pN+, n (%)	2 (0.8)	0 (0.0)	2 (1.7)	0.23

P value represent the result of statistical tests of two groups stratified by size. TS, total size; IQR, interquartile range; IS, invasive size; IAD, invasive adenocarcinoma; pl, pleural invasion; ly, lymphatic invasion; v, vascular invasion; pN, pathological nodal metastasis.

The cross tabulations of SS against IS and SV against IS were presented as Tables S1,S2, diagnostic abilities of SS and SV with cut-off values of 5 mm and 300 mm^3, respectively, in predicting IAD are presented in *Table 4*. In the whole cohort, with nodules measuring ≤3 cm, sensitivities and accuracies were similar for both the parameters. The sensitivity of SV was lower (0.55) than that of SS (0.67) in tumors measuring ≤2 cm but higher in tumors >2 cm. Eleven out of 18 IAD cases (61.1%) with SS ≤5 mm were diagnosed accurately by SV. Furthermore, the diagnostic abilities of SS and SV with cut-off values of 12 mm and 655 mm^3 being set based on ROC curves, respectively, in predicting aggressive IAD are presented in Table S3. Sensitivities of SS and SV were similar. No adverse events were reported during this retrospective diagnostic study.

Discussion

Key findings

We finally demonstrated that TS and SS, not 3D parameters were significantly associated with IAD in the whole cohort, although we documented higher sensitivity

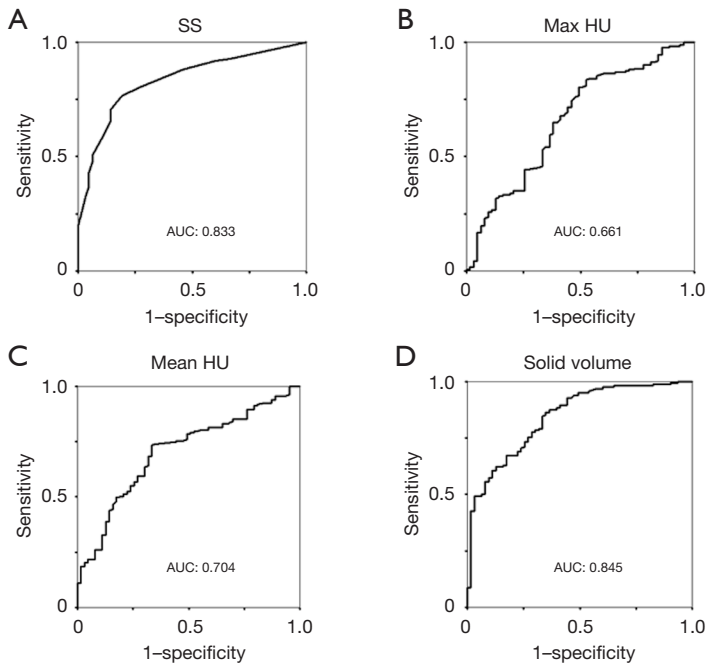

Figure 3 ROC curve for the diagnosis of IAD. (A) The curve of SS, (B) the curve of max HU with cut-off value of 320, (C) the curve of mean HU with cut-off value of −600, and (D) the curve of SV with cut-off value of 300. SS, solid size; AUC, area under the curve; HU, Hounsfield unit; ROC, receiver operating characteristic; IAD, invasive adenocarcinoma; SV, solid volume.

Table 3 Univariate and multivariate analyses of factors predicting IAD

Variables	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
TS >20 mm	5.984	2.989–11.98	<0.001	3.496	1.442–8.476	0.006
SS >5 mm	11.11	4.879–25.33	<0.001	5.984	2.167–16.52	0.001
CTR >0.5	7.741	3.350–17.88	<0.001	1.168	0.342–3.990	0.80
HU max >320	4.215	2.281–7.786	<0.001	2.064	0.927–4.597	0.08
HU mean >−600	5.393	2.915–9.975	<0.001	2.164	0.921–5.082	0.08
SV >300 mm^3	8.659	4.531–16.55	<0.001	1.168	0.342–3.990	0.80

IAD, invasive adenocarcinoma; OR, odds ratio; CI, confidence interval; TS, total tumor size; SS, solid size; CTR, consolidation tumor ratio; HU, Hounsfield unit; SV, solid volume.

of SV in the diagnosis of IAD with a TS of 2.1–3.0 cm. Sensitivities of SS and SV for IAD were similar (0.76 and 0.77, respectively). And 44 of 94 cTis-T1mi lesions (45.7%) were diagnosed as IAD after surgery. Among those 44 cases, we observed only one patient with recurrence and two patients with aggressive IAD; most false negative cases might be less aggressive IAD with favorable prognosis (13).

Strengths and limitations

In the present study, we focused on excluding potential biases in patient selection and measurement in the CT images by using 3D measurement. The measurements were semi-automatically performed using a volume analyzing application after setting the region of interest before

Table 4 Diagnostic abilities of SS and SV for IAD

TS	Parameters	Sensitivity	Specificity	PPV	NPV	Accuracy
Total	SS	0.76	0.82	0.93	0.53	0.77
	SV	0.77	0.72	0.89	0.51	0.76
0–2.0 cm	SS	0.67	0.82	0.85	0.61	0.72
	SV	0.55	0.82	0.83	0.53	0.65
2.1–3.0 cm	SS	0.83	0.83	0.98	0.36	0.83
	SV	0.93	0.33	0.93	0.36	0.87

SS, solid size; SV, solid volume; IAD, invasive adenocarcinoma; TS, total size; PPV, positive predictive value; NPV, negative predictive value.

analyses. Although we did not observe a superior sensitivity of SV to SS for IAD diagnosis, SV sensitively detected 11 (61.1%) out of 18 IAD cases missed by SS.

Since our study was conducted in a single center and was retrospective in nature, it had several limitations. First, our study cannot exclude potential bias completely. We enrolled patients who were indicated for pulmonary resection; therefore, the number of patients with less aggressive adenocarcinoma of smaller SS and AIS/MIA were limited. Large series studies were required to evaluate diagnostic abilities in less aggressive adenocarcinoma furthermore and to validate our findings. Second, the lack of objective pathology review may be another limitation. In the present study, we focused on the issue about subjectivity in SS measurement and explore the potential usefulness of 3D measurement. Subjectivity by pathologists in measurement of IS might be another issue. However, Thunnissen *et al.* had reported fair reproducibility distinguishing invasive from *in-situ* tumors (14), and Boland *et al.* reported that good agreement was present between observers when classifying tumor as AIS, MIA, and IAD (15). According their reports, impact of this issue may not be so significant. However, there is a limitation in 3D measurement by the application itself; the application cannot discriminate anatomical structures from solid part of the tumor. Especially, centrally located lesions, compared with peripheral lesions, tend to be more affected by this problem, and SV of central lesions can be overestimated.

Comparison with similar researches

Earlier this century, researchers had focused on GGO, its corresponding lepidic proliferative components, and survival outcomes. Kodama *et al.* reported extremely favorable relapse-free survival rates of patients with GGO >50% (1). Matsuguma *et al.* also reported that a proportion of GGO can predict the tumor aggressiveness of nodal involvement, lymphovascular invasion, and histological subtype (2). Ohde *et al.* reported that CTR <0.5 could diagnose the least invasive disease, which had neither nodal nor lymphovascular involvement, with 100% specificity (3). To confirm these retrospective findings, JCOG tentatively defined radiological non-invasive lung cancer as a tumor with CTR <0.5 and evaluated its abilities to diagnose pathological non-invasive lung cancer (JCOG 0201 study) (5). Although this study did not meet the primary endpoint, the exploratory analysis revealed a 98.7% specificity with a cut-off value of 0.25 in tumors measuring ≤2 cm. Furthermore, according to the subsequent survival outcomes, a cut-off value of 0.5 was suggested to diagnose radiological non-IAD measuring 2–3 cm (16); thereafter, several limited resection trials have been carried out using these criteria (17-20). In 2011, the International Association for the study of Lung Cancer/American Thoracic Society/European Respiratory Society proposed an international multidisciplinary classification of lung adenocarcinoma (21). According to the new concepts, AIS and MIA with IS ≤5 mm will have approximately 100% disease-specific survival after complete resection. This proposal was validated by researchers (22-24). The 8th TNM classification of malignant tumors has defined the clinical T descriptor using SS and the pathological one using IS (6). Therefore, discrimination of IAD from AIS or MIA by pre-operative estimation of 5 mm IS has become more important. Lee *et al.* documented a strong correlation between the SS on CT and invasive component on pathology in the lung window setting (25). Sakao *et al.* (26), Sakakura *et al.* (7), and Samejima *et al.* (8) reported the usefulness of predicting IS

using the tumor diameter in the mediastinal window setting. The diagnostic abilities of SS >5 mm for IAD varied among reports. Roberts *et al.* documented a 59% sensitivity (27), whereas higher sensitivities of 89–95.4% were also reported (7,25). Many studies have discussed the indications of limited resections in small-sized lung cancers, the discrepancy between cT and pT status has not been resolved to date. Some studies reported the potential usefulness of 3D-CT, however, those results are inconsistent. Kitazawa *et al.* reported that a mean CT value of –489 HU could predict IAD in ground-glass lung nodules sized <20 mm (28). Shimada *et al.* documented a significant association between SV and overall survival and disease-free survival in clinical stage I (TNM 8th), wherein enrollment was based on SS (12). Kawaguchi *et al.* also evaluated the usefulness of SV in predicting IAD in clinical stage IA (TNM 8th) adenocarcinoma including pure solid nodules (11); however, similar to our results, their findings failed to demonstrate the superior diagnostic abilities of SV over SS.

Explanations of findings

In the present study, we did not reveal significant associations between 3D parameters and IAD diagnosed based on pathological IS. These results may be attributed to IS being a one-dimensional parameter based on the selection of a specific section by pathologists. SS, measured on specific HR-CT slices by physicians, but not the SV measured semi-automatically, may correlate well with it. Another reason is the underlying discrepancy between the radiological solid portion and invasion. As we described above SV may contain the anatomical structures of the vessels and bronchus, especially in the central area. Moreover, collapse of the lung parenchyma and fibrotic lesions might also present a solid pattern. These limitations in measurement might have influenced our results.

Implications and actions needed

Herein, we presented the differences in the sensitivities of SS and SV, according to TS, in the diagnosis of IAD. It is presumed that SS tends to underestimate the IS in 2.1–3.0 TS tumors compared to that in the smaller ones. Therefore, SS may be less useful in predicting IS in large tumors.

Conclusions

The diagnosis of IAD was closely associated with one-dimensional pathological measurement, such as SS and TS, but not with 3D parameters, including SV. SV measurement may compensate for the sensitivity of the current cT diagnosis to predict IAD in radiological adenocarcinoma sized 2.1–3.0 cm.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1603/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1603/dss

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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-22-1603/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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Shizuoka Cancer Center (No. J2020-1-2020-1-3). The need for obtaining written informed consent from each patient was waived due to the retrospective nature of the study.

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Supplementary

Table S1 Cross tabulation of SS against IAD

Variables	SS ≤5 mm	% in SS ≤5 mm	SS >5 mm	% in SS >5 mm
AIS-MIA	50	53.2	11	13.8
IAD	44	46.8	141	86.2
Total	94	100.0	152	100.0

SS, solid size; IAD, invasive adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

Table S2 Cross tabulation of SV against IAD

Variables	SV ≤300 mm^3	% in SV ≤300 mm^3	SV >300 mm^3	% in SV >300 mm^3
AIS-MIA	44	51.2	17	10.6
IAD	42	48.8	143	89.4
Total	86	100.0	160	100.0

SV, solid volume; IAD, invasive adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma.

Table S3 Diagnostic abilities of SS and SV for Aggressive IAD

TS	Parameters	Sensitivity	Specificity	PPV	NPV	Accuracy
Total	SS	0.70	0.71	0.20	0.96	0.71
	SV	0.74	0.64	0.17	0.96	0.65
0–2.0 cm	SS	0.50	0.86	0.11	0.98	0.85
	SV	0.50	0.89	0.16	0.98	0.87
2.1–3.0 cm	SS	0.73	0.52	0.23	0.91	0.56
	SV	0.78	0.33	0.18	0.89	0.40

SS, solid size; SV, solid volume; IAD, invasive adenocarcinoma; TS, total size; PPV, positive predictive value; NPV, negative predictive value.

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