Original Article

The role of primary tumor SUVmax in the diagnosis of invasion depth: a step toward clinical T2N0 esophageal cancer

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Background: The controversy regarding optimal clinical T2N0 esophageal cancer treatment ultimately stems from the clinical staging modalities' inaccuracy. Because most inaccuracies lie in clinical T2 to pathological T1, it is vital to discriminate whether the muscularis propria is invaded.

Methods: We investigated the association between the primary tumor maximal standard uptake value (SUVmax), and the pathological features and overall survival. We attempted to construct a discriminative model through logistic regression analysis.

Results: A total of 140 cN0 esophageal squamous cell carcinoma (ESCC) patients were enrolled. Primary tumor SUVmax differed significantly in paired pathological T categories (P<0.05), but not pT2 *vs.* pT3 (P=0.648). Age (≤65 *vs.* >65), biopsy differentiation grades (well or moderately *vs.* poorly *vs.* unknown), and primary tumor SUVmax (continuous) were independent risk factors for invasion depth. Subsequently, the age categories, the biopsy differentiation grade categories, and the primary tumor SUVmax categories (≤7.4 *vs.* >7.4) were included in the logistic regression analysis to construct a discriminative model, showing a good performance in discriminating pT2–3 *vs.* pT1 in terms of accuracy 87.1%, sensitivity 93.6%, specificity 73.9%, and area under the curve (AUC) 0.887 [95% confidence interval (CI): 0.822 to 0.951]. Of these factors, biopsy differentiation grades and primary tumor SUVmax showed significant differences in overall survival (P<0.05), while the age categories did not.

Conclusions: The novel baseline model comprised of age, biopsy differentiation grades, and primary tumor SUVmax provide much discriminative performance in determining whether the muscularis propria is invaded. Further studies are necessary to validate the findings and guide clinical practice for cT2N0 esophageal cancer.

Keywords: Esophageal cancer; invasion depth; positron emission tomography with computed tomography (PET-CT); maximal standard uptake value (SUVmax)

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Introduction

Esophageal cancer is one of the most common malignancies worldwide, with a dismal prognosis (1). Histologically, esophageal cancer includes two major subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) (2). In recent decades, much attention has been paid towards improving patients' long-term survival with esophageal cancer. Nowadays, induction therapy (chemotherapy or chemoradiotherapy), followed by surgery, can provide a survival benefit for locally advanced esophageal cancer (3-6). Local therapy (endoscopic or surgical resection) is usually applied for early-stage esophageal cancer, but this remains the subject of much debate.

This debate is derived from the inaccuracy of esophageal cancer's clinical staging, which is particularly evident in clinical T2N0 (cT2N0). Crabtree *et al.* found that 34%, 25.3%, and 0.6% of cT2N0 were pathological T0–1 (pT0–1), pT3, and pT4, respectively (7). The Esophageal Cancer Study Group found that 44.5%, 31%, and 1% of cT2N0 were pT0–1, pT3, and pT4, respectively (8). Other groups have reported that more than 50% of cT2 esophageal cancers were pT1 after surgery, even when staged by experienced clinicians (9,10). Consequently, there is much debate surrounding the optimal treatment for cT2N0 esophageal cancer, namely, between primary surgery or induction therapy (11-13).

The current pathological T staging is based on invasion depth. Thus, an accurate clinical T staging demands a high resolution of the esophagus (14), especially for flat tumors and diffused infiltration (15). The fact that most migration of the cT2 category lies in cT2 to pT1 indicates that the common modalities cannot accurately discriminate whether or not the muscularis propria is invaded. Thus, one natural question is whether the metabolic activity may play a role in this process.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) with computed tomography (CT) is included as part of the initial workup (3-5), but it is usually used to detect distant metastasis (16). Recent studies have found that the maximal standard uptake value (SUVmax) of the primary tumors was associated with pathological features (17-26). We, therefore, hypothesized that metabolic activity would determine whether or not the muscularis propria was invaded. We investigated the potential association between the primary tumor SUVmax and pathological features and overall survival. Furthermore, we attempted to construct certain models to discriminate invasion depth. We present the following article in accordance with the STARD reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4430).

Methods

Patients

From January 2015 to December 2017, 234 consecutive patients underwent baseline ^{18}F-FDG PET/CT, followed by primary esophagectomy in Zhongshan Hospital Fudan University. Of these patients, 67 were clinically staged as cN+, while 2 had received endoscopic dissection (ESD) before ^{18}F-FDG PET/CT, and 25 were histologically confirmed as not ESCC. Eventually, 140 patients were enrolled in this retrospective study. This study had been approved by the Institutional Review Board of Zhongshan Hospital Fudan University (HGBB-202006001) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent was waived as the nature of retrospective studies.

As the reference standard, the pathological staging was based on the TNM Staging System (8th edition, 2017) (14). Tumors that invaded the lamina propria or muscularis mucosae, the submucosa, the muscularis propria, the adventitia, and the adjacent structures were defined as pT1a, pT1b, pT2, pT3, and pT4, respectively. All of the patients had discernible pT categories in this study.

Follow-up

Patients were asked to receive physical examination, tumor markers testing, thoracic CT, and cervical and abdominal ultrasonography in the outpatient clinic. For patients with particular signs or symptoms, additional examinations were conducted. A combination of clinical service records and phone calls were used to determine each patient's status as of March 2020. In this study, overall survival was defined as the interval between the date of esophagectomy and the date of death or the last follow-up date.

PET/CT protocol and interpretation

According to the routine protocol of ^{18}F-FDG PET-CT at our institution, the patients fasted for at least 6 hours, and the serum glucose levels were required to be lower than 11.0 mmol/L before imaging. ^{18}F-FDG PET/CT scans were performed on a hybrid GE Discovery VCT 64 PET/CT scanner (General Electric, Milwaukee, WI, USA) from

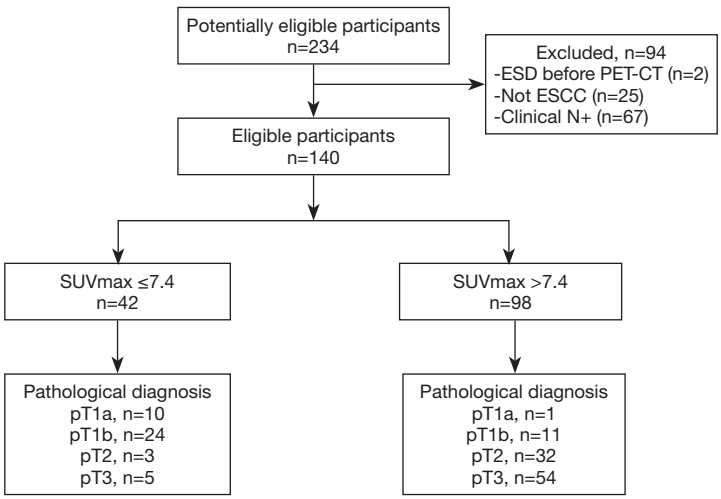

Figure 1 The flowchart of the enrollment and the discriminating outcomes of SUVmax (categorized). SUVmax, maximal standard uptake value; ESD, endoscopic dissection; PET-CT, positron emission tomography with computed tomography; ESCC, esophageal squamous cell carcinoma.

the proximal thigh to the skull base. Metabolic images were obtained approximately 60 minutes after intravenous administration of 3.7 to 5.6 MBq of FDG per kilogram of body weight. PET images were acquired for 2 minutes per bed position. The CT scanning was performed on the same scanner without contrast administration (200 mA, 120 kV, matrix 512×512, 0.8 s per rotation). The SUV was normalized to body weight as a determinate index. All PET-CT scans were performed within 1 month before surgery.

Statistical analyses

Continuous data were presented as mean with standard deviation (SD) or median with interquartile ranges (IQRs). Categorical data were presented as numbers with a proportion (%). Both parametric and non-parametric tests were used, including the Chi-square test and the Kruskal-Wallis test. The association between baseline characteristics and pathological findings was determined by univariate and multivariate logistic regression analysis. The variables with P<0.10 in the univariate regression were included in the multivariate regression. The independent factors were included in the predictive model. The receiver operator curve (ROC) with Youden's index (27) was used to determine the predictive performance and identify the optimal cutoff of continuous parameters. The area under the curve (AUC) with 95% confidence interval (CI) was used to measure the discriminating performance. The Kaplan-Meier method was used to generate survival curves, and the log-rank test was used to evaluate survival differences. All patients included in the survival analysis were followed up for at least 3 months after surgery or until death.

Statistical analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA) and R software version 1 3.5.1 (Packages: survival and survminer). P<0.05 was considered statistically significant.

Results

Preoperative characteristics of the patients

As shown in *Figure 1* and *Table 1*, a total of 140 cN0 patients were enrolled in this study, including 25 females and 115 males, with a median age of 65 (IQR: 60.25–71.00). Of the 140 patients, 74 (52.9%) were clinically staged as cT1–2, and 66 (47.1%) were clinically staged as cT3. Based on the endoscopic biopsy, 41 (29.3%) tumors were poorly differentiated, 84 (60.0%) tumors were well or moderately differentiated, while 15 (10.7%) tumors had no grading information. The median and mean SUVmax were 11.35 (IQR: 6.28–15.68) and 11.37 (SD: 6.10), respectively.

Postoperative characteristics and their association with SUVmax

For all patients, surgical resection with the pathological

Table 1 Preoperative characteristics in the cN0 patients

Characteristics	Median (IQR) or number (percentage)
Age	
Median (IQR)	65 (60.25–71.00)
Sex	
Female	25 (17.9)
Male	115 (82.1)
Smoking history	
Non-smoking	93 (66.4)
Smoking	47 (33.6)
Drinking history	
Non-drinking	95 (67.9)
Drinking	45 (32.1)
Clinical T	
cT1–2	74 (52.9)
cT3	66 (47.1)
Differentiation of biopsy sample	
bG1, 2, x (well, moderately)	84 (60.0)
bG3 (poorly)	41 (29.3)
Unknown	15 (10.7)
Surgical procedure	
MIE	84 (60.0)
Open	56 (40.0)
SUVmax	
Median (IQR)	11.35 (6.28–15.68)
Mean (SD)	11.37 (6.10)
Surgery year	
2015	26 (18.6)
2016	46 (32.8)
2017	68 (48.6)

IQR, interquartile range; bG, biopsy differentiation grade; MIE, minimally invasive esophagectomy; open, open esophagectomy; SUVmax, maximal standard uptake value; SD, standard deviation.

examination was conducted within 1 month after the completion of PET-CT, and no cancer-related treatment was administered during this interval. Histologically, 11 (7.9%), 35 (25.0%), 35 (25.0%), and 59 (42.1%) tumors

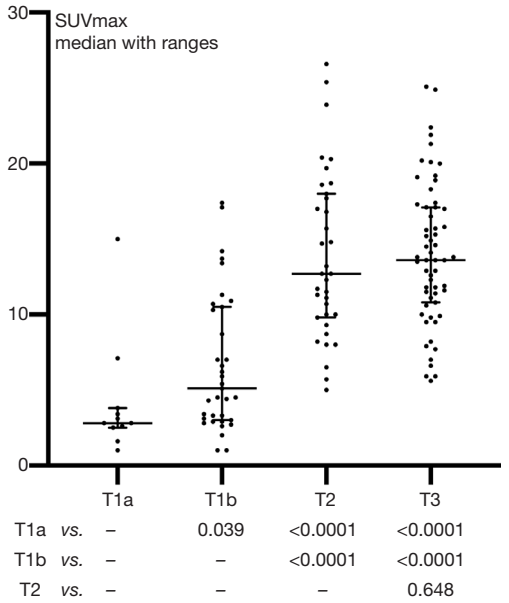

Figure 2 The primary tumor SUVmax in pathological T categories. SUVmax of primary tumors differed significantly in paired pT categories (all P<0.05) but not pT2 *vs.* pT3 (P=0.648). SUVmax, maximal standard uptake value.

were confirmed as pT1a (mucosa), pT1b (submucosa), pT2 (muscularis propria), and pT3 (adventitia), respectively, while 36 (25.7%) were staged as pN+. There was a significant correlation between invasion depth and node metastasis (P=0.017, Table S1). Ultimately, 110 (78.6%) were in pathological stage I–II, and 30 (21.4%) were in pathological stage III–IV. Lymphatic or nerve invasion (LNI) was present in 43 (30.7%) patients.

As shown in *Figure 2*, the primary tumor SUVmax differed significantly between any paired pT categories (all P<0.05), but not between pT2 *vs.* pT3 (P=0.648). As shown in *Table 2*, although SUVmax also differed significantly between pathological stage categories (pStage I *vs.* II *vs.* III–IV, P<0.0001), we found it was not significantly different in pN categories (pN0 *vs.* pN+, P=0.187), pG categories (well or moderately *vs.* poorly, P=0.254), and LNI categories (absence *vs.* presence, P=0.062).

Baseline risk factors for invasion depth

According to the univariate and multivariate logistic regression analysis, age (≤65 *vs.* >65), biopsy differentiation (well or moderately *vs.* poorly *vs.* unknown), and SUVmax (continuous) were identified as the baseline risk factors for

Table 2 Postoperative characteristics and the association with SUVmax in the cN0 patients

Characteristics	Number (percentage)	SUVmax, median (IQR)	P value
Pathological T			<0.0001*
pT1a	11 (7.9)	2.80 (2.50–3.80)	
pT1b	35 (25.0)	5.10 (3.00–10.50)	
pT2	35 (25.0)	12.70 (9.80–18.00)	
pT3	59 (42.1)	13.60 (10.80–17.10)	
Pathological N			0.187†
pN0	104 (74.3)	11.10 (5.90–14.88)	
pN1	28 (20.0)	11.95 (7.73–16.30)	
pN2	7 (5.0)	11.90 (8.20–22.40)	
pN3	1 (0.7)	5.70	
Number of dissected nodes			
Median [IQR]	26 [18–32]	NA	NA
Number of metastatic nodes			
Median (IQR)	0 (0–0.75)	NA	NA
Differentiation of resection sample			0.254
pG1, 2 (well, moderately)	90 (64.3)	11.20 (5.08–14.78)	
pG3 (poorly)	50 (35.7)	12.25 (7.53–15.58)	
Tumor location			0.894
Upper	8 (6.0)	8.85 (5.93–21.85)	
Middle	67 (47.9)	11.50 (7.00–15.70)	
Lower or cardiac	65 (46.4)	11.30 (5.35–14.95)	
Pathological TNM stage			<0.0001*‡
I	40 (28.6)	4.40 (2.90–9.90)	
II	70 (50.0)	12.80 (9.50–17.15)	
III	29 (20.7)	14.70 (10.85–17.85)	
IV (pN3)	1 (0.7)	5.70	
Lymphatic or nerve invasion			0.062
Absence	97 (69.3)	10.70 (4.80–15.10)	
Presence	43 (30.7)	12.30 (8.70–17.30)	

*, statistically significant; †, pN0 *vs.* pN1–3; ‡, pathological stage I *vs.* stage II *vs.* stage III–IV. SUVmax, maximal standard uptake value; IQR, interquartile range; NA, not applicable.

the invasion of the muscularis propria (*Table 3*).

Of these factors, the ROC analysis suggested that SUVmax (continuous) demonstrated good discriminative performance for both pT2 *vs.* pT1 (n=81, AUC: 0.866, 95% CI: 0.790 to 0.942, P<0.0001, *Figure 3A*) and for pT2–3 *vs.* pT1 (n=140, AUC: 0.877, 95% CI: 0.811 to 0.943, P<0.0001, *Figure 3B*). Youden's index was used to determine the cutoff as 7.4 for SUVmax (categorized) in all patients to fit clinical applications. The discriminating outcomes are presented in *Figure 1*.

Table 3 Baseline risk factors for pT2–3 identified by univariate and multivariate logistic regression

Characteristics	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Age						
≤65 (ref.)	Ref.			Ref.		
>65	2.321	1.118–4.819	0.024	3.642	1.201–11.046	0.022*
Sex						
Female	Ref.					
Male	1.463	0.600–3.569	0.403			
Smoking history						
Non-smoking	Ref.					
Smoking	1.681	0.771–3.666	0.192			
Drinking history						
Non-drinking	Ref.					
Drinking	1.803	0.812–4.003	0.147			
Differentiation of biopsy sample						
bG1, 2, x (well, moderately)	Ref.			Ref.		
bG3 (poorly)	2.698	1.067–6.825	0.036	4.584	1.264–16.621	0.021*
Unknown	0.370	0.120–1.141	0.084	0.124	0.018–0.865	0.035*
SUVmax of the primary tumors						
Continuous, by 0.1	1.423	1.267–1.599	<0.0001	1.447	1.277–1.640	<0.0001*

*, statistically significant. OR, odds ratio; 95% CI, 95% confidence interval; bG, biopsy differentiation grade; SUVmax, maximal standard uptake value.

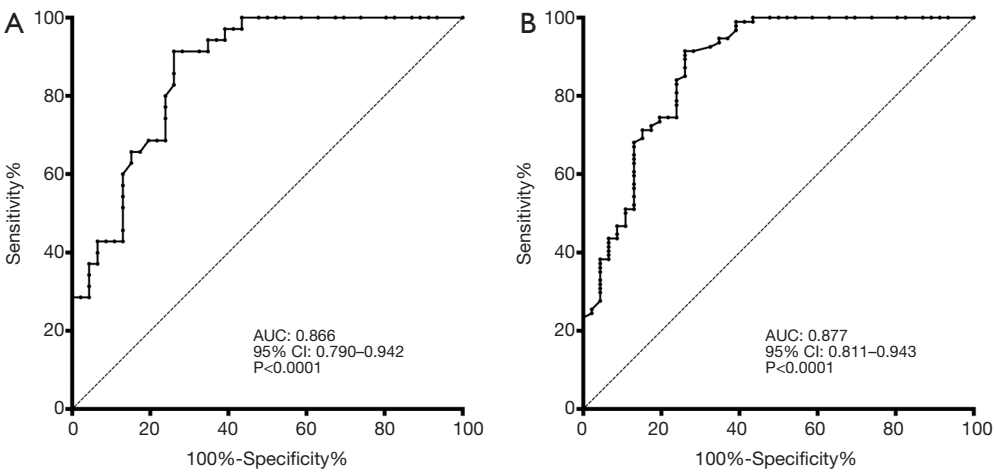

Figure 3 The discriminating performance of SUVmax (continuous) for invasion depth: SUVmax (continuous) had a good discriminating performance for (A) pT2 *vs.* pT1 (AUC: 0.866, 95% CI: 0.7900 to 0.9423) and for (B) pT2–3 *vs.* pT1 (AUC: 0.877, 95% CI: 0.811 to 0.943). SUVmax, maximal standard uptake value; AUC, area under the curve; 95% CI, 95% confidence interval.

Table 4 The predictive model derived from independent baseline risk factors for pT2–3 *vs.* pT1

Characteristics	Multivariate		
	OR	95% CI	P value
Age			
≤65 (ref.)	Ref.		
>65	3.288	1.129–9.574	0.029*
Differentiation of biopsy sample			
bG1, 2 (well or moderately)	Ref.		
bG3 (poorly)	3.913	1.043–14.676	0.043*
Unknown	0.324	0.074–1.426	0.136
SUVmax			
≤7.4 (ref.)	Ref.		
>7.4	35.293	11.779–105.748	<0.0001*

*, statistically significant. Model performance: accuracy 87.1%; sensitivity 93.6%; specificity 73.9%; PPV 88.0%; NPV 85.0%; positive likelihood ratio 3.586; negative likelihood ratio: 0.086. PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; 95% CI, 95% confidence interval; bG, biopsy differentiation grade; SUVmax, maximal standard uptake value.

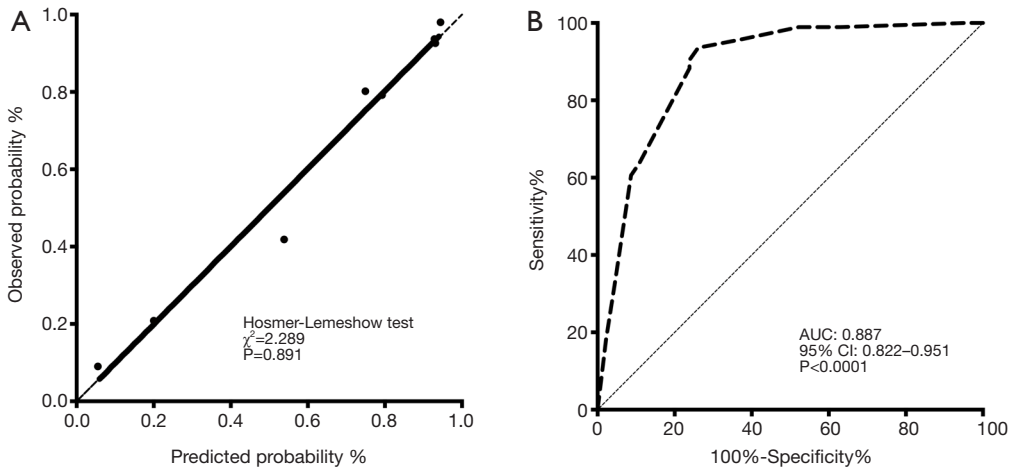

Figure 4 The discriminating performance of the novel model for pT2–3 *vs.* pT1. (A) The Hosmer-Lemeshow test indicated a good calibration (Chi-square 2.289, P=0.891) and (B) the receiver operating curve indicated a high discrimination (AUC: 0.887, 95% CI: 0.822 to 0.951) of the discriminating model. AUC, area under the curve; 95% CI, 95% confidence interval.

The discriminating model for pT2–3

According to the identification of baseline risk factors, the age categories (≤65 *vs.* >65), biopsy differentiation categories (well or moderately *vs.* poorly *vs.* unknown), and the primary tumor SUVmax categories (≤7.4 *vs.* >7.4) were included in the logistic regression analysis (enter method) to construct a novel model. As shown in *Table 4*, this model demonstrated good performance: accuracy 87.1%, sensitivity 93.6%, specificity 73.9%, positive predictive value (PPV) 88.0%, and negative predictive value (NPV) 85.0%. The Hosmer-Lemeshow test indicated a good calibration (Chi-square 2.289, P=0.891, *Figure 4A*), and the ROC analysis indicated high discrimination (AUC: 0.887, 95% CI: 0.822 to 0.951, P<0.0001, *Figure 4B*) of the new model. The distribution of pT2–3 *vs.* pT1 in the

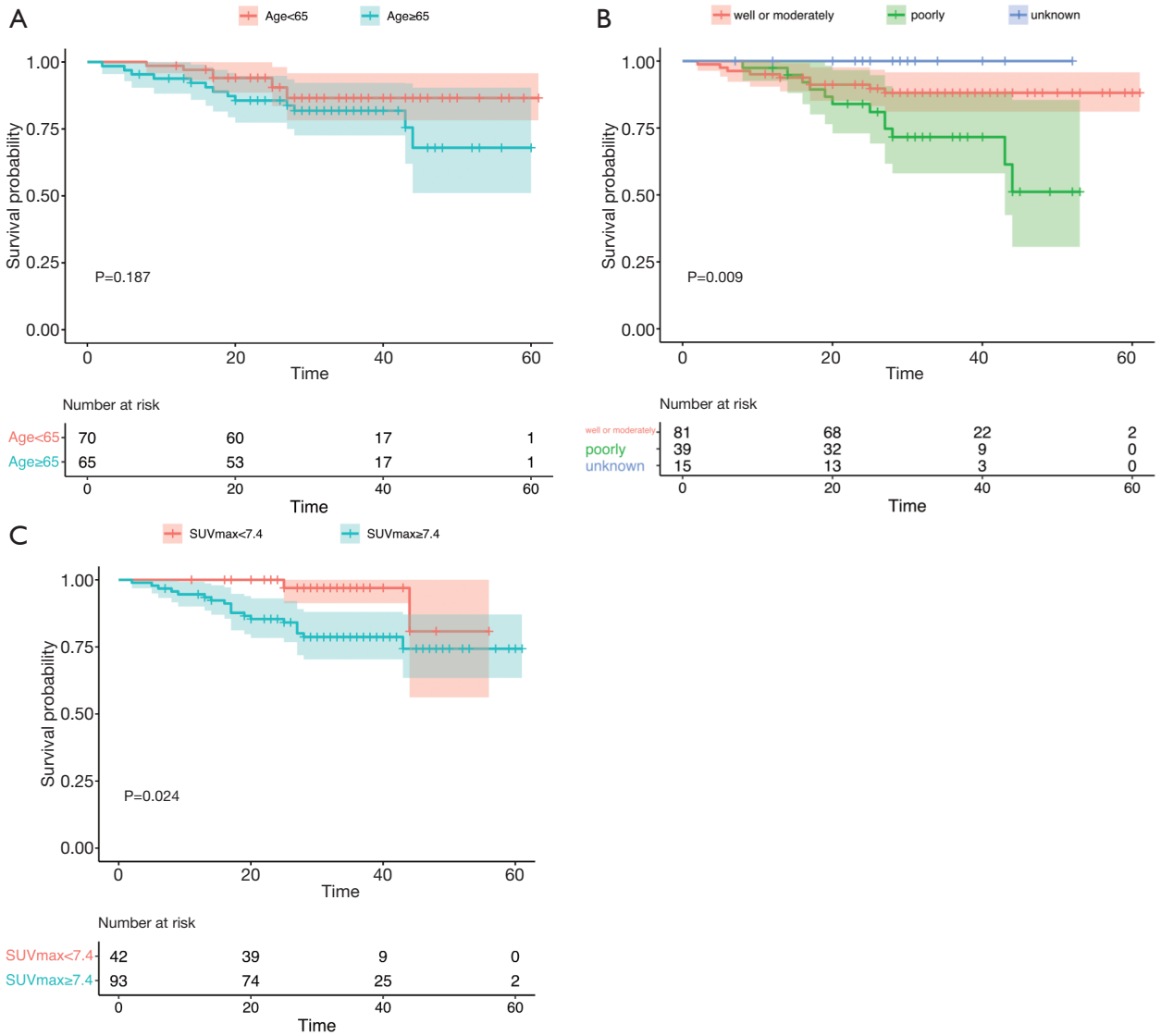

Figure 5 The survival curves of the risk factors for invasion depth: (A) age <65 *vs.* ≥65, P=0.187; (B) non-poorly differentiated *vs.* poorly differentiated, P=0.009; and (C) SUVmax <7.4 *vs.* ≥7.4, P=0.024. SUVmax, maximal standard uptake value.

stratification of the model is shown in Table S2.

Prognostic value of the baseline risk factors

We then investigated whether the baseline risk factors were associated with overall survival. After excluding 5 patients lost to follow-up, 135 patients were included in the survival analysis. The median follow-up period was 35 months, and the 3-year overall survival rate was 84.3% (78.0% to 91.1%). We found that age (P=0.187, *Figure 5A*) showed no significant difference, while biopsy differentiation (P=0.009, *Figure 5B*) and primary tumor SUVmax (P=0.024, *Figure 5C*) showed significant differences in overall survival.

Discussion

The heated debate regarding cT2N0 esophageal cancer ultimately stems from the current clinical staging model's considerable inaccuracy. Pech *et al.* reported that the accuracy of cT1, cT2, and cT3 staged by endoscopic ultrasound (EUS) was 92%, 37%, and 68%, respectively (28). Dhupar *et al.* reported that the accuracy

of cT1a, cT1b, cT2, and cT3 staged by EUS was 56%, 58%, 10%, and 70%, respectively (29). Apart from EUS, CT, which relies on wall thickness, cannot provide adequate information (30-32). Therefore, further study in this field would be on shaky ground as long as this problem remains unsolved. Because most of the cT2 category's migration lies in cT2 to pT1, finding effective methods to discriminate muscularis propria invasion is of great importance.

Consistent with previous studies (17-26), an increasing trend of primary tumor SUVmax was observed in the advanced pT categories. In this circumstance, the core question was whether this increasing trend could be translated to discriminate invasion depth prospectively. Huang *et al.* previously reported a positive result in a small study (n=45), where it showed great discriminative performance for pT categories (≥ pT1, AUC: 1.00; ≥ pT2, AUC: 0.88; and ≥ pT3, AUC: 0.95) (17). However, in our study, we found SUVmax differed significantly in paired pT categories but not pT2 *vs.* pT3. Consequently, we found SUVmax (continuous) had good discrimination for pT2–3 *vs.* pT1, and pT2 *vs.* pT1, but not for pT3 *vs.* pT1–2 (AUC: 0.730, 95% CI: 0.648 to 0.812). The discrepancy between studies might be attributed to institutional variations and selection bias. However, in general, the current published studies have similar outcomes regarding the difference in metabolic uptake between pT1 and their counterparts (9,17-19,31).

Although SUVmax (continuous) demonstrated good performance, we determined its optimal cutoff to fit clinical applications. The subsequent logistic regression model comprised of SUVmax (categorized), age, and biopsy differentiation achieved better discriminative performance. To our knowledge, this is the first comprehensive baseline model aimed at discriminating invasion depth. Furthermore, the model elements are more objective and less variable compared to EUS, which is technically demanding. Although endoscopic resection or dissection is useful to identify the mucosal or submucosal status, it cannot evaluate muscularis propria invasion due to the risk of severe perforation and delayed treatment. In our opinion, this novel model warrants consideration in future clinical trials.

With regards to the other pathological features, however, the published findings are not consistent. Some studies have reported that primary tumor SUVmax was correlated significantly with node metastasis, tumor differentiation, lymphatic invasion, and perineural invasion (17-20). However, other groups have reported contradictory outcomes (24-26). In our study, although invasion depth (pT2–3 *vs.* pT1) was correlated with SUVmax (Spearman, P<0.0001), and with pN, pG, and LNI categories (Spearman, P=0.016, P=0.001, P<0.001, respectively), SUVmax was not significantly correlated with pN, pG, and LNI categories. However, regarding the correlation between SUVmax and pathological staging (Spearman, P=0.008), we believed that it was the correlation between SUVmax and invasion depth (pT2–3 *vs.* pT1) that worked as a bridge.

To our study, the sharp question is what is the foundation of this bridge, considering the limited spatial resolution of ^{18}F-FDG PET. This is currently not well understood. However, in a previous study in small-sized lung adenocarcinoma, evidence has demonstrated that SUVmax differed significantly between different histological subtypes and correlated with node metastasis (33). Although several studies have reported the differences of SUVmax in invasion depth (9,17-19,31), the biological mechanism remains to be elucidated. We posit that in early-stage cancer, the metabolic activity can provide certain information ahead of the visualization of spatial changes on current imaging modalities.

Previous studies have found that the current modalities are inadequate to determine the cT2 category (9,10,28,29,34,35). Thus, EUS is not mandatory at our institution despite the guideline recommendations (3-5). It is often absent in real-world studies with large cohorts (8), including clinical trials (36). This is one limitation of our study. However, the satisfactory performance of SUVmax (continuous) and our newly proposed model highlight a promising role for metabolic activity in discriminating invasion depth.

There were some other limitations in our study. Firstly, this was a retrospective study with inherent selection bias. However, all patients received baseline PET-CT in our institution, which ensured a consistent protocol and interpretation. Secondly, some preoperative characteristics, such as endoscopic tumor diameter or length, were not included. However, the endoscopic measurement can have some errors in early-stage esophageal cancer. Moreover, in our study, 15 patients had no grading information, which would have certain effects on the model. Finally, although this model showed a satisfactory performance, it was not able to further discriminate against the invasion of muscularis propria (pT2) and adventitia (pT3), though cT3 tumors can often be identified by current modalities (37). This study is, therefore, a step toward addressing the heated debate on cT2N0 esophageal cancer. A prospective trial

led by a multidisciplinary team is necessary to validate the findings and guide clinical practice.

Conclusions

Our novel baseline model comprised of age, biopsy differentiation grades, and primary tumor SUVmax provides a considerable discriminative performance in determining whether or not the muscularis propria is invaded. Further studies are necessary to validate the findings and guide clinical practice for cT2N0 esophageal cancer.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-4430

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-4430

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4430). Dr. HW serves as an unpaid editorial board member of *Annals of Translational Medicine* from Jul 2019 to Jun 2021. The other 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 had been approved by the Institutional Review Board of Zhongshan Hospital Fudan University (HGBB-202006001) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The informed consent was waived as the nature of retrospective studies.

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Supplementary

Table S1 Lymph node metastasis in pathological T categories

Pathological T	pN0	pN1	pN2	pN3	pN+	P value
pT1a	10 (90.9)	1 (9.1)	0	0	1 (9.1)	0.017*§
pT1b	30 (85.7)	5 (14.3)	0	0	5 (14.3)	
pT2	27 (77.1)	4 (11.4)	3 (8.6)	1 (2.9)	8 (22.9)	
pT3	37 (62.7)	18 (30.5)	4 (6.8)	0	22 (37.3)	

*, Statistically significant; §, pT1a, 1b, 2, 3 and pN0, pN+.

Table S2 The distribution of pT2–3 *vs.* pT1 in the stratification of the discriminating model

SUVmax category	bG category	Age category	pT1, n (%)	pT2–3, n (%)
≤7.4	Well or moderately	≤65	15 (93.8)	1 (6.3)
≤7.4	Well or moderately	>65	7 (70.0)	3 (30.0)
≤7.4	Poorly	≤65	5 (71.4)	2 (28.6)
≤7.4	Poorly	>65	0	2 (100.0)
≤7.4	Unknown	≤65	2 (100.0)	0
≤7.4	Unknown	>65	5 (100.0)	0
>7.4	Well or moderately	≤65	6 (20.7)	23 (79.3)
>7.4	Well or moderately	>65	2 (6.9)	27 (93.1)
>7.4	Poorly	≤65	1 (7.1)	13 (92.9)
>7.4	Poorly	>65	1 (5.6)	17 (94.3)
>7.4	Unknown	≤65	1 (25.0)	3 (75.0)
>7.4	Unknown	>65	1 (25.0)	3 (75.0)

SUVmax, maximal standard uptake value; bG category, biopsy differentiation grade category; pT, pathological T (invasion depth).

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