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Limited Prognostic Value of SUV_{max} Measured by F-18 FDG PET/CT in Newly Diagnosed Small Cell Lung Cancer Patients

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Keywords

FDG PET/CT · Small cell lung cancer · Prognosis · Survival · SUV_{max}

Summary

Background: The purpose of this study was to evaluate the prognostic value of the maximum standard uptake value (SUV_{max}) measured by 18-F fluoro-2-deoxy-d-glucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) in newly diagnosed small cell lung cancer (SCLC) patients. **Methods:** We reviewed the medical records of newly diagnosed SCLC patients who were given a histological diagnosis from June 2008 to June 2014. 82 patients who satisfied the inclusion criteria were enrolled for final analysis (male n = 75, female n = 7). The relationship between SUV_{max} and overall survival (OS) and progression-free survival (PFS) was evaluated. **Results:** Median follow-up was 25.0 months (range 11.6–55.5 months). The median OS was 11.2 months (range 1.6–55.5 months), and the median PFS was 6.1 months (range 0.9–55.5 months). Survival analysis showed no statistical differences in OS and PFS between high and low SUV_{max} groups. **Conclusion:** This study does not support the use of SUV_{max} of pretreatment F-18 FDG PET/CT scans as a prognostic tool for patients with SCLC.

Introduction

Small cell lung cancer (SCLC) accounts for approximately 15% of all diagnosed lung cancer [1, 2]. When compared with non-small cell lung cancer (NSCLC), SCLC generally has a more rapid doubling time, a higher growth fraction, and earlier development of widespread metastases, all of which lead to frequent relapse and poor prognosis despite high sensitivity to initial chemotherapy and radiotherapy [3–5].

The introduction of chemotherapy to the treatment of SCLC led to significant improvements in median and 5-year survival rates in the 1970s through 1990s, but recently survival seems to have reached a plateau for both localized and advanced SCLC [6, 7].

SCLC patients are classified as having either limited disease (LD) or extensive disease (ED), for the purpose of treatment. LD is defined as disease confined to the ipsilateral hemithorax which can be encompassed by a single radiotherapy port [8].

Recently, it has been advocated to stage SCLC similar to NSCLC according to the tumor, node, metastasis (TNM) system, where in general stages I–III are treated with chemoradiotherapy and stage IV with chemotherapy alone [7, 9]. Also, a number of parameters have been studied as possible prognostic factors in SCLC, but none are eligible enough to change treatment options [9–11].

Although F-18 fluoro-2-deoxy-d-glucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) is used in SCLC patients, little is known regarding its clinical utility [12, 13]. F-18 FDG uptake in the primary tumor is thought to correlate with poor survival in several types of malignancies on the basis of previous studies [14–17]. Conventional F-18 FDG PET alone or PET/CT have been also shown to have superior staging accuracy in NSCLC over CT alone [18]. The current study aimed to investigate the prognostic value of F-18 FDG PET/CT in newly diagnosed SCLC patients.

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Material and Methods

Patients

From June 2008 to June 2014, newly diagnosed SCLC patients were enrolled in the current study. All staging workups comprising history taking, physical examination, hematologic and biochemical test, chest X-ray, chest CT, bronchoscopy with biopsy, bone scintigraphy, brain CT or magnetic resonance imaging (MRI), and F-18 FDG PET/CT were completed before initiation of therapy. We retrospectively reviewed medical records including age, conventional stage, ECOG performance status, lactate dehydrogenase (LDH), pleural effusion, sex, and maximum standard uptake value (SUV_{max}). The following inclusion criteria were used: i) histologically or cytologically confirmed diagnosis of primary SCLC; ii) adequate clinical data in the medical record; and iii) at least 1 cycle of chemotherapy. The medical records of 82 patients were analyzed. The study was approved by the institutional review board, and written informed consent was waived.

Treatment and Response Evaluation

Patients with LD were treated with combined concurrent chemoradiotherapy, and patients with ED were treated with chemotherapy alone. Radiotherapy to the chest started with chemotherapy cycle 1 or 2 with 1.8–2.0 Gy once daily in 30 fractions (patients with LD). Both LD and ED patients underwent chemotherapy regimens containing platinum with either etoposide or irinotecan as first-line treatment. Both regimens were repeated every 3 weeks. Patients who showed a complete or partial response after initial therapy received prophylactic cranial irradiation. Response evaluation was done with a CT scan every 2 cycles according to the Response Evaluation Criteria in Solid Tumors (RECIST) [19]. After completion of treatment, patients were evaluated with CT scans every 3months for 3 years, every 6 months in the following year, and annually thereafter.

F-18 FDG PET-CT Imaging

All patients fasted for at least 6 h before undergoing F-18 FDG PET/CT. Serum glucose levels were less than 120 mg/dl before F-18 FDG administration. F-18 FDG PET/CT imaging studies were performed 60 min after intravenous injection of F-18 FDG. Patients were examined with 2 different PET/CT scanners (Biograph™ 40, Siemens, Knoxville, TN, USA). Emission scan time per bed position was 3 min; 6 bed positions were acquired. PET data were obtained using a high resolution whole body scanner with an axial field of view of 21.6 cm. The average axial resolution varied between 2.0 mm full width at half maximum in the center and 2.4 mm at 28 cm. The average total PET/CT examination time was 20 min. Attenuation correction was performed for all patients with iterative reconstruction. PET/CT images were analyzed in 3 different planes: axial, sagittal, and coronal.

Image Analysis

The F-18 FDG PET/CT images were independently reviewed by 2 experienced nuclear physicians, and any disagreement was resolved by consensus. The SUV_{max} of the primary lesion in each individual patient was selected to perform the statistical analyses. To calculate SUV_{max}, manually defined circular regions of interest (ROI) were drawn on the attenuation-corrected emission images throughout axial planes in which a suspicious lesion could be delineated.

Statistical Analysis

Clinical and demographic characteristics were compared using the chi-square test. Response of treatment according to SUV_{max} was compared using the Fisher's exact test. To evaluate the prognostic value of F-18 FDG PET/CT, overall survival (OS) and progression-free survival (PFS) were chosen as end points. OS was defined as the time interval from the date of F-18 FDG PET/CT scanning to the date of death from any cause. PFS was defined as the time interval from the date of F-18 FDG PET/CT scanning to the date of the first progression or death from any cause without previous progression. Survival curves stratified by SUV_{max} and clinical parameters were estimated by the Kaplan-Meier method. The median value of SUV_{max} was used to compare the OS and PFS. All clinical parameters were considered as categorical variables. The Cox proportional hazards model was used for a multivariate analysis of survival which was conducted with variables with a p value less than 0.2. All statistical analyses were performed using MedCalc® (MedCalc Software, Mariakerke, Belgium) for Windows version 12.0.4.0, and a p value less than 0.05 was regarded as significant.

Table 1. Clinical characteristics

Clinical characteristics	Patients, n (%)	SU_{Vmax}		p
		low (< 8.2)	high (≥ 8.2)	
Gender				0.94
Male	75 (91.5)	37	38	
Female	7 (8.5)	3	4	
Age, years				0.81
< 65	37 (45.1)	17	20	
≥ 65	45 (54.9)	23	22	
ECOG				0.69
0–1	68 (82.9)	32	36	
2–4	14 (17.1)	8	6	
LDH, IU/l				0.27
< 472	45 (54.9)	19	26	
≥ 472	37 (45.1)	21	16	
Stage				0.09
LD	31 (37.8)	11	20	
ED	51 (62.2)	29	22	
Pleural effusion				0.69
Positive	28 (34.1)	15	13	
Negative	54 (65.9)	25	29	
Total	82 (100)	40	42	

SUV_{max} = Maximum standard uptake value; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; LD = limited disease; ED = extensive disease.

Results

Clinical Characteristics

The clinical and pathologic characteristics of the 82 patients are shown in table 1. 75 patients were male and 7 were female; the median age was 65 years (range 44–77 years). The SUV_{max} ranged between 2.8 and 25.4 with a median value of 8.2 (95% confidence interval 7.1–8.8). Of the enrolled patients, 31 had LD and 51 had ED. When patients were divided into 2 groups according to the SUV_{max}, none of clinical data including age, conventional stage, ECOG performance status, LDH, pleural effusion, and sex showed statistically significant differences.

Overall Survival

The median follow-up for the patients was 25 months (range 11.6–55.5 months). At the time of analysis, 10 (12%) patients were still alive. The median OS was 11.2 months (range 1.6–55.5). The high SUV_{max} group showed longer survival than the low SUV_{max} group (median OS 15 vs. 11 months; p = 0.37). However, no significant statistical difference was found in OS between the high and low SUV_{max} group. The univariate analysis of OS determined that

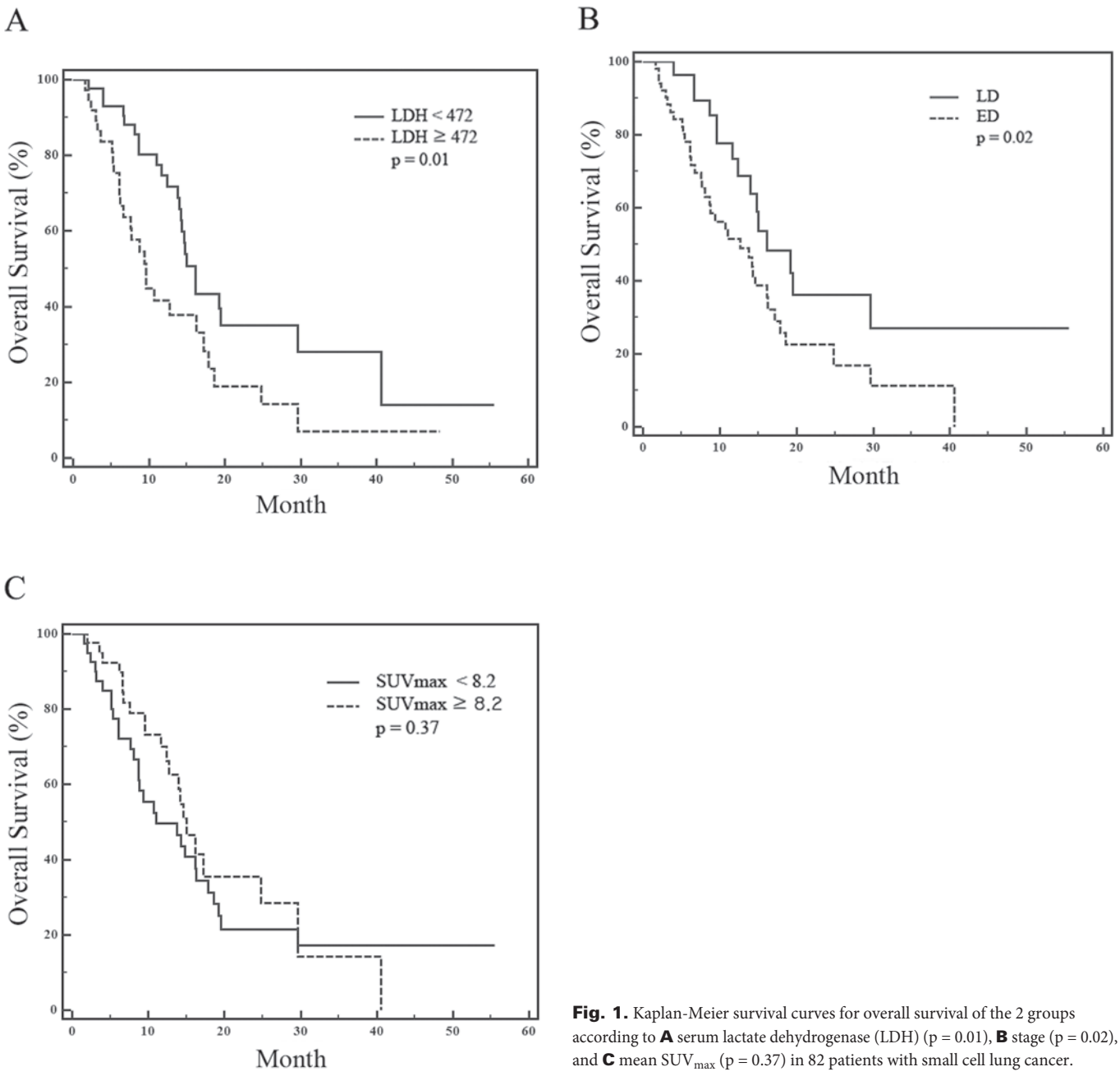

Fig. 1. Kaplan-Meier survival curves for overall survival of the 2 groups according to **A** serum lactate dehydrogenase (LDH) (p = 0.01), **B** stage (p = 0.02), and **C** mean SUV_{max} (p = 0.37) in 82 patients with small cell lung cancer.

conventional stage and LDH were the independent prognostic factors. Patients with LD showed significantly longer survival compared with patients with ED (16.2 vs. 12.7 months; p = 0.02) (fig. 1 B). LDH ≥ 472 IU/l was associated with poor OS (16.2 vs. 9.6 months; p = 0.01) (fig. 1 A). However, age, ECOG performance status, pleural effusion, sex, and SUV_{max} (fig. 1 C) were not associated with prognosis (table 2). In the multivariate analysis, increased LDH, ED, and an ECOG performance status > 2 were significant predictors for poor OS.

Progression-Free Survival

The median PFS was 6.1 months (range 0.9–55.5 months), and there was no significant difference between the 2 groups according to the SUV_{max} (median PFS 6.8 vs. 5.3 months; p = 0.87) (fig. 2 C). In the univariate analysis of PFS, sex and age of the patients were demonstrated as the significant predictors. Female patients showed significantly longer PFS compared with male patients (13 vs. 6.1 months; p = 0.05) (fig. 2 A). Age older than 65 was associated with poor PFS (7.1 vs. 5.9 months; p = 0.03) (fig. 2 B). In the multivariate analysis, none of the clinical parameters was associated with poor PFS (table 3).

Subgroup Analysis by Stage

No significant statistical difference was noted according to SUV_{max} in OS when patients were divided into 2 groups according to stage. Patients with LD and high SUV_{max} showed shorter median

Table 2. Univariate and multivariate analysis of overall survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Gender				
Male	2.40 (1.08–5.49)	0.11		N/A
Age				
≥ 65 years	1.50 (0.90–2.74)	0.09	1.47 (0.84–2.59)	0.17
ECOG				
2–4	1.78 (0.79–4.01)	0.07	2.11 (1.06–4.18)	0.03
LDH				
≥ 472 IU/l	1.96 (1.11–3.48)	0.01	1.98 (1.12–3.49)	0.01
Stage				
ED	1.94 (1.12–3.38)	0.02	1.90 (1.03–3.51)	0.03
Pleural effusion				
Positive	1.22 (0.68–2.19)	0.48		
SUV_{max}				
≥ 8.2	0.78 (0.45–1.35)	0.37		

HR = Hazard ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ED = extensive disease; N/A = not available; SUV_{max} = maximum standard uptake value.

Table 3. Univariate and multivariate analysis of progression-free survival

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Gender				
Male	2.14 (1.15–3.98)	0.05	2.10 (0.88–5.02)	0.09
Age				
≥ 65 years	1.58 (1.01–2.48)	0.03	1.39 (0.87–2.23)	0.16
ECOG				
2–4	1.03 (0.55–1.93)	0.90		
LDH				
≥ 472 IU/l	1.41 (0.88–2.24)	0.12	1.45 (0.90–2.32)	0.12
Stage				
ED	1.37 (0.87–2.15)	0.17		N/A
Pleural effusion				
Positive	1.11 (0.69–1.79)	0.64		
SUV_{max}				
≥ 8.2	0.96 (0.61–1.50)	0.87		

HR = Hazard ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; LDH = lactate dehydrogenase; ED = extensive disease; N/A = not available; SUV_{max} = maximum standard uptake value.

OS than the low SUV_{max} group but without statistical significance (median OS 14 vs. 19.5 months; p = 0.50) (fig. 3 A). On the other hand, patients with ED and high SUV_{max} showed longer median OS than the low SUV_{max} group (median OS 16.2 vs. 8.8 months; p = 0.13) (fig. 3 B); however, there was no statistical significance either. Similar findings were replicated in PFS. Patients with LD and high SUV_{max} showed shorter median OS than the low SUV_{max} group (median OS 6.8 vs. 7.9 months; p = 0.32) (fig. 3 C) whereas patients with ED and high SUV_{max} showed longer median OS than the low SUV_{max} group (median OS 6.9 vs. 4.7 months; p = 0.49) (fig. 3 D); however, there also was no statistical significance.

Discussion

In this retrospective study, we attempted to investigate whether the SUV_{max} measured by F-18 FDG PET/CT has prognostic value in newly diagnosed SCLC patients. However, the findings of the current study could not support a prognostic role of F-18 FDG PET/CT SUV_{max} in this group of patients.

Little is known about the prognostic value of SUV_{max} in SCLC since only a limited number of studies have been conducted so far. Moreover, there have been contradictory reports as to whether F-18 FDG uptake can predict prognosis in SCLC. 1 study found significantly higher SUV_{max} in patients with stage IV disease com-

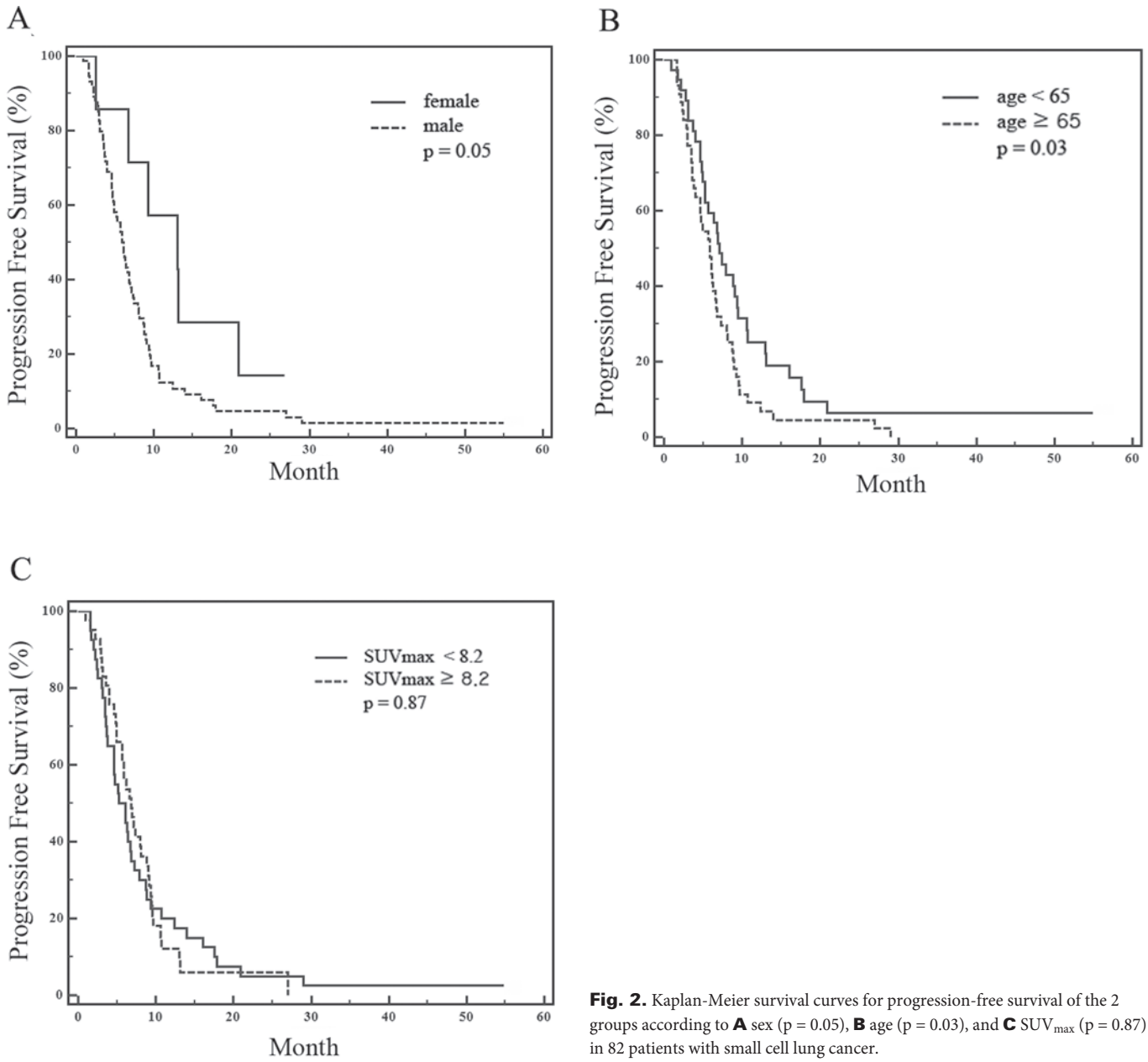

Fig. 2. Kaplan-Meier survival curves for progression-free survival of the 2 groups according to **A** sex (p = 0.05), **B** age (p = 0.03), and **C** SUV_{max} (p = 0.87) in 82 patients with small cell lung cancer.

pared to stage I–III disease [20]. However, a recent study reported no significant survival difference between high and low SUV_{max} groups divided by a mean SUV_{max} of 10.4 [21].

Several possible explanations could be suggested for the observed limited prognostic value in SCLC patients. SCLC belongs to the category of pulmonary neuroendocrine tumor, along with carcinoids and large-cell neuroendocrine carcinoma, according to morphological, biological, and clinical properties [22]. Neuroendocrine tumors typically have a wide range of cellular differentiation [23]. Moreover, F-18 FDG PET/CT is of limited value in well-differentiated neuroendocrine tumors because these tumors have a near normal glucose turnover [24]. Because high FDG uptake is usually associated with more aggressive tumors and a less favorable prognosis, the usefulness of 18F-FDG in imaging neuroendocrine tumors depends to some extent on the grade of differentiation and biologic aggressiveness [24–26]. The SUV_{max} only represents 1-pixel ROI corresponding to the maximum pixel value in the tumor [27]. Furthermore, SCLC is characterized by early dissemination and a high growth fraction. Therefore, the high extent of malignancy at the time of diagnosis makes SCLC not a suitable candidate for use of SUV_{max} as a prognostic factor.

Because of the retrospective design of the study, several limitations are present. The patient population was too small and heterogeneous to really draw clinically relevant conclusions. The relative heterogeneity of the chemotherapy regimens depending on various clinical considerations could have affected the clinical outcome of the SCLC patients in the current study. Furthermore, the SUV_{max} can be influenced by compounding factors such as metabolic status

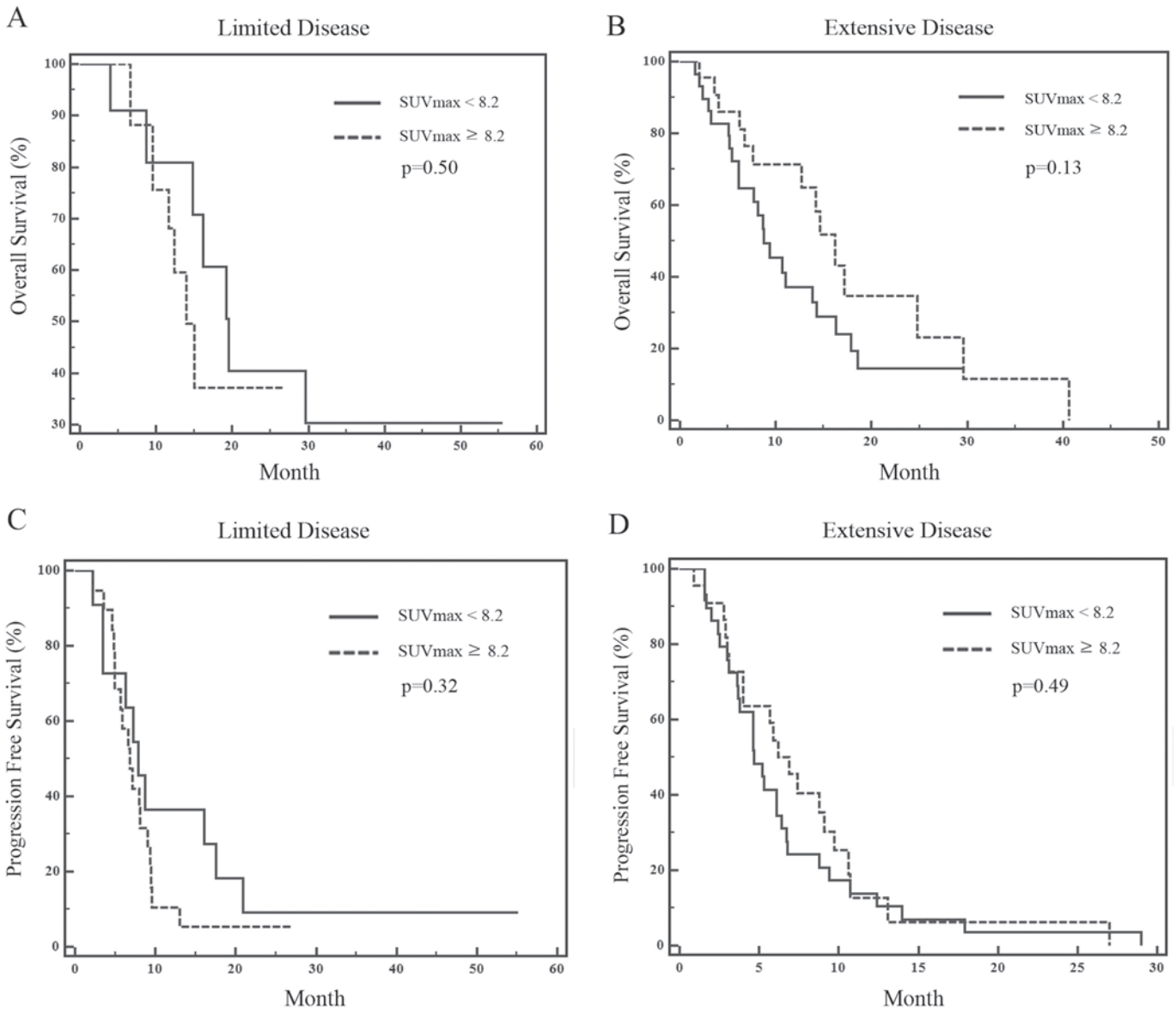

Fig. 3. Kaplan-Meier survival curves for overall survival according to the SUV_{max} in **A** limited disease (p = 0.50) and **B** extensive disease (p = 0.13), and progression-free survival according to the mean SUV_{max} in **C** limited disease (p = 0.32) and **D** extensive disease (p = 0.49) in 82 patients with small cell lung cancer.

of the patient, tumor size, time interval between tracer injection and scan acquisition, and reconstruction parameters used [28]. However, in this study, all scans were performed in the same institution according to the same set of protocols so that such variability can be disregarded. Although we used 2 different PET/CT scanners, which could have affected the reproducibility of this study, daily quality control of the scanners can minimize the impact of such a limitation.

Conclusion

In this study, the SUV_{max} of F-18 FDG PET/CT showed limited prognostic value in patients with newly diagnosed SCLC. Further investigation into the prognostic role of metabolic parameters in SCLC patients is warranted.

Disclosure Statement

The authors declare no conflicts of interest related to the current study.

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