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Relationships between SUVmax of lung adenocarcinoma and different T stages, histological grades and pathological subtypes: a retrospective cohort study in China

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ABSTRACT

Objectives Cancer cell has aberrant metabolism. The purpose of this study aimed to investigate relationships between maximum standard uptake value (SUVmax) of ^{18}fluoro-2-deoxy-d-glucose and T stages, histological grades and pathological subtypes of lung adenocarcinoma.

Design Retrospective cohort study, employing the Kruskal-Wallis, Bonferroni-Dunn and Mann-Whitney tests to compare SUVmax of different T stages, histological grades and pathological subtypes of lung adenocarcinoma.

Setting The outpatients who had aberrant positron emission tomography/CT (PET/CT) images in chest were enrolled this study from August 2016 to November 2018 in Shanghai, China.

Participant Initial 11 270 patients with suspected lung cancer who underwent PET/CT examinations were surveyed. A total of 1454 patients who were diagnosed as lung adenocarcinoma by pathologist were included in this project.

Primary outcome measures SUVmax value at different tumour-node-metastasis stages of lung adenocarcinoma before surgery.

Results The mean SUVmax of patients with lung adenocarcinoma was significantly elevated with the increase in T stages. There were significant evident differences in SUVmax among T1a–T1c ($p<0.05$). However, after the staging of patients was more than T1 stage, SUVmax of T2a, T2b, T2 visceral pleural invasion, T3 and T4 had not dramatic changes. SUVmax value of lung adenocarcinoma in the same T stage group was the highest in patients with the high grade of malignancy and solid-predominant invasive adenocarcinoma.

Conclusions SUVmax value was significantly associated with T stages, grades of malignancy and pathological subtypes of lung adenocarcinoma.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Maximum standard uptake value (SUVmax) of ^{18}fluoro-2-deoxy-d-glucose reflects glucose metabolism status of cancer cell.
⇒ Measurement of SUVmax value in this study was used to differentiate lung adenocarcinoma T stage, high grade and invasive pathological subtypes.
⇒ SUVmax value measurement can be a reliable method to differentiate low T stages.
⇒ SUVmax detection has not indicated the predictive value in this study.

INTRODUCTION

Lung cancer is a highly heterogeneous tumour, which is classified into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) based on pathological features. This classification can stratify the malignant grades of tumour and guide therapy or prognosis.[1–6] Maximum standard uptake value (SUVmax), as a metabolic parameter of ^{18}fluoro-2-deoxy-d-glucose (18-FDG) positron emission tomography–CT (PET/CT), is so far the most reflective of malignant tumour. The detection of SUVmax has been shown to be positively correlated with the tumour-node-metastasis (TNM) staging of lung adenocarcinoma.[7] Therefore, it was widely studied in predicting prognosis of lung adenocarcinoma.[8–12] Our previous study showed that SUVmax of patients can predict the histological grades of cancer using the receiver operating characteristic curve to find the cut-off value of low, medium and high histological grades of lung adenocarcinoma.[13]

Current lung cancer TNM staging system is mainly used to describe the growth and metastasis pattern of lung cancer, which has an important guiding role for clinical treatment and prognosis judgement. Studies showed that the size of lung adenocarcinoma was relevant to SUVmax.[14–16] However, there is no clear conclusion about the relationship between T staging and SUVmax. Therefore, the study of the relationship between

Table 1 Baseline characteristics of the study cohort and each T stage group of the 1454 patients with lung adenocarcinoma

Characteristic	Sample size					
	Total	T1	T2	T3	T4	P value
Total number	1454	977	410	47	20	
Age, yr, mean±SD	61.22±9.65	60.69±9.71	62.20±9.59	63.02±8.19	60.95±9.87	0.099
Sex, n (%)						**<0.001**
Male n (%)	610 (41.95%)	375 (38.40%)	193 (47.07%)	32 (68.09%)	11 (55%)	
Female n (%)	844 (58.05%)	602 (61.60%)	217 (52.93%)	15 (31.91%)	9 (45%)	
Smoking history, n(%)	486 (33.42%)	292 (30.05%)	157 (38.05%)	27 (57.45%)	10 (50%)	**<0.001**
Male, n (%)	951 (65.41%)	671 (74.37%)	250 (79.27%)	20 (42.55%)	10 (50%)	
Female, n (%)	17 (1.17%)	14 (1.43%)	3 (1.38%)	0	0	
Family history of malignancy, n (%)	452 (31.09%)	325 (33.26%)	113 (27.56%)	11 (23.40%)	7 (35%)	0.217
Male, n (%)	205 (33.61%)	133 (35.38%)	60 (31.09%)	9 (28.12%)	4 (36.36%)	
Female, n (%)	247 (29.27%)	192 (31.94)	53 (24.42%)	2 (13.33%)	3 (33.33%)	
Mass location, n (%)						0.23
Upper right, n (%)	513 (35.28%)	349 (35.72%)	141 (34.39%)	19 (40.43%)	4 (20%)	
Middle right, n (%)	99 (6.81%)	74 (7.59%)	22 (5.37%)	3 (6.38%)	0	
Low right, n (%)	250 (17.19%)	166 (17.01%)	69 (16.83%)	11 (23.40%)	4 (20%)	
Upper left, n (%)	392 (26.96%)	263 (26.95%)	112 (27.32%)	9 (19.15%)	8 (40%)	
Left lower, n (%)	200 (13.76%)	124 (12.73%)	66 (16.09%)	5 (10.64%)	4 (20%)	
N stage		/				**<0.001**
NX	17 (1.20%)	10 (1.07%)	7 (1.71%)	0)	0	
N0	1200 (82.51%)	897 (91.9%)	273 (66.59%)	23 (48.94%)	10 (50%)	
N1	154 (10.62%)	46 (4.71%)	92 (22.44%)	13 (27.66%)	1 (5%)	
N2	77 (5.31%)	22 (2.25%)	36 (8.78%)	9 (19.15%)	9 (45%)	
N3	5 (0.35%)	1 (0.11%)	2 (0.48%)	2 (4.25%)	0	

n, case number; N, node; T, tumour; yrs, years.

SUVmax and different T stages as well as histological grades of tumours is also a potential new direction for the application of PET/CT in the field of lung cancer.

The purpose of our study was to explore the relationship between SUVmax and T stages, histological grades and pathological subtypes of lung adenocarcinoma.

MATERIALS AND METHODS

Patients' study population and inclusion criteria

We retrospectively analysed 11 270 patients with suspected lung cancer who underwent PET/CT examinations in our hospital from August 2016 to November 2018. From these patients, 1454 patients were pathologically confirmed as lung adenocarcinoma by two special pathologists after surgery. The diagnosed cases were based on the criteria recommended by the international association for the study of lung cancer.[17] T stages, grades and subtypes of lung carcinoma were categorised according to tumour growth pattern, pathological diagnosis of resection specimens or biopsy and whole body PET/CT images. Another 9816 cases were excluded because of the following reasons: non-lung cancer, unclear pathological subtypes and tumour boundary, other malignant tumours.

Measurement of SUVmax

The PET-CT (Siemens Biograph 64) results were reviewed by two attending nuclear medicine physicians. SUVmax values were obtained using attenuation-corrected transaxial images, the injected doses of 18-FDG, the patient's body weight and the cross-calibration factor between PET and the dose calibrator. SUVmax was defined as the highest value of interest in the primary lung tumour of each patient.

Definition of T stages, pathological grades and subtypes

T stages were divided into T1 (≤3 cm), T2 (>3 cm, ≤5 cm), T3 (>5 cm, ≤7 cm) and T4 (>7 cm) according to the tumour size. T1 was further divided into T1a (≤1 cm), T1b (>1 cm, ≤2 cm) and T1c (>2 cm, ≤3 cm) groups. T2 stage was divided into T2a (>3 cm, ≤4 cm) and T2b (>4 cm, ≤5 cm) groups. In addition, cases with lesions smaller than 3 cm but with visceral pleural invasion (VPI) were named as the T2VPI type. The above staging was abbreviated as Tnx (Tnx, n=1, 2, x=a, b, c, VPI). The pathological subtypes of lung adenocarcinoma were divided into adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and invasive adenocarcinoma, which was further divided into lepidic-predominant invasive

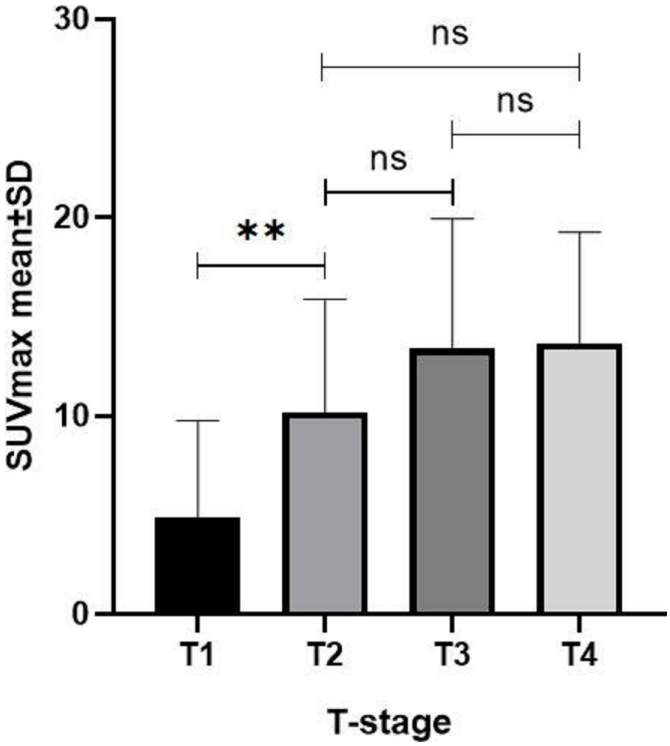

Figure 1 Comparison of SUVmax in T1–4 stages lung adenocarcinoma. This figure shows comparison of SUVmax among T1, T2, T3 and T4.** p<0.01; NS, no significant difference; SUVmax, maximum standard uptake value.

adenocarcinoma (LPA), acinar-predominant invasive adenocarcinoma (APA), papillary predominant invasive adenocarcinoma (PPA), micropapillary-predominant invasive adenocarcinoma (MPA), and solid-predominant invasive adenocarcinoma (SPA).[18] The subtypes were divided into low grade (AIS, MIA and LPA), intermediate grade (APA and PPA) and high grade (MPA and SPA).[19]

Statistical analysis

Continuous variables with a normal distribution (age, weight and SUVmax) were expressed as mean±SD. Use one-way analysis of variance to analyse the distribution of all variables. χ^2 test, Student's t test and non-parametric Wilcoxon rank sum test were used to compare the clinical characteristics of each group. The Kruskal-Wallis, Bonferroni-Dunn and Mann-Whitney tests were used to compare the differences and perform univariate analysis on the continuous values between the groups. SPSS V.20.0 (IBM, Armonk, New York) was used for data analysis. p<0.05 is considered statistically significant.

Patient and public involvement

No patients were involved in the design and reporting of this study.

RESULTS

Patient demographic and baseline characteristics

The clinical characteristics of 1454 patients are shown in table 1.The average age of the patients was 61.22±9.65 years old. Among these patients, there were significant differences in gender, smoking history and N stages. Women were more than that of men (58.05% vs 41.95%, p<0.001). Patients with smoking history were significantly more than those non-smokers (66.58% vs 33.42%, p<0.001). The majority of smokers were men (98.2% vs 1.8%, p<0.001). The number of patients with T1 stage lung adenocarcinoma was the largest population with 977 patients (67.19%). The number of lung adenocarcinomas from T2 to T4 decreased successively and was 410 cases (28.20%), 47 cases (3.23%) and 20 cases (1.38%), respectively. Among enrolled cases, T1 stage group contained all pathological subtypes except MPA subtype. The T2 stage group contained five pathological subtypes: LPA,

Table 2 P value tables of Tn and Tnx staging groups after lung adenocarcinoma was grouped according to histological grades and pathological subtypes

Classification	T1	T2	T3	T4	T1a	T1b	T1c	T2a	T2b	T2c
Kruskal-Wallis test										
Histological grade (low–intermediate–high grade group)	**<0.001**	**<0.001**	/	/	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.149*
Pathological subtype	**<0.001**	**<0.001**	**0.032**	0.188	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.019**
Bonferroni-Dunn test										
Low–intermediate grade group	**<0.001**	**0.027**	/	/	**<0.001**	**<0.001**	**<0.001**	0.149	0.728	/
Low–high grade group	**<0.001**	**<0.001**	/	/	**0.002**	**<0.001**	**<0.001**	**0.001**	0.063	/
Intermediate–high grade group	**<0.001***	**<0.001**	**0.007***	0.049*	0.278	**<0.001**	**<0.001**	**<0.001**	**0.004**	/

Tn, tumour staging was divided into groups including T1 (≤3 cm), T2 (>3,≤5 cm), T3 (>5,≤7), T4 (>7 cm) a. The above is abbreviated as Tn (n=1–4); Tnx (Tnx, n=1, 2, x=a, b, c, VPI).
VPI, visceral pleural invasion.

Table 3 P value table of histological grade and subtype groups after grouping according to Tn and Tnx stages of lung adenocarcinoma

Classification	Total	L	I	H	AIS	MIA	LPA	APA	PPA	MPA	SPA
Kruskal-Wallis *(P value)											
T1–T4	**p<0.001***	**p<0.001* (T1–2)**	**p<0.001***	**p<0.001***	/	/	**0.001*(T1-2)**	**p<0.001**	**p<0.001**	0.031	**p<0.001**
T1a–T2b	**p<0.001***	**p<0.001***	**p<0.001***	**p<0.001***	0.738* (T1a–T1b)	0.014* (T1a–T1b)	**p<0.001**	**p<0.001**	**p<0.001**	0.048	**p<0.001**
Bonferroni-Dunn test(P value)											
T1–T2	**p<0.001**	/	**p<0.001**	**0.001**	/	/	**0.001**	**p<0.001**	**p<0.001**	0.078	**0.019**
T1–T3	**p<0.001**	/	**p<0.001**	**p<0.001**	/	/	/	**p<0.001**	**0.008**	0.290	**0.002**
T1–T4	**p<0.001**	/	**p<0.001**	**0.020**	/	/	/	**0.005**	**0.034**	0.822	0.112
T2–T3	0.900	/	0.741	0.614	/	/	/	1.000	1.000	1.000	1.000
T2–T4	0.249	/	0.624	0.994	/	/	/	0.932	1.000	1.000	0.566
T3–T4	1.000	/	1.000	1.000	/	/	/	1.000	1.000	1.000	1.000

Tn, tumour staging was divided into groups including T1 (≤3 cm), T2 (>3,≤5 cm), T3 (>5,≤7), T4 (>7 cm) a. The above is abbreviated as Tn (n=1–4); Tnx (Tnx, n=1, 2, x=a, b, c, VPI).

AIS, adenocarcinoma in situ; APA, acinar-predominant invasive adenocarcinoma; H, high grade group; I, intermediate grade group; L, low grade group; LPA, lepidic-predominant invasive adenocarcinoma; MIA, minimally invasive adenocarcinoma ; MPA, micropapillary-predominant invasive adenocarcinoma ; PPA, papillary predominant invasive adenocarcinoma ; SPA, solid-predominant invasive adenocarcinoma; VPI, visceral pleural invasion.

APA, PPA, MPA and SPA. Both T3 and T4 stage groups included four subtypes: APA, PPA, MPA and SPA.

Analysis of the relationship between SUVmax and T staging of lung adenocarcinoma

Relationship of SUVmax in Tn staging groups of lung adenocarcinoma is shown in figure 1. The mean SUVmax of patients with lung adenocarcinoma of T1–T4 stage increased with the increase in T stages (T1<T2<T3<T4). There were statistical differences in SUVmax of the four T stage groups (Kruskal-Wallis test, p<0.001, table 2).

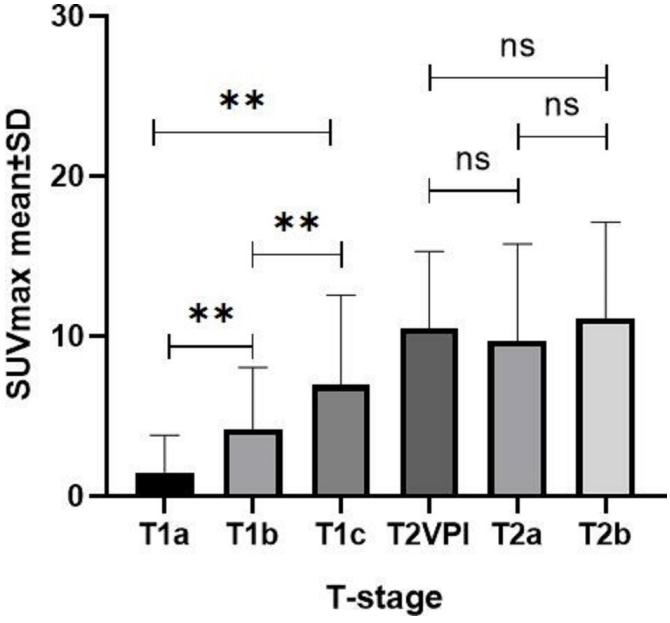

Figure 2 Comparison of SUVmax in T1 and T2 subtypes lung adenocarcinoma. This figure shows comparison among T1a–c, T2a, T2b and T2VPI.** p<0.01; NS, no significant difference; SUVmax, maximum standard uptake value; VPI, visceral pleural invasion.

After pairwise comparison, it was found that there were significant differences between T1 and T2–4 (p<0.001), but the differences among T2–4 stages were not significant (table 2, Bonferroni-Dunn correction test, p>0.05) (figure 1).

We also compared SUVmax of different histological grades and pathological subtype groups in the same T stage group. The results are shown in table 2. T1 and T2 were divided into low, medium and high-grade groups. T3 and T4 were divided into medium and high-grade groups. The median SUVmax followed the rule of low<-medium<high grade groups. There was a difference in SUVmax value between the middle and high-level groups in the T3 and T4 groups, and the middle level < high level (Mann-Whitney test, p<0.05). According to Kruskal-Wallis test, except T4 (p=0.188), there were differences in SUVmax values of each pathological subtype group contained in each (any) Tn and Tnx stage groups (T3, p=0.032; others) p<0.001).

We further evaluated the relationship between SUVmax of different Tn stage groups and histological grades (table 3). SUVmax value of the same histological grade or the same pathological subtype group increases with the increase in T stages, and the difference was statistically significant. After pairwise comparison, there were significant differences in SUVmax between T1 and T2–4 of lung adenocarcinoma groups, but there were no significant differences among T2–4 groups.

The relationship between SUVmax of each Tnx substage group of T1 and T2 lung adenocarcinoma and histological grade or pathological subtype

Since it was found that there were significant different SUVmax values between T1 stage and T2 stage, we further evaluated the relationship between SUVmax and Tnx subtypes. Figure 2 shows comparison of SUVmax among

Table 4 P value table of histological grade group and pathological subtype group after grouping according to Tn and Tnx stages of lung adenocarcinoma

Classification	Totle	The low-grade group	The intermediate-grade group	The high-grade group	LPA	APA	PPA	MPA	SPA
Bonferroni-Dunn test (P value)									
T1a–T1b	**p<0.001***	0.102	**p<0.001***	1.000	0.192	**0.003***	0.180	/	1.000
T1a–T1c	**p<0.001***	**p<0.001***	**p<0.001***	0.189	**0.012***	**p<0.001***	**p<0.001***	/	0.100
T1a–T2a	**p<0.001***	**0.002***	**p<0.001***	0.064	**0.006***	**p<0.001***	**p<0.001**	/	**0.044***
T1a–T2b	**p<0.001***	**0.048***	**p<0.001***	**0.025***	**0.017***	**p<0.001***	**p<0.001***	/	**0.032***
T1a–T2VPI	**p<0.001**	/	**p<0.001**	0.342	/	**p<0.001**	**p<0.001**	/	0.366
T1b–T1c	**p<0.001**	**0.028**	**p<0.001**	**0.001**	0.793	**p<0.001**	0.014	1.000	**0.002**
T1b–T2a	**p<0.001**	0.055	**p<0.001**	**p<0.001**	0.228	**p<0.001**	**p<0.001**	0.151	**p<0.001**
T1b–T2b	**p<0.001**	0.270	**p<0.001**	**p<0.001**	0.279	**p<0.001**	**p<0.001**	0.074	**0.001**
T1b–T2VPI	**p<0.001**	/	**p<0.001**	**0.045**	/	**p<0.001**	**p<0.001**	1.000	0.215
T1c–T2a	**p<0.001**	1.000	**p<0.001**	1.000	1.000	**0.002**	**0.030**	1.000	1.000
T1c–T2b	**p<0.001**	1.000	**0.003**	1.000	1.000	0.111	0.072	0.965	1.000
T1c–T2VPI	**p<0.001**	/	**p<0.001**	1.000	/	**p<0.001**	**0.037**	1.000	1.000
T2a–T2b	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
T2a–T2VPI	0.901	/	0.233	1.000	/	0.055	1.000	1.000	1.000
T2b–T2VPI	1.000	/	1.000	0.723	/	1.000	1.000	1.000	1.000

Tn, tumour staging was divided into groups including T1 (≤3 cm), T2 (>3,≤5 cm), T3 (>5,≤7), T4 (>7 cm) a. The above is abbreviated as Tn (n=1–4); Tnx (Tnx, n=1, 2, x=a, b, c, VPI).
The italics indicate a significant difference in P values.
APA, acinar-predominant invasive adenocarcinoma; H, high grade group; I, intermediate grade group; L, low grade group; LPA, lepidic-predominant invasive adenocarcinoma; MPA, micropapillary-predominant invasive adenocarcinoma; PPA, papillary predominant invasive adenocarcinoma; SPA, solid-predominant invasive adenocarcinoma; VPI, visceral pleural invasion .

the same Tnx staging group. SUVmax values of T stage subgroups from T1a to T2b also followed the increasing law (T1a<T1b<T1c<T2a<T2VPI<T2b). SUVmax value of the same histological grade or the same pathological subtype group increases with the increase in Tnx stage, and the difference is statistically significant (see table 4 for p value). AIS and MIA did not include in this table because AIS and MIA only are minimal local tumour. Pairwise comparison of SUVmax values of each group showed differences among T1a-T1b, T1b-T1c and T1a-T1c were statistically significant (Bonferroni-Dunn correction test, p<0.001). However, no significant differences among T2a-T2b, T2a-T2VPI and T2b-T2 VPI were found (Bonferroni-Dunn calibration test, p>0.05, figure 2). Comparing the T1x group with the T2x group, comparing T1a, T1b and T1c with T2a, T2 VPI and T2b, respectively, the difference in SUVmax value of each group was statistically significant (Bonferroni-Dunn-adjusted test, p<0.001).

DISCUSSION

This study revealed that SUVmax value of lung adenocarcinoma was associated with T stages. When lung adenocarcinoma was at stage T1, SUVmax values of different size lung adenocarcinoma (T1x) groups were significantly different, but when the lung adenocarcinoma stage was more than T1 stage, the mean SUVmax of the T2VPI group was higher than that of the T1 stage. The APA subtypes in the T2VPI group showed higher FDG uptake compared with the APA subtypes of other T stage groups.

Previous studies have confirmed that SUVmax increased with the grades of malignancy of pathological subtypes.[5 19–22] These data revealed that FDG reflected tumour biometabolic activity. SUVmax has been shown to be positively correlated with the mitotic count of tumours in lung adenocarcinoma patients.[18 23–34] As the size of the tumour increases, the blood supply of the tumour may be insufficient, resulting in tumour hypoxia and necrosis.[35–38] However, tumour cells can increase glucose metabolism to adapt low-oxygen environment and switch anaerobic glycolysis, which give rise to SUVmax elevation.[39] Therefore, tumour size may roughly reflect the number of tumour cells.[40] SUVmax also is significantly correlated with tumour cell density.[41] However, some patients with NSCLC with specific gene mutations or biomarker expressions had great benefits from targeted therapy or immunotherapy,[42] which SUVmax values of these patients need to explore it. Reportedly, SUVmax value in patients with parietal pleural invasion was significantly higher than that of those without it.[33] We believe that these factors are superimposed on the process of tumour.

We found that SUVmax was not as significant when tumour size was more than 3 cm. This result implied that there may be differences in the metabolic pattern of

lung adenocarcinoma tumour diameter with < or >3 cm. Li *et al*[43] and Ippolito *et al*[44] reports demonstrated that there was a significant difference in perfusion between tumours with a diameter of <3 cm and tumours with a diameter of >3 cm. Based on the above results, we speculated that the changes in glucose metabolism patterns may be related to the blood supply of the tumour before and after the T1 stage. This may be one of the reasons why the tumour size and the SUVmax values were significantly different in <3 cm tumour size, and the difference was no longer significant in >3 cm tumour size.

VPI is one of the factors that increases the T staging of lung cancer with a diameter of <3 cm. Some meta-analyses have shown that VPI with tumour sizes less than 2 cm and 2–3 cm had a poor prognosis.[45 46] Our study showed that the mean value of T2 VPI SUVmax (10.49±4.81) was higher than that of any T1x group (p<0.001). Previous studies suggested that the prognosis of T2VPI group was worse than that of T1 stage.[45 46] After the T stage grouping, SUVmax value of APA subtypes in the T2VPI group was higher than that of T3 and lower than that of the T4 group.

Our data indicated that SUVmax value was closely associated with T stages, the grades of malignancy and some pathological subtypes. However, current study has following limitations: (1) SUVmax value did not tell predictive value of preoperative and estimate likelihood of recurrence in operative treatment of lung adenocarcinoma, (2) no clear relationship between SUVmax in different T stages and metastasis, (3) SUVmax did not provide correlations of those patients with minor T stages, but potentially high-grade patterns. Therefore, our future work will explore these relationships between SUVmax measurement and predictive, recurrence and metastasis roles of patients.

CONCLUSION

SUVmax values of lung adenocarcinoma in the same T stage group increase with the grades of malignancy. SUVmax value of the same histological grade or pathological subtype group increased in T1a-1c stages, but no significant differences in T2–T4 stages.

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Contributors Conceptualisation, WX and CC; methodology, XS; statistics, TC; validation, XS. TC and CX; formal analysis, LL; investigation, BL, LW, MR; resources, HY; data curation, QZ; writing—original draft preparation, XS, and TC; writing—review and editing, WX; visualisation, CC; supervision, WX; project administration, WX; funding acquisition, WX and CC. WX and CC: Guarantor

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study protocol was reviewed and approved by the Ethical Committee of Shanghai Chest Hospital (approval number:KS2035) with a waiver of informed consent. The ethical guidelines were compliance with the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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