Lymph Node Maximum Uptake of 18F-ALF-NOTA-PRGD2 II PET/CT Predicts Lung Cancer Survival

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Abstract

Background:

Tumor angiogenesis plays a key role in tumor growth, development, and metastasis, so the exploratory study of tumor neovascularization imaging is one of the potential methods to predict survival. This study aims to examine the predictive capacity of ^{18}F-ALF-NOTA-PRGD2 II (denoted ^{18}F-Alfatide II) positron emission tomography (PET)/computed tomography (CT) before antitumor therapy (ATR) in patients with lung cancer.

Results

The median follow-up was 31 (1.3~57.0) months. Among the patients, 6 were lost to follow-up. The overall survival (OS) and progression-free survival (PFS) were 40.0 (3.50~57.0) months and 21.30 (2.0~56.0) months, respectively. The maximum uptake values (SUV_{max}) of the metastatic lymph nodes (SUV_{LN}) and tumor node metastasis (TNM) staging were significant predictors of PFS and OS (all $P<0.05$) in a multivariate Cox regression analysis. Statistical significance was not reached by any other variable in the multivariate analysis. Receiver operating curve (ROC) analysis for survival revealed an area under the curve of 0.93 ($P<0.001$) for SUV_{LN} and 0.96 for the TNM stage ($P<0.001$). The SUV_{LN} and TNM stage cutoff values were 2.50 and II, and their sensitivity, specificity and positive and negative prediction were 77.42%, 80.0% and 82.76% and 74.07%; and 87.10%, 60.0% and 72.97% and 78.95%, respectively. Patients with a lower SUV_{LN} and early stage had a longer PFS and OS (all $P<0.05$).

Conclusions

For lung cancer, low SUV_{LN} and an early TNM stage (≤stage II) as assessed before ATR by ^{18}F-alfatide II PET/CT represents a favorable subgroup with increased PFS and OS.

1. Background

Lung cancer remains the leading cause of cancer incidence and mortality worldwide [1], with 2.1 million new lung cancer cases and 1.8 million deaths predicted in 2018, representing close to 1 in 5 (18.4%) cancer deaths [2]. The treatment methods are surgery, radiotherapy, chemotherapy, targeting and so on; the therapeutic effect is poor, and there is a significant difference in outcomes [3], the main reason for which is the widespread heterogeneity of tumors. The functional molecular imaging of positron emission tomography (PET) can be used to detect the internal characteristics of the whole tumor, such as glucose metabolism, angiogenesis, and hypoxia. With the development of individualized functional metabolic imaging, molecular imaging techniques are promising to predict the prognosis of lung cancer.

Arginine-glycine-aspartic acid peptide (Arg-Gly-Asp, RGD) enables a new kind of positron drug, which is approved for clinical trials and can safely [4] and effectively image the angiogenesis of non-small-cell lung cancer (NSCLC) [5,6] with clarity and desirable image contrast. Tumor angiogenesis plays an important role in regulating growth, local invasiveness, and metastatic potential [7]. Previously, we performed a pilot clinical study that demonstrated the feasibility of using ^{18}F-ALF-NOTA-PRGD2 II (denoted ^{18}F-alfatide II)

PET/computed tomography (CT) to predict the short-term outcome of concurrent chemoradiotherapy in patients with advanced NSCLC [6]. However, there are few reports on whether ^{18}F-alfatide II can predict the long-term survival of lung cancer.

In the present study, we analyze standard uptake values (SUVs) of ^{18}F-alfatide II on PET/CT before antitumor therapy (ATR) and explore its predictive value in overall survival (OS) and progression-free survival (PFS) of patients with lung cancer.

2. Material And Methods

2.1 Patients

Between June 10, 2015, and Dec 28, 2016, a total of sixty-two patients with pathologically confirmed lung cancer were enrolled in the study. This prospective study was approved by the local ethics committee of Shandong Cancer Hospital and Institute, and each patient gave written informed consent before the study. All patients were treated in Shandong Cancer Hospital and satisfied the following criteria: ① diagnosed by histological and imaging examination such as CT or ^{18}F-fluorodeoxyglucose (FDG) PET/CT; ② an Eastern Cooperative Oncology Group (ECOG) score of ≤ 1; ③ clearly measurable metastatic lymph nodes and primary tumors; and ④ no ATR before the ^{18}F-alfatide II PET/CT scan.

2.2 Radiotracer preparation

A simple lyophilization kit for labeling PRGD2 peptide was purchased from the Jiangsu Institute of Nuclear Medicine, and the synthesis process was carried out by reference to the previous study [8]. The radiochemical purity of the ^{18}F-alfatide exceeded 99%, and its specific radioactivity exceeded 37 GBq (1,000 mCi)/μmol.

2.3 PET/CT scanning

Patients were given an intravenous injection of 4.81 MBq/kg (0.12 mCi/kg) ^{18}F-alfatide II and allowed to rest for approximately 60 minutes. Patients were not requested to fast but were requested to specify their recent diet to allow estimation of blood glucose levels. Scanning was performed with an integrated inline PET/CT system (GEMINI TF Big Bore; Philips Healthcare). PET images were acquired from the head to the thigh, and the spiral CT component was obtained with an X-ray tube voltage peak of 120 kV, 300 mAs. A full-ring dedicated PET scan of the same axial range followed. The patients exhibited normal shallow respiration during image acquisition. The images were attenuation-corrected with the transmission data from CT. The attenuation-corrected PET images, CT images, and fused PET/CT images, displayed as coronal, sagittal, and transaxial slices, were viewed on a MEDEX workstation (Beijing, China).

2.4 Image analysis

Two experienced nuclear medicine physicians assessed the ^{18}F-alfatide II PET/CT images visually, referring to the PET fusion and CT images, until consensus was reached. The acquired ^{18}F-alfatide II PET/CT data were transferred into a workstation in the DICOM format. The radiotracer concentration in the region of interest (ROI) was normalized to the injected dose per kilogram of the patients' body weight to derive the

standardized uptake values (SUVs). PET/CT parameters such as the maximum uptake values for the primary tumor (SUV_P) or metastatic lymph node (SUV_{LN}) and the mean SUVs for the mediastinal blood pool (SUV_{blood}) were generated using a vendor-provided automated contouring program.

In addition, tumor-to-background ratios (TBRs) were calculated. Then, the SUV ratios of the primary tumor to blood pool, metastatic lymph node to blood pool, and primary tumor to metastatic lymph node were calculated and are denoted TBR_P, TBR_{LN}, and TBR_{P-LN}, respectively.

2.5 Antitumor therapy

Surgery is the first choice for patients who can be surgically resected. Patients without surgical indications or who are unable to tolerate surgery should choose comprehensive treatment based on radiotherapy and chemotherapy. The chemotherapy scheme is a platinum-based dual-drug.

An intensity-modulated radiotherapy technique (IMRT) or a three-dimensional conformal radiotherapy technique (3D-CRT) was delivered to patients with megavoltage equipment (6 MV). Radiotherapy was given as the conventionally fractionated regimen, 180 cGy to 200 cGy for five days per week, and the total dose administered to patients ranged from 5040 cGy to 6600 cGy (median dose, 6000 cGy).

The pathological type of adenocarcinoma is routine gene detection, and patients with targeted treatment can choose epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) drug therapy.

2.6 End points and assessments

The two primary end points were PFS (as assessed by investigators according to RECIST criteria) and OS in all patients with lung cancer. Patients were followed up by enhanced CT every 6 weeks during treatment, every 2 months in the first year after treatment, and every six months from the second year after treatment. The OS time was from the date of diagnosis to the date of follow-up or death, and the date of PFS was from the date of diagnosis to the date of tumor recurrence or progression.

General case data that might have affected the prognosis of the patients were recorded, including the sex, age, pathological type, and TNM stage (clinical stage or postoperative stage).

2.7 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 20.0 (IBM, Armonk, USA). The Pearson test was used for continuous variables in correlation analysis, and the Spearman test was used for classified variables. Data derived from SUV measurements were analyzed for correlation with survival using receiver operating characteristic (ROC) curve analysis and the Youden index for independencies using the χ^2 test. The PFS and OS were assessed by Kaplan-Meier analysis. Cox regression proportional hazards models were used to obtain hazard ratio estimates of significant parameters derived from univariate analysis using $P \leq 0.1$ for the parameters to qualify for multivariate analysis. All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

3. Results

Of the sixty-two patients (Table 1), 6 cases were lost to follow-up, including 2 cases (1 of stage III and 1 of stage IV) of adenocarcinoma and 4 cases (2 of stage II and 2 of stage III) of squamous cell carcinoma. As of Dec 31, 2019, the median follow-up was 31 months (range 1.30 ~ 57 months), of which 55.36% (31/56) of the patients had died. The median PFS and OS were 21.30 (range 2.0 ~ 56.0) months and 40.0 (range 3.50 ~ 57.0) months, respectively.

Table 1
Baseline Characteristics

Characteristics	**Total (n = 62)**
Median age, years (range)	59.5 (24–84)
Sex	No. (%)
Male	46 (74.19)
Female	16 (25.81)
Histology	No. (%)
Small-cell lung cancer	7 (11.29)
Adenocarcinoma	24 (38.71)
Squamous cell carcinoma	25 (40.32)
NSCLC not otherwise specified	6 (9.68)
Stage	No. (%)
Stage I	8 (12.90)
Stage II	13 (20.97)
Stage III	33 (53.23)
Stage IV	8 (12.90)
Pretreatment SUVs on PET/CT	Mean ± SD
SUV_P	5.18 ± 2.53
SUV_{LN}	2.98 ± 1.68
TBR_{P-LN}	2.15 ± 1.54
TBR_{LN}	3.92 ± 2.29
TBR_P	6.67 ± 3.32

NSCLC, non-small-cell lung cancer; SUV_P, maximum standardized uptake values for primary tumor; SUV_{LN}, maximum standardized uptake values for metastatic lymph node; TBR_P, primary tumor to blood pool; TBR_{LN}, metastatic lymph node to blood pool; TBR_{P-LN}, metastatic lymph node to primary tumor.

Table 2 shows the results of univariable and multivariable linear regression analyses performed to determine which tracked parameters are potential predictors of PFS and OS. Following multivariable analysis, two parameters remained significantly associated with PFS: SUV_{LN} (P = 0.001, HR 1.44, 95% CI 1.17 ~ 1.77) and stage (P = 0.026, HR 1.77, 95% CI 1.07 ~ 2.93); the same applied to OS: SUV_{LN} (P = 0.001, HR 1.43, 95% CI 1.15 ~ 1.78) and stage (P = 0.048, HR 1.66, 95% CI 1.0 ~ 2.76). Of note, differences in sex, histology, SUV_P, TBR_{LN} and TBR_P were significant by univariable assessment but did not retain significance following multivariable analysis. Table 3 shows the correlation between different factors with PFS and OS. SUV_{LN} and stage were negatively correlated with OS and PFS, all P < 0.05.

Table 2
Univariate and multivariate COX regression associating baseline variables and SUVs with PFS and OS

Variable	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Sex	3.534 (1.232 ~ 10.141)	0.019	ND	0.231	3.594 (1.250 ~ 10.335)	0.018	ND	0.108
Age	1.015 (0.983 ~ 1.048)	0.361§	-	-	1.012 (0.978 ~ 1.047)	0.494§	-	-
Histology	0.597 (0.368 ~ 0.968)	0.036	ND	0.85	0.504 (0.301 ~ 0.844)	0.009	ND	0.08
Stage	2.105 (1.359 ~ 3.259)	0.001	1.770 (1.071 ~ 2.926)	0.026*	2.099 (1.343 ~ 3.280)	0.001	1.664 (1.004 ~ 2.760)	0.048*
SUV_P	1.168 (1.040 ~ 1.313)	0.009	ND	0.166	1.174 (1.042 ~ 1.322)	0.008	ND	0.58
SUV_{LN}	1.551 (1.281 ~ 1.877)	< 0.001	1.441 (1.171 ~ 1.772)	0.001*	1.562 (1.282 ~ 1.902)	< 0.001	1.431 (1.152 ~ 1.777)	0.001*
TBR_{P-LN}	0.750 (0.542 ~ 1.038	0.082	ND	0.907	0.748 (0.529 ~ 1.056)	0.099	ND	0.776
TBR_{LN}	1.333 (1.150 ~ 1.546)	< 0.001	ND	0.403	1.318 (1.138 ~ 1.527)	< 0.001	ND	0.519
TBR_P	1.134 (1.031 ~ 1.248)	0.01	ND	0.2	1.140 (1.034 ~ 1.257)	0.009	ND	0.154

Variable	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value

PFS, progression-free survival; *OS*, overall survival; *HR*, hazard ratio; *CI*, confidence interval.

Statistical method: Forward, LR, Cox proportional-hazards model. §Findings with P > 0.10 are not included in the multivariate Cox regression analysis. ND, not displayed; *Significant result.

Table 3
Analysis of correlation between general parameters with OS/PFS and survival risk

	PFS		OS	
	r	P	r	P
Sex	-0.273	0.032	-0.302	0.017
Age	0.011	0.933	0.108	0.402
Histology	0.349	0.005	0.453	< 0.001
Stage	-0.328	0.009	-0.34	0.007
SUV_P	-0.29	0.022	-0.287	0.024
SUV_{LN}	-0.509	< 0.001	-0.501	< 0.001
TBR_{P-LN}	0.263	0.039	0.206	0.109
TBR_{LN}	-0.513	< 0.001	-0.511	< 0.001
TBR_P	-0.357	0.004	-0.385	0.002

The ROC curve analysis of the respective parameters, applying survival as the dichotomous characteristic, revealed a significant area under the curve of 0.93 ($P < 0.001$) for SUV_{LN} (Fig. 1). At a cutoff value of 2.50, derived by the Youden index, the sensitivity, specificity, and positive and negative prediction were 77.42%, 80.0%, and 82.76% and 74.07%, respectively. A significant area under the curve of 0.96 ($P < 0.001$) was found for stage (Fig. 1). At a cutoff value of II, derived by the Youden index, the sensitivity, specificity, and positive and negative prediction were 87.10%, 60.0%, and 72.97% and 78.95%, respectively.

The corresponding Kaplan-Meier curves are given in Fig. 2. Patents with a higher SUV_{LN} (> 2.50) had a PFS of 12.35 ± 12.90 months, whereas that for patients with a lower SUV_{LN} was 34.41 ± 17.02 months ($P < 0.001$). Patients with a higher SUV_{LN} had an OS of 22.88 ± 15.71 months, whereas patients with a lower SUV_{LN} survived 41.91 ± 11.10 months ($P < 0.001$). Patents with a higher stage (≥ stage III) had a PFS of 16.30 ±

15.03 months, whereas that for patients with a lower stage (≤ stage II) was 36.02 ± 18.24 months ($P < 0.001$). Patients with a higher stage (≥ stage III) had an OS of 27.33 ± 15.99 months, whereas patients with a lower stage (≤ stage II) survived 41.26 ± 14.03 months ($P = 0.002$).

4. Discussion

Due to the existence of heterogeneity, the prognosis of lung cancer varies greatly, so it is very important to screen relevant prognostic indicators. With the advancement of image analysis tools, tumor metabolic characteristics can now be assessed rapidly and consistently with no interobserver variability, with the potential for routine assessment in clinical practice. Various molecular imaging techniques have been developed to predict the tumor response to therapy, such as FDG PET [9], ^{18}F-fluorothymidine (FLT) PET [10], ^{18}F-fluroerythronitroimidazole (FETNIM) PET [11] and ^{18}F-fluoromisonidazole (FMISO) PET [12].

Studies on the capabilities of ^{18}F-alfatide II PET/CT have increased in recent years and have shown the advantages of this imaging technique for evaluating chest tumors due to the high in vivo TBR identified in PET imaging [5,8,13]. In this study, sex, histology, stage, SUV_P, SUV_{LN}, TBR_{P-LN}, TBR_{LN} and TBR_P were significantly associated with PFS and OS in the correlation analysis, and SUV_{LN} before treatment in ^{18}F-alfatide II PET/CT and TNM staging were revealed to independently predict PFS and OS of lung cancer through multivariate Cox regression analysis.

Why is ^{18}F-alfatide II PET/CT useful in predicting survival in patients with lung cancer? ^{18}F-alfatide II can bind to integrin αvβ3, which is upregulated in the activated endothelial cells with tumor angiogenesis, with high affinity and specificity. Li et al. reported that ^{18}F-alfatide II uptake on PET/CT can predict the response to antiangiogenic therapy, with higher ^{18}F-alfatide II uptake in tumors predicting a better response to apatinib therapy in a variety of tumors [14]. Luan X et al. found that SUV_P and tumor-to-blood ratios can predict the short-term outcome of concurrent chemoradiotherapy (CCRT) in patients with advanced NSCLC. Patients with lower SUV_P and tumor-to-blood ratios responded to CCRT (all $P < 0.05$) [6].

Lymph metastasis is a well-characterized negative factor affecting survival in cancer patients and reducing tumor staging. Wu C et al. suggested that tumors often drive inflammation both in primary tumor tissue and in tumor-draining lymph nodes, and the inflamed tissue can also show high uptake of ^{18}F-FDG and ^{18}F-alfatide II [4]. Chen et al. found that RGD PET provides better imaging of mediastinal lymph nodes and contralateral metastases than ^{18}F-FDG by providing better imaging [15,16]. Studies have also indicated that SUV_{LN} both in ^{18}F-FDG PET/CT and in ^{18}F-alfatide II PET/CT is influenced by the pathological stage, lymph node states, and tumor differentiation and that it may serve as a useful new parameter for risk stratification with esophageal squamous cell carcinoma [17]. In this study, we found that SUV_{LN} not only is significantly negative associated with PFS and OS but also may be an independent predictor for PFS and OS in patients with lung cancer. The SUVs from ^{18}F-alfatide PET/CT imaging represent the expression of integrin αvβ3: the higher the expression is, the higher the malignant degree of the tumor and the worse the prognosis.

In this study, it was found that the PFS and OS of patients with lung cancer in stages I-II were better than those in stages III-IV. TNM staging is recognized as one of the useful factors for predicting tumor survival [13,18]. Clinical studies have confirmed that ^{18}F-alfatide II PET/CT offers good differentiation and imaging of lung cancer [5,13], breast cancer [19], esophageal cancer [17], glioblastoma [20], brain metastases [21], and other diseases. The sensitivity, specificity, and accuracy of ^{18}F-alfatide PET/CT in the diagnosis of lymph node metastasis of NSCLC were 92.7%, 95.7% and 95.4%, respectively [16]. ^{18}F-alfatide II PET/CT is superior to ^{18}F-FDG PET/CT in the detection of skeletal and bone marrow metastases, with nearly 100% sensitivity for osteolytic, mixed and bone marrow lesions [22]. The above studies show that ^{18}F-alfatide II PET/CT is capable of accurately measuring TNM of lung cancer.

This study has several limitations in addition to the relatively small subgroup sample sizes. First, it was a single-center study. In addition, ^{18}F-alfatide II PET/CT imaging was performed only once in patients with lung cancer before treatment, but not during or after treatment. The idea that changes of SUVs in ^{18}F-alfatide II PET/CT are related to prognosis is a proposition worth exploring. Nevertheless, these shortcomings diminish neither the potential of our findings nor the importance of dedicated prospective investigations to corroborate these findings.

Conclusion

In this prospectively study, it was confirmed that the high uptake of SUV_{LN} in ^{18}F-alfatide II PET/CT predicted poor PFS and OS in patients with lung cancer. This threshold could serve as a selection criterion for a new subgroup of lung cancer patients with poor prognosis.

Abbreviations

^{18}F-Alfatide: ^{18}F-ALF-NOTA-PRGD2; PET: positron emission tomography; CT:computed tomography; ATR: antitumor therapy; NSCLC: non-small-cell lung cancer; SUV_P: maximum standardized uptake values for primary tumor; SUV_{LN}: maximum standardized uptake values for metastatic lymph node; TBR_P: primary tumor to blood pool; TBR_{LN}: metastatic lymph node to blood pool; $TBR_{P\text{-}LN}$: metastatic lymph node to primary tumor; SUV_{blood}: mean uptake values of the blood pool; OS: overall survival; PFS: progression-free survival; TNM: tumor node metastasis; ROC: Receiver operating curve; FDG: fluorodeoxyglucose; IMRT: intensity-modulated radiotherapy technique; 3D-CRT: three-dimensional conformal radiotherapy technique; EGFR-TKI: epidermal growth factor receptor-tyrosine kinase inhibitor.

Declarations

Ethics approval and consent to participate

This prospective study was approved by the local ethics committee of Shandong Cancer Hospital and Institute, and each patient gave written informed consent before the study.

Consent for publication

All the personal data involved in this article have been signed with informed consent.

Availability of data and material

The datasets used and/or analyzed during the current study are available form the corresponding author on reasonable request.

Competing interests: None.

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Author contributions

Shuanghu Yuan and Yongzheng Wang: Conceptualization, Methodology. Yuchun Wei: Data curation, Writing-Original draft preparation. Li Ma and Jinsong Zheng: Visualization, Investigation, Software. Yanqing Pei: Statistical analysis, Xueting Qin: Follow-up care. Xiaohui Luan and Yue Zhou: Case collection and supervision.

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Figures

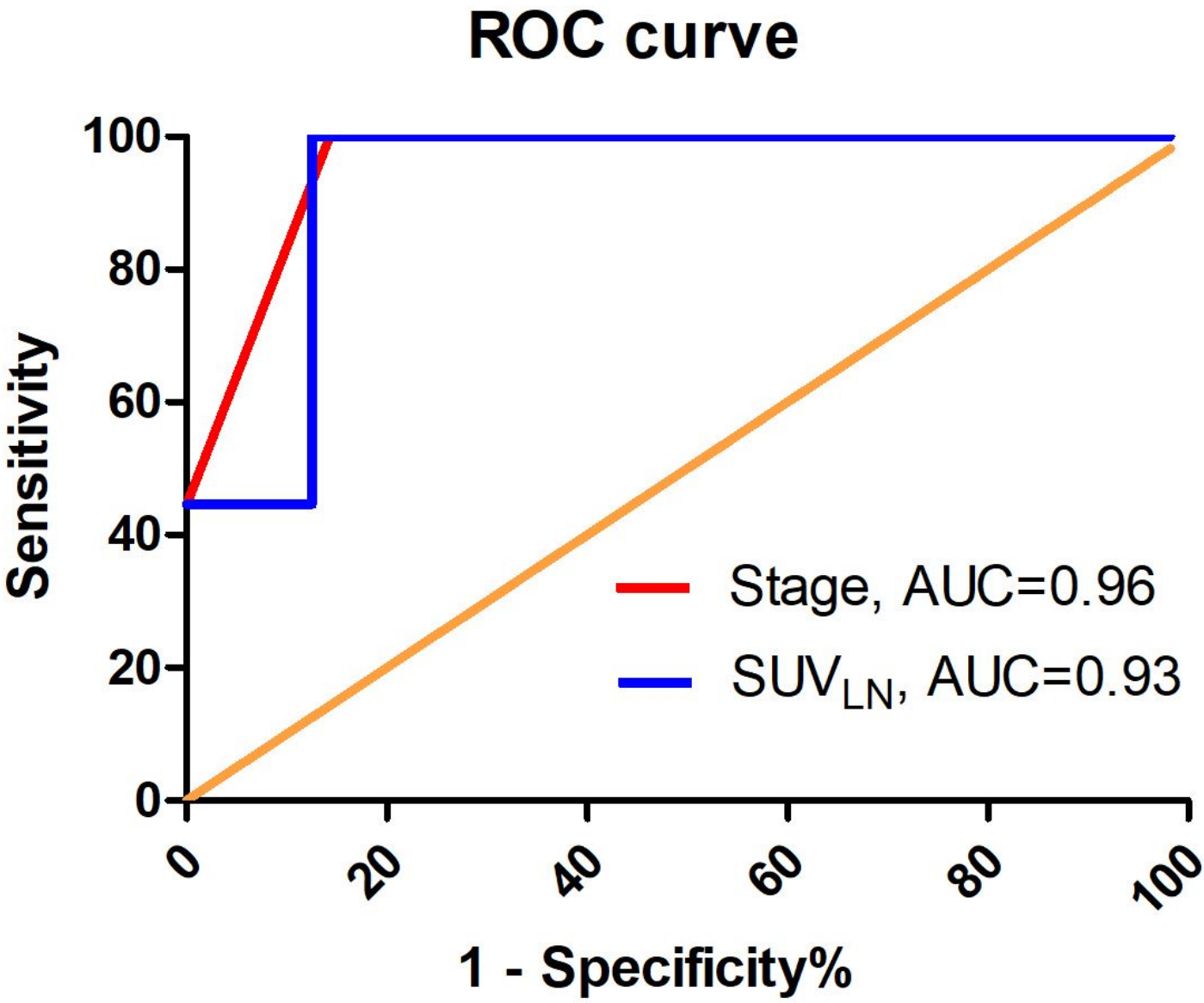
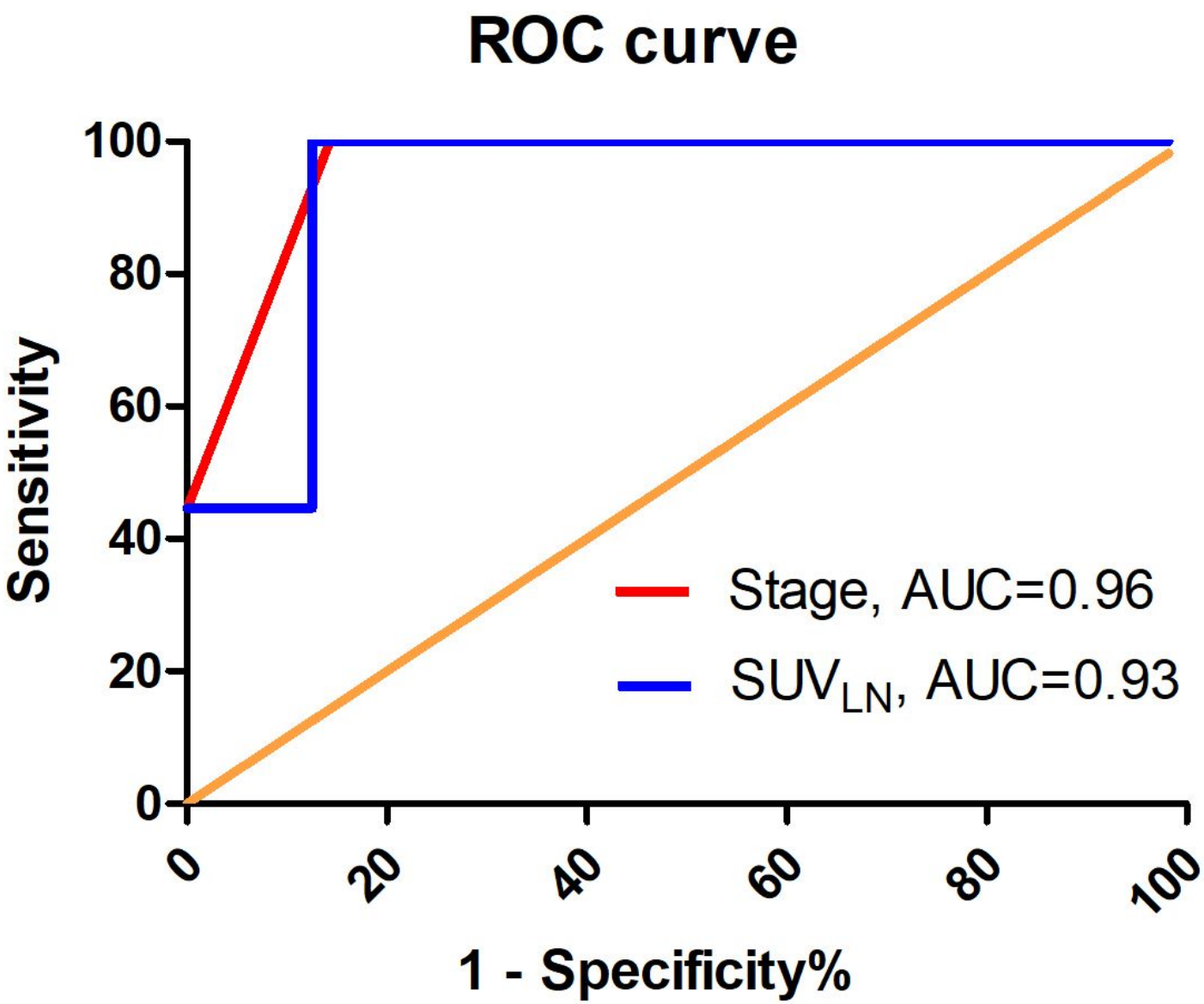


Figure 1

ROC curve analysis of the TNM stage and SUVLN, applying survival as the dichotomous characteristic, revealing a significant area under the curve of 0.93 (P<0.001) for SUVLN and 0.96 (P<0.001) for stage.



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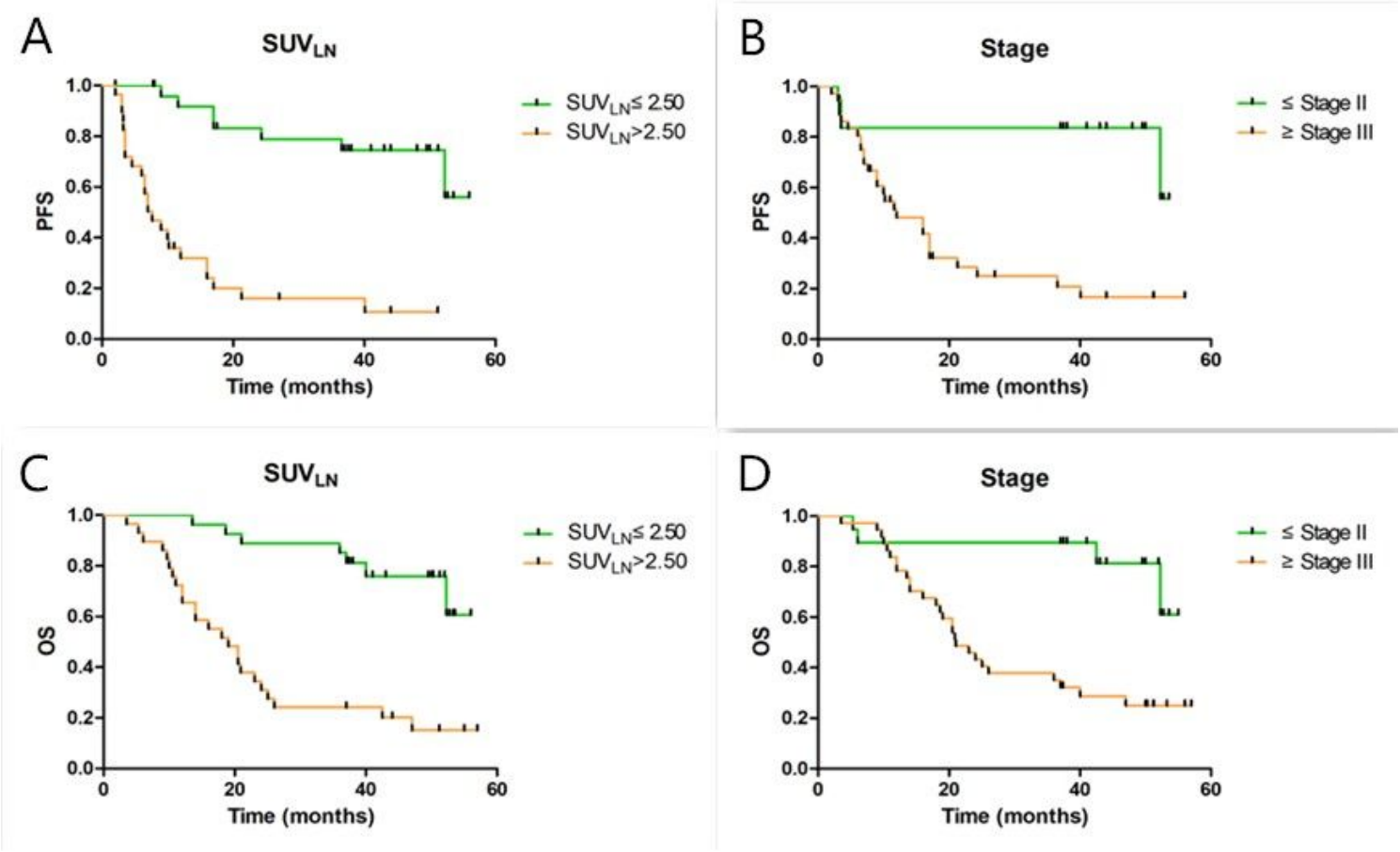
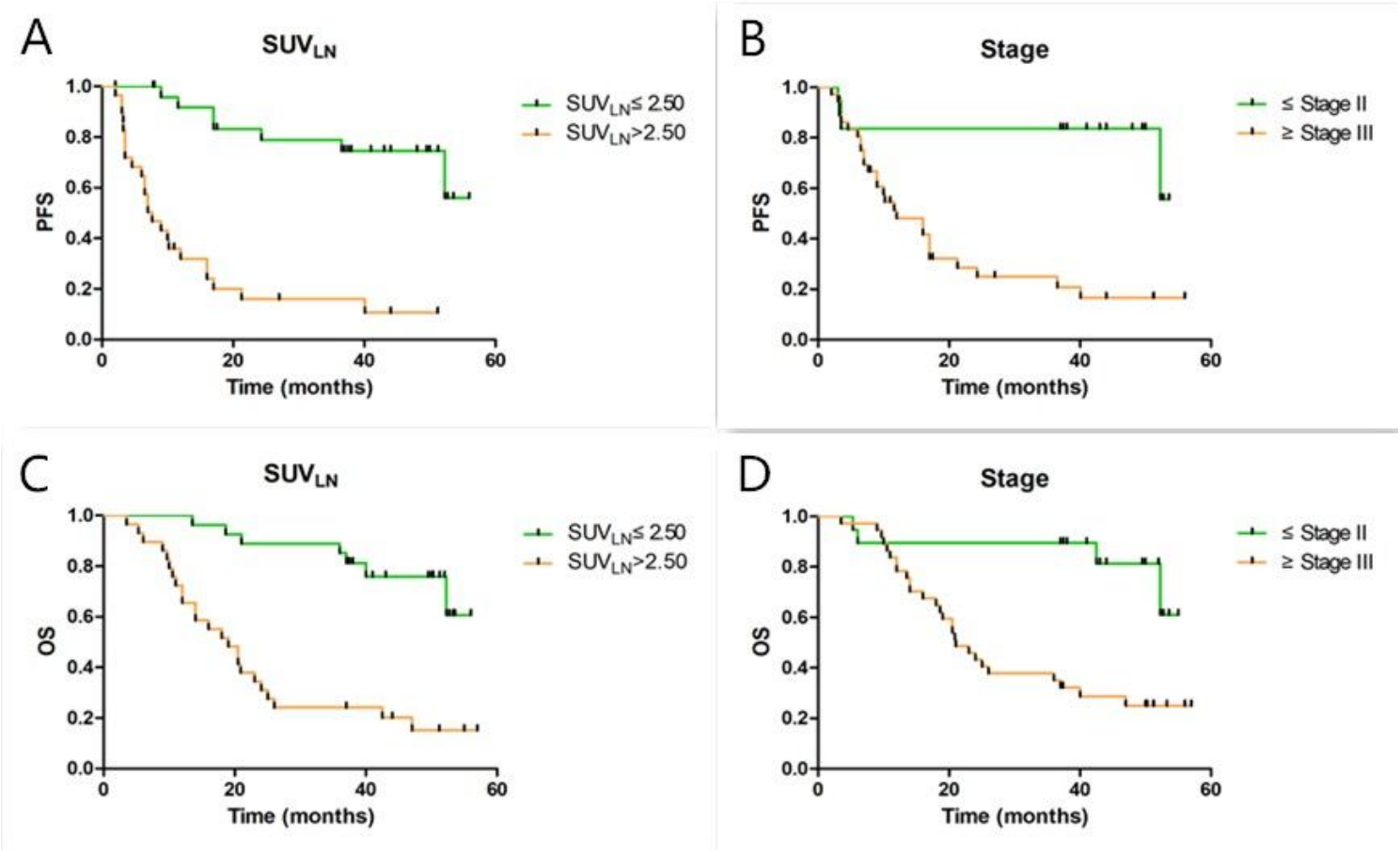


Figure 2

A shows that patents with a higher SUVLN (>2.50) had a worse PFS of 12.35±12.90 months, whereas that for patients with a lower SUVLN was 34.41±17.02 months (P<0.001). B shows that patents at a higher stage (≥stage III) had a PFS of 16.30±15.03 months, whereas patients at a lower stage (≤stage II) was 36.02±18.24 months (P<0.001). C shows that patients with a higher SUVLN had a worse OS of 22.88±15.71 months, whereas patients with a lower SUVLN survived 41.91±11.10 months (P<0.001). D shows that patients at a higher stage (≥stage III) had an OS of 27.33±15.99 months, whereas patients at a lower stage (≤stage II) survived 41.26±14.03 months (P=0.002).



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