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Prognostic value of ^{18}F-FDG-PET/CT parameters in patients with pancreatic carcinoma
A systematic review and meta-analysis

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Abstract

Background: The identification of pancreatic carcinoma (PC) patients with poor prognosis is a priority in clinical oncology because of their high 5-year mortality. However, the prognostic value of pretreatment ^{18}F-fluorodeoxyglucose (^{18}F-FDG)- positron emission tomography (PET)/computed tomography (CT) parameters in PC patients is controversial and no consensus exists as to its predictive capability. This meta-analysis was performed to comprehensively explore the prognostic significance of ^{18}F-FDG-PET/CT parameters in patients with pancreatic carcinoma.

Methods: Extensive literature searches of the PubMed, Embase, Web of Science, and Cochrane Library databases were conducted to identify literature published until March 5, 2017. Comparative analyses of the pooled hazard ratios (HRs) for event-free survival (EFS) and overall survival (OS) were performed to assess their correlations with pretreatment maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). Either the fixed- or the random-effects model was adopted, depending on the heterogeneity observed across studies. Subgroup and sensitivity analyses were performed to assess the robustness of the results.

Results: Sixteen studies including 1146 patients were identified. The pooled HRs for the probability of EFS were 1.90 (95% confidential interval (CI): 1.48–2.45) for SUVmax, 1.76 (95% CI: 1.20–2.58) for MTV, and 1.81 (95% CI: 1.27–2.58) for TLG. The pooled HRs for the probability of OS were 1.21 (95% CI: 1.12–1.31) for SUVmax, 1.56 (95% CI: 1.13–2.16) for MTV, and 1.70 (95% CI: 1.25–2.30) for TLG. A slight publication bias was detected using Begg test. After adjustment using the trim and fill procedure, the corrected HRs were not significantly different. The results of the subgroup analyses by SUVmax, MTV, and TLG showed that these factors may have similar prognostic significance.

Conclusion: ^{18}F-FDG-PET/CT parameters, such as SUVmax, MTV, and TLG, may be significant prognostic factors in patients with pancreatic carcinoma. ^{18}F-FDG-PET/CT imaging could be a promising tool to provide prognostic information for these patients.

Abbreviations: CI = confidence interval, DFS = disease-free survival, DMFS = disease metastasis-free survival, EFS = event-free survival, HR = hazard ratio, LAPC = locally advanced pancreatic cancer, MTV = metabolic tumor volume, OS = overall survival, PC = pancreatic carcinoma, PFS = progress-free survival, ROC = receiver operating characteristic curve, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis, VOI = volume of interest.

Keywords: pancreatic carcinoma, PET, SUVmax, volume

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1. Introduction

Pancreatic carcinoma (PC) is the fourth most common cause of cancer-related mortality in the United States, with a 5-year survival rate of less than 5%; additionally, the incidence of this cancer is steadily increasing in most countries.[1] At initial diagnosis, 30% of patients already have locally advanced pancreatic cancer (LAPC),[2] and less than 20% of cases will be considered for curative surgery;[3,4] furthermore, more than 50% of patients present with metastatic disease and may only be treated with palliative chemotherapy.[5] Among the patients who survive surgical resection, the 5-year survival rate remains low at approximately 15% to 40%.[6] Accurate predictors would be helpful and invaluable in stratifying patients for disease management, including predicting outcomes.

Glucose analogue ^{18}F-fluorodeoxyglucose (^{18}F-FDG) has become extensively used as a tracer of positron emission tomography/computed tomography (PET/CT) in clinical cancer imaging.[7] The most widely used PET-derived parameter designed to measure tracer accumulation in PET is the maximum standardized uptake value (SUVmax), which quantifies the rate of glucose metabolic uptake in tumor cells.[8,9] Several studies have shown ^{18}F-FDG-PET/CT to play a significant role in the diagnosis, staging and restaging, planning of treatment, evaluation of response to treatment, and prognosis in PC.[10–12] Recent studies have supported the use of volumetric parameters, such as metabolic tumor volume (MTV) and FDG total lesion glycolysis (TLG), which have also proven to be beneficial as prognostic factors in PC.[13–15] While SUVmax, a single pixel value within a region of interest, is subject to considerable noise,[16] other FDG-PET parameters, such as MTV and TLG, lend support to its continued use as a summary of tumor FDG activity in PC that may be used in studies to predict disease progression. Although the impact of ^{18}F-FDG-PET/CT parameters has been evaluated in patients with pancreatic carcinoma in previously published studies, there is little knowledge regarding the consistency of SUV and volumetric PET parameters in the prediction of PC prognosis.

Therefore, we conducted a systematic literature review and meta-analysis to identify, appraise, and synthesize results from all available studies and provide an unprecedented summary to address the prognostic value of pretreatment SUVmax, MTV, and TLG in patients with PC.

2. Materials and methods

2.1. Literature search

We searched the PubMed, EMBASE, Web of Science, and Cochrane Library databases for studies published in English language until March 5, 2017. The search strategy involved using on the following terms: ("pancreatic" or "pancreas" or "pancreatic ductal adenocarcinoma) AND ("neoplasm" or "tumor" or "cancer" or "carcinoma" or "adenocarcinoma") AND ("positron emission tomography" OR "FDG" or "positron emission tomography-computed tomography" OR "positron emission tomography computed tomography" OR "PET" OR "PET-CT" OR "PET CT" OR "PET/CT" OR "fluorodeoxy-yglucose") and ("prognostic" OR "prognosis" OR "predictive" OR "survival" OR "outcome"). Additionally, the reference lists of relevant studies were scrutinized to identify additional eligible studies. We performed all the analyses based on previously published studies, thus no ethical approval was required.

2.2. Selection of studies

The inclusion criteria included the following: patients were pathologically diagnosed with PC; case control or cohort study; at least 1 ^{18}F-FDG-PET/CT scan performed before and/or in treatment; at least 1 relevant prognosis factor was assessed, such as overall survival (OS), disease-free survival (DFS), event-free survival (EFS), progress-free survival (PFS), disease metastasis-free survival (DMFS) or EFS; hazard ratios (HRs) and 95% confidence intervals (CIs) were available or able to be calculated based on data from the original articles; and published in English. Articles meeting the following criteria were excluded: in vitro studies and animal experiments; reviews, comments, letters, case reports, or conference abstracts; insufficient data available to calculate the HRs and 95% CIs; research limited to investigating the role of PET-CT scans in diagnosis and tumor staging, and prognostic parameter data were not provided; and less than 10 patients were included. When eligible studies were published more than once, only data from the most complete or recent studies were included. Two authors (JC and HZ) independently evaluated the studies for eligibility. When data from the same patient population were published more than once, only the most recent or complete report was included in the review. Any discrepancies were resolved by consensus.

2.3. Data extraction and quality assessment

Data were independently extracted from each article by 2 reviewers and recorded on a standardized form. Univariate and multivariate HRs and their 95% CIs, P values for the log-rank test, and necessary statistics such as 95% CIs, the number of events, and the number included in each group assessed using Kaplan–Meier curves were recorded. Then, we used the methods suggested by Parmar et al and Williamson et al to convert these data into logHRs and SEs.[17,18] HR values were calculated by applying a spreadsheet and using the methods suggested by Tierney et al.[19] Relevant files or supplementary files included with the publications were also carefully scrutinized to identify available data.

The following data were also extracted from the publications: first author, year of publication, country of origin, study period, follow-up duration, age of patients, number of patients, and study design. The technical details of the ^{18}F-FDG-PET/CT examinations, such as the PET/CT scanner used, duration of fasting before FDG injection, preinjection blood glucose level, radiation doses of FDG, and interval periods, were also extracted.

We assessed the quality of each included article using the Newcastle–Ottawa Scale (NOS) (www.ohri.ca/programs/clinical_epidemiology/oxford.asp), a comprehensive, systematic reviewing tool that was designed for retrospective and prospective studies. Studies with scores ≥6 points on the NOS were considered high-quality studies and included in this meta-analysis. Discrepancies were resolved by consensus (Table 1).

2.4. Statistical analysis

In this meta-analysis, we followed the same methodology as used in the previous study.[20]The primary endpoint was EFS. DFS, PFS, DMFS in the included studies were obtained as primary outcomes and newly defined as EFS, which was measured from the date of initiation of therapy to the date of recurrence or metastasis.[21] The secondary endpoint was OS, which was measured from the date of initiation of therapy to the date of

Table 1

Methodological quality for potentially included studies according to Newcastle–Ottawa scale in this meta-analysis.

1st author (Ref)	Selection (score)	Comparability (score)	Outcome/exposure (score)	Total (score)
Im	3	1	3	7
Pimiento	4	2	3	9
Cui	4	2	3	9
Wang	3	1	2	6
Chirindel	3	1	3	7
Yamamoto	3	1	3	7
Choi	3	1	2	6
Dholakia	3	1	3	7
Lee	3	2	3	8
Xu	4	1	3	8
Kitasato	3	1	3	7
Choi	3	1	2	6
Moon	3	2	3	8
Shinoto	3	1	2	6
Hwang	3	2	3	8
Schellenberg	4	2	3	9

Figure 1. Flowchart for the identification of eligible studies.

death from any cause. The effects of ^{18}F-FDG-PET-derived parameters on survival outcomes were estimated by pooling the HR effect size and 95% CI data. An HR >1 indicated worse prognosis in patients with high parameter values, and an HR <1 indicated these patients to have better prognosis. The level of heterogeneity across studies was evaluated using the χ^2 test and I^2 statistic, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (http://handbook.cochrane.org). If the P value was >.1 and/the I^2 value was <50%, no or moderate heterogeneity was indicated, and the fixed-effects model was used; otherwise, the random-effects model was used when significant heterogeneity was observed. Begg funnel test and Egger test were performed to assess publication bias. The trim and fill method was applied adjust for asymmetry in the funnel plot.[22] The analyses described above were conducted using STATA version 12.0 (STATA Corp, College Station, TX). P values less than .05 were considered statistically significant.

3. Results

3.1. Study characteristics and qualitative assessment

Sixteen eligible articles remained after applying the inclusion and exclusion criteria (a total of 1146 patients), and these articles were included in the meta-analysis.[13,14,23–36] A flowchart of the literature review process is shown in Fig. 1. Six of the 16 studies had been conducted in South Korea,[13,23,28,30–32] 5 studies had been conducted in America,[14,24,26,33,36] 2 studies had been conducted in China,[25,34] and 3 studies had been conducted in Japan.[27,29,35] One study was prospective,[14] and the remaining studies were retrospective. Of these included studies, 16 provided the sample size data, and sample sizes ranged from 21 to 165 (median 72). The follow-up duration varied from 8.7 to 48.9 months (median 23.3 months). The principal characteristics of the 16 studies are listed in Table 2.

Table 3 shows the patterns identified in ^{18}F-FDG-PET/CT scanning. SUVmax was measured in all 16 studies, and values standardized by body weight were provided. MTV was measured in 6 studies,[13,14,23,26,28,34] and TLG was measured in 8 studies.[13,14,23,26,28,33,34,36] Different scanners and various
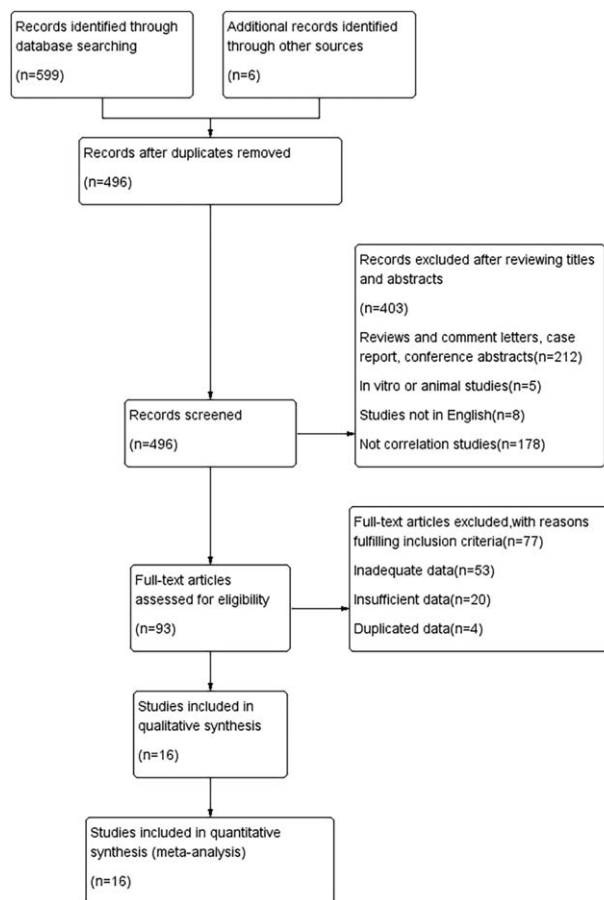
scanning protocols were used in each study. The duration of fasting varied from 4 hours to 8 hours, and this duration was not reported in 1 study. Preinjection serum blood glucose levels ranged from 67 to 340 mg/dL, and these data were not reported in 3 studies. The injected dose varied from 200 to 666 MBq, and the postinjection interval ranged from 45 to 90 minutes. Two threshold methods were used to calculate the cut-off values; receiver operating characteristics (ROCs) were used in 5 studies,[13,23,26–28] and median values were used in 11 study. Four threshold methods were applied for the measurement of MTV and TLG based on primary PC lesion volume. A fixed SUV of 2.5 was used in 4 articles;[13,23,28] the gradient segmentation method was used in 1 study,[26] and the isocontour method was used in 1 study.[34] In 1 study, a threshold was measured using the mean liver background SUV plus 2 standard deviations.[14] The median cut-off point was 5.1 (3.4–6.8) for SUVmax. The cut-off values for MTV ranged from 7.38 to 31.2 cm^3, and TLG values were between 15.0 and 92. The NOS scores for the studies are shown in Table 1, and all the included studies had scores greater than 6.

3.2. Outcome and publication bias

3.2.1. Primary outcome: EFS. Thirteen studies were included in the analysis of the association between SUVmax and EFS, and the pooled data revealed that high SUVmax values predicted poor EFS (HR=1.90; 95% CI=1.48–2.45, P=.000; I^2=59.8%) (Fig. 2A). Additionally, we conducted a sensitively analysis to

Table 2

Characteristics of eligible studies included in the meta-analysis.

Study	Year of publication	Patient source	Study period	Follow-up duration (range), mo	Median age ± SD (range), y	Number of patients	TNM staging	End points provided	Study design
Im	2016	South Korea	2007–2014	23 (1–78)	63 (29–84)	51	IIA IIB	OS EFS	Retro
Pimiento	2016	America	2004–2010	12.3 (0–56)	67 (24–89)	105	I II	OS EFS	Retro
Cui	2016	America	2004–2014	8,7 (0.7–64.9)	71 (38–92)	49	III	OS	Retro
Wang	2015	China	2006–2013	36 (3–64)	ND	69	III	OS EFS	Retro
Chirindel	2015	America	2007–2012	11 (1–47)	64.3 (40–86)	106	II–IV	OS EFS	Retro
Yamamoto	2015	Japan	2002–2011	49 (at least 24 mo)	67 (60–73)	128	ND	OS EFS	Retro
Choi	2014	South Korea	2007–2010	13 (3–67)	64.7 (39.3–87.7)	60	III	OS EFS	Retro
Dholakia	2014	America	2004–2011	13.4 (4.0–35.31)	ND	32	III	OS EFS	Pros
Lee	2014	South Korea	2008–2012	16 (4–60)	63 ± 9	57	I–IV	OS EFS	Retro
Xu	2014	China	2008–2012	ND	62 (35–84)	122	I/IIA/IIB	OS EFS	Retro
Kitasato	2014	Japan	2004–2010	ND	65 (43–81)	41	I–IV	OS EFS	Retro
Choi	2013	South Korea	2004–2009	ND	63.5 (45–80)	64	I–III	OS EFS	Retro
Moon	2013	South Korea	2006–2012	3.6 (1–10)	66 ± 9	21	III–IV	EFS	Retro
Shinoto	2013	Japan	2003–2010	48.9 (36.8–79.6)	67 (47–79)	21	IIA IIB	OS EFS	Retro
Hwang	2012	South Korea	2004–2009	ND	67 (29–90)	165	I–IV	OS	Retro
Schellenberg	2010	America	2004–2008	12.7 (2.8–37.7)	67 (39–92)	55	III	OS	Retro

ND = not described, SD = standard deviation, Pros = prospective, Retro = retrospective, OS = overall survival, EFS = event-free survival.

further estimate the impact of each study on the pooled HR. When the study conducted by Shinoto et al[29] was omitted from the analysis, an HR of 1.73 (1.50–2.00) and a decreased I^2 value (49.3%) were identified using a fixed-model. Begg and Egger tests were performed to assess publication bias. The funnel plots illustrated the correlation between SUVmax and EFS (Fig. 3). Visual inspection of the Begg funnel plot and the results of the quantitative tests (Begg test = 0.077, Egger test = 0.191) indicated the presence of no significant publication bias.

On the one hand, 5 studies were included in the analysis of the prognostic value of MTV for EFS. Since significant heterogeneity ($\chi^2 = 8.81$, $P = .066$; $I^2 = 54.6\%$) was observed across the included studies, the random-effects model was used. Using this model, the HR was 1.76 (95% CI = 1.20–2.58, $P = .004$) (Fig. 2C). When the study conducted Xu et al[34] was excluded, the observed heterogeneity decreased from 54.6% to 0% ($P = .640$), and the pooled HR reached 2.16 (95% CI = 1.49–3.13). The results of the quantitative tests (Begg test, z = 0.73, $P = .462$; Egger tests, $t = 3.42$, $P = .042$) indicated the possibility of publication bias, as illustrated by the statistically insignificant P value derived based on the Begg test. Therefore, we performed a trim and fill analysis to ensure the reliability of the pooled HR. A symmetrical funnel plot was observed after the trim and fill analysis was performed (Fig. 4). When potentially missing studies were added, the results (pooled HR = 1.30; 95% CI = 1.13–1.49, $P = .033$) of the sensitivity analysis still indicated that the correlation between MTV and EFS was significant.

On the other hand, the results from 6 studies were pooled in the analysis of the prognostic value of TLG for EFS. Significant heterogeneity ($\chi^2 = 11.99$, $P = .035$; $I^2 = 58.3\%$) was observed across these studies; therefore, we used the random-effects model to calculate the HR (1.81, 95% CI = 1.27–2.58, $P = .001$) (Fig. 2E). When the study conducted by Xu et al[34] was excluded from the analysis, the observed heterogeneity decreased from 58.3% to 0% ($P = .760$), and the pooled HR reached 2.13 (95% CI = 1.56–2.92). Potential publication bias was evaluated using 2 statistical test methods (Begg test and Egger test). The results (Begg test, z = 1.13, $P = .260$; Egger tests, $t = 5.63$, $P = .005$) indicated the possibility of publication bias, as illustrated by the statistically insignificant P value derived based

on the Begg test. The symmetrical funnel plot was demonstrated after the trim and fill analysis (Fig. 5). When potentially missing studies were added, the results (pooled HR = 1.40; 95% CI = 1.02–1.92, $P = .012$) of this sensitivity analysis still indicated that the correlation between TLG and EFS was significant.

We conducted subgroup analyses by cut-off method, threshold, and analysis method. Among articles including data for SUVmax, the HR for studies that determined cut-off values using ROCs was 1.87 (95% CI: 1.26–2.77, $P = .002$), and the HR for studies using other methods was 1.96 (95% CI: 1.38–2.77, $P = .000$). Based on the median value of SUVmax, cut-off values groups were divided into the following 2 subgroups: high value (≥5.1) and low value (<5.1). The results of the subgroup meta-analyses indicated that the pooled HRs for SUVmax were 1.83 (95% CI: 1.28–2.64, $P = .001$) and 2.01 (95% CI = 1.36–2.98, $P = .000$) for high and low cut-off values, respectively. In the subgroup analysis by the analytic method, the HR for studies using univariate analyses was 2.17 (95% CI = 1.50–3.14, $P = .000$), and the HR for studies using multivariate analyses was 1.50 (95% CI = 1.18–1.91, $P = .001$). In the subgroup analysis by TNM staging method, the HR for studies using I/II staging was 2.03 (95% CI = 1.06–3.91, $P = .034$), and the HR for studies using III/IV staging was 1.99 (95% CI = 1.52–2.61, $P = .000$) (Table 4). We performed subgroup analyses stratified by cut-off method, tumor delineation, and disease stage to assess the impact of these factors on the associations between MTV and TLG and the outcomes of interest. One study[28] included their populations with stage I to IV tumors, and, thus, this study was not included in the additional subgroup meta-analysis of stage. The results of each subgroup analysis indicated the presence of a significant HR for death (Table 5).

3.2.2. Secondary outcome: OS.
Fifteen studies were included in the assessment of the correlation between SUVmax and OS. Significant heterogeneity ($P = .000$, $\chi^2 = 48.95$; $I^2 = 71.4\%$) was observed across these studies; thus, the random-effects model was applied to calculate the pooled HR (1.21, 95% CI = 1.12–1.31; $P = .000$) (Fig. 2B). When the study conducted by Chirindel et al[26] was omitted from the analysis, an HR of 1.82 (1.54–2.14) and a decreased I^2 of 27.7% were calculated using the fixed-

Table 3

Methods of ^{18}F-FDG PET imaging of the included studies.

Study	PET scanners	Duration of fasting	Preinjection blood glucose test	Post injection interval	Dose of ^{18}F-FDG	PET parameters	Determination of cutoff values	Tumor delineation	SUV	MTV (cm³)	TLG
Im	Biograph 40 Truepoint, Siemens Healthcare, Knoxville, TN	6 h	<180 mg/dL	60 min	5.18 MBq/kg	SUVmax, MTV, TLG	ROC curve	SUV2.5	4.2	7.38	18.6
Pimiento	GE Medical Systems, Milwaukee, WI	4 h or 6 h	<200 mg/dL	90 min	10-mCi	SUVmax	Median value		5		
Cui	GE Medical Systems, Milwaukee, WI or Siemens Healthcare, Erlangen, Germany	8 h		45–60 min	10–18 mCi	SUVmax, TLG	Median value		6.2		57.45
Wang	GE Medical Systems, Milwaukee, WI	4 h	4.5–6.5 mmol/L	60 min	5.55 MBq/kg	SUVmax	Median value		5.5		
Chirindel	Discovery VCT, GE Healthcare or Discovery LS, GE Healthcare	4 h	113.9 mg/dL (range, 60–193 mg/dL)	64.1 min	580.9 MBq	SUVmax, MTV, TLG	ROC curve	Gradient segmentation method	4.9	31.2	92
Yamamoto	GE Medical Systems, Milwaukee, WI, USA	4 h	<150 mg/dl	50–60 min	200–250 MBq	SUVmax	ROC curve		6.0		
Choi	Discovery STe, GE Healthcare, Milwaukee, WI, USA or Biograph TruePoint 40, Siemens Medical Systems, CTI, Knoxville, TN, USA	6 h	72–210 mg/dL	60 min	5.5 MBq/kg	SUVmax, MTV, TLG	ROC curve	SUV ≥2.5	6.5	10.0	45.0
Dholakia	General Electric Medical Systems, Waukesha, WI	4 h	<180 mg/dL	60 min	8.1 MBq/kg	SUVmax, MTV, TLG	Median value	Livermean+ [2 × Liversd]*	4.6	26.8	70.9
Lee	Discovery Ste [GE Healthcare] or Biograph TruePoint 40 [Siemens Healthcare]	6 h	67.0–340.0 mg/dL	60 min	5.5 MBq/kg	SUVmax, MTV, TLG	ROC curve	SUV ≥2.5	4.7or 3.7[a]	30	20.0 or 15.0[b]
Xu	Siemens CTI RDS Eclipse ST; Knoxville, TN	6 h	<8 mmol/L	60 min	7.4 MBq/kg	SUVmax, MTV, TLG	Median value	Isocontour SUV threshold method	6.2	15.7	57.5
Kitasato	Gemini-GXL 16; Philips Medical Systems, Inc, Cleveland, Ohio	6 h	75–127 mg/dL	60 min	4.59–9.56 mCi	SUVmax	Median value		3.4		
Choi	GE Healthcare, Milwaukee, WI, USA or Philips-ADAC medical systems, Cleveland, OH, USA	4 h	<130 mg/dL	60 min	5.18 MBq (0.14 mCi)/kg	SUVmax	Median value		3.5		
Moon	Philips Medical Systems, Cleveland, OH, USA	6 h	<200 mg/dL	60 min	4.8 MBq/kg	SUVmax	Median value		6.8		
Shinoto	Biograph duo and Biograph 16; Siemens CTI, Knoxville, TN and Aquiduo; Toshiba Medical Systems Corporation, Otawara-shi, Tochigi-ken	6 h		60 min	515±56 MBq	SUVmax	Median value		4.3		
Hwang	Biograph 6, Siemens Healthcare or Discovery LS, GE Healthcare	6 h		60 min	370–444 MBq	SUVmax	Median value		4.1		
Schellenberg	GE Medical Systems, Milwaukee, WI	8 h	<180 mg/dL	45–60 min	10–18 mCi	SUVmax, MTB	Median value		6.2		57.45

^{18}F-FDG = ^{18}F-fluorodeoxyglucose, PET = positron emission tomography, SUVmax = maximum standardized uptake value, MTV = metabolic tumor volume, TLG = total lesion glycolysis, ROC = receiver operating characteristic curve.

* A modification of the threshold criteria used in PET PERCIST, version 1.0.
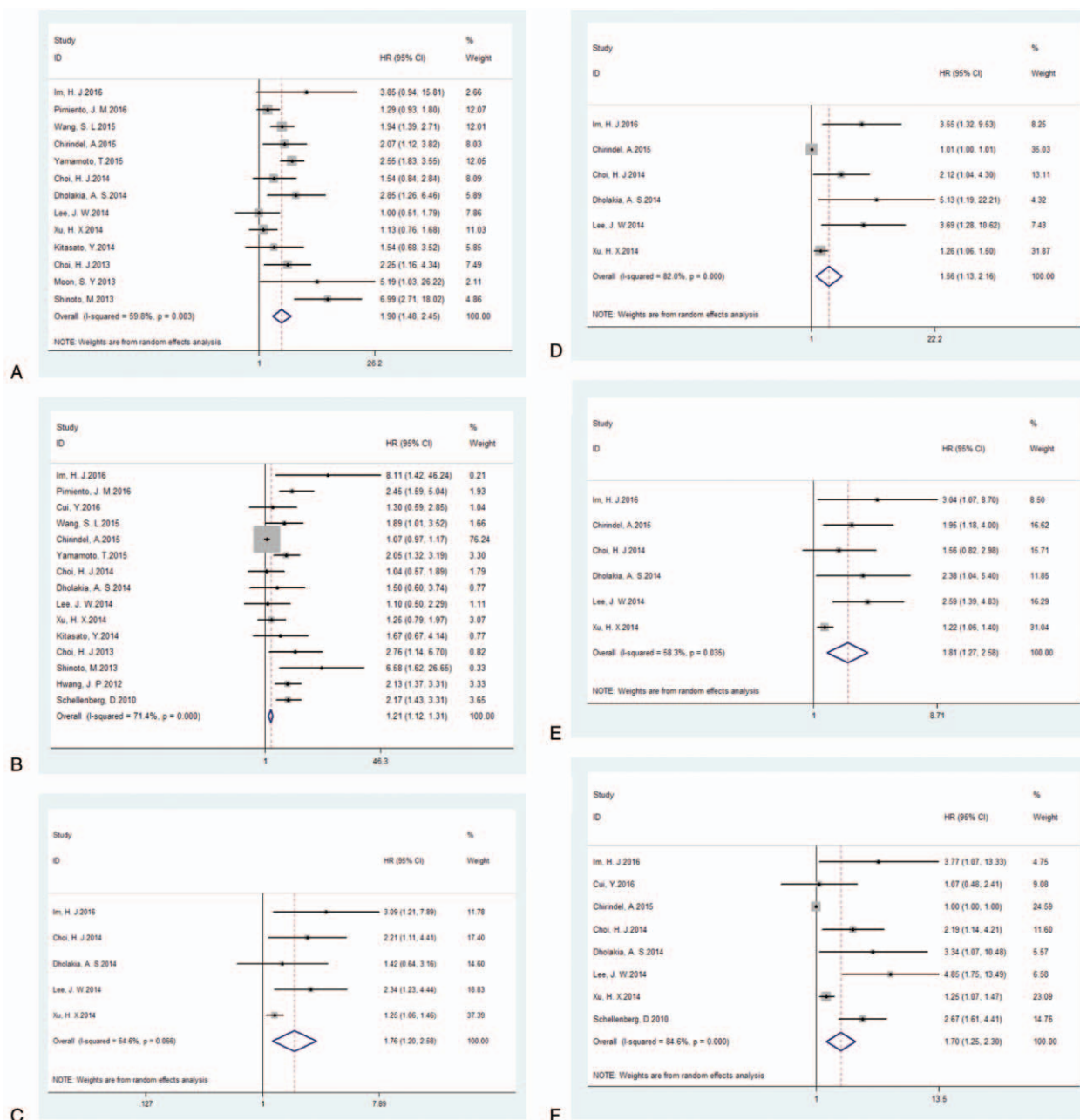
Figure 2. Forest plots of HR for EFS and OS with SUVmax (A, EFS; B, OS), MTV (C, EFS; D, OS) and TLG (E, EFS; F, OS). The χ^2 test is a measurement of heterogeneity. $P < .05$ indicates significant heterogeneity. Squares = individual study point estimates. Horizontal lines = 95%CIs. Rhombus = summarized estimate and its 95% CI. Fixed = fixed effect model. Random = random effect model. CI = confidence interval, EFS = event-free survival, HR = hazard ratio, MTV = metabolic tumor volume, OS = overall survival, TLG = total lesion glycolysis, SUVmax = maximum standardized uptake value.

effects model. The results of the quantitative tests (Begg test, z = 0.10, $P = .921$; Egger tests, $t = 4.47$, $P = .001$) indicated the possibility of publication bias, as represented by the statistically insignificant P value derived based on Begg test. A symmetrical funnel plot was generated after the trim and fill analysis performed (Fig. 6). When potentially missing studies were added, the results (pooled HR = 1.68; 95% CI = 1.30–2.17, $P = .000$) of this sensitivity analysis still indicated that the correlation between SUVmax and OS was significant.

At the same time, 6 studies were included in the analysis of the association between MTV and OS. High MTV values were significant predictors of poor OS (HR = 1.56, 95% CI 1.13–2.16;

$P = .007$), and significant heterogeneity was observed ($\chi^2 = 27.78$, $P = .000$; $I^2 = 82.0\%$) (Fig. 2D). When the study conducted by Chirindel et al[26] was excluded from the analysis, the observed heterogeneity decreased from 82.0% to 67.4% ($P = .015$), and the pooled HR reached 2.36 (95% CI = 1.31–4.25) using the random-effects model. The results of the quantitative tests (Begg test, z = 0.00, $P = 1.000$; Egger tests, $t = 21.25$, $P = .000$) indicated the possibility of publication bias, as illustrated by the statistically insignificant P value derived based on Begg test. A symmetrical funnel plot was observed after the trim and fill analysis was performed (Fig. 7). When the hypothesized literatures were added, the results (pooled HR = 1.006; 95% CI = 1.000–1.014,
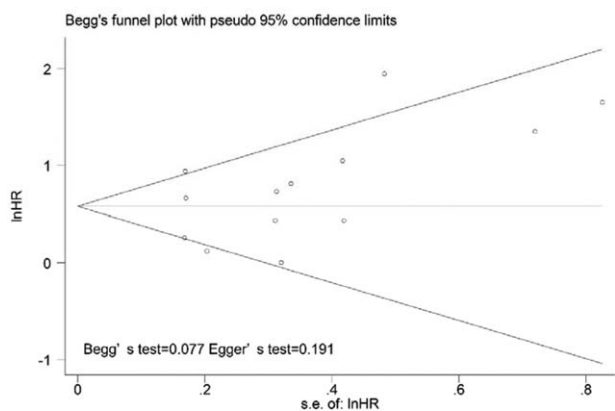
Figure 3. Publication bias test for the correlations of SUVmax with event-free survival. No significant publication bias was detected by Begg funnel plots (no apparent asymmetry was found) and estimation of *P* values. SUVmax = maximum standardized uptake value.

$P = .000$) of this sensitivity analysis still indicated that the correlation between MTV and OS was significant.

Eight studies were included in the evaluation of the association between TLG and OS, and the results indicated that high TLG was a significant predictors of poor OS (HR = 1.70; 95% CI: 1.25–2.30; $P = .01$), and significant heterogeneity ($\chi^2 = 45.49$, $P = .000$; $I^2 = 84.6\%$) was observed across these studies (Fig. 2F). When the study by Chirindel et al[26] was excluded

Figure 4. Funnel plots without (up column) and with (low column) trim and fill of MTV with event-free survival. MTV = metabolic tumor volume.
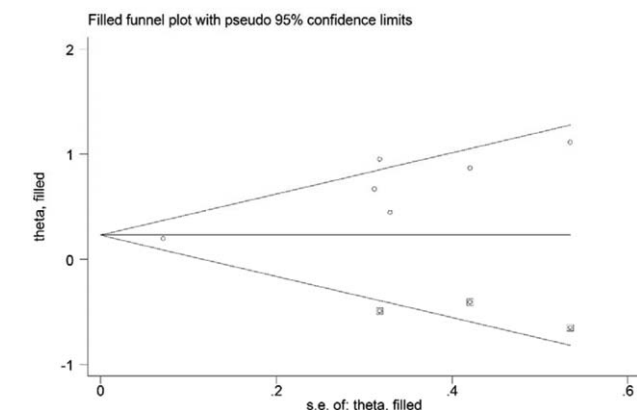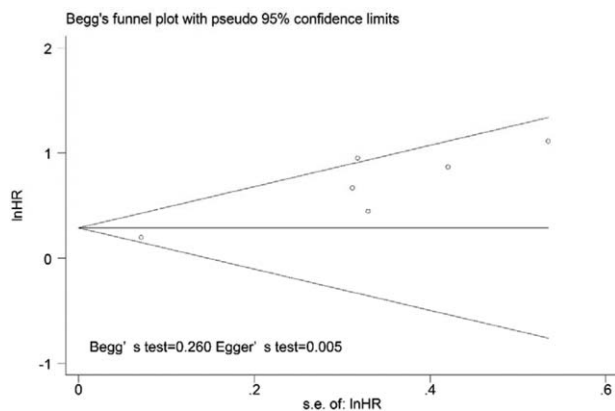

Figure 5. Funnel plots without (up column) and with (low column) trim and fill of TLG with event-free survival. TLG = total lesion glycolysis.
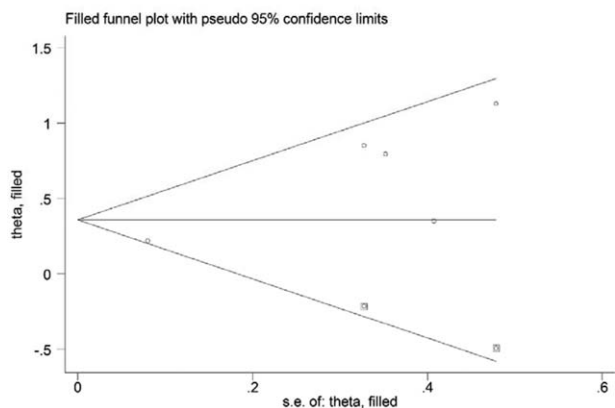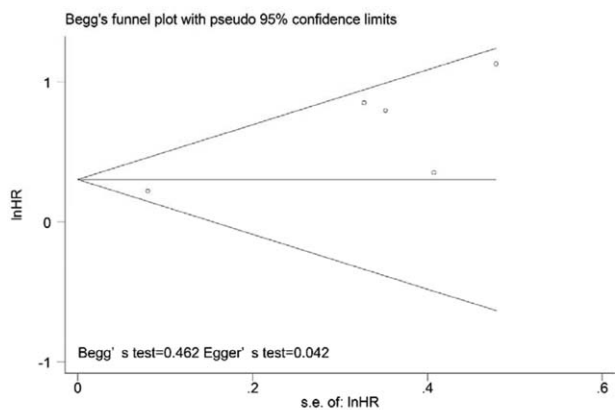
from the analysis, the level of heterogeneity decreased from 82.0% to 70.9% ($P = .002$), and the pooled HR reached 2.14 (95% CI = 1.37–3.35) using the random-effects model. The presence of publication bias was evaluated using 2 statistical tests (Begg test and Egger test). The results of the tests (Begg test, $z = 1.71$, $P = .087$; Egger tests, $t = 2.61$, $P = .028$) indicated the possibility of publication bias, as illustrated by the statistically insignificant P value derived based on the Begg test. Therefore, we performed a trim and fill analysis to ensure the reliability of the pooled HR. A symmetrical funnel plot was generated after the trim and fill analysis was performed (Fig. 8). When potentially missing studies were added, the results (pooled HR = 1.42; 95% CI = 1.07–1.88, $P = .00$) of this sensitivity analysis still indicated that the correlation between TLG and OS was significant.

The results of the subgroup meta-analyses were demonstrated as follows. Among the studies in which SUVmax was assessed, the HR for those identifying cut-off values using the ROC method was 1.38 (95% CI: 0.92–2.09, $P = .122$), and the HR for using other methods was 1.91 (95% CI: 1.56–2.34, $P = .000$); studies with high cut-off values had an HR of 1.65 (95% CI: 1.34–2.04, $P = .000$), and the HR for studies with low cut-off values was 1.94 (95% CI: 1.28–2.94, $P = .002$). Studies using univariate analyses had an HR of 2.12 (95% CI: 1.69–2.66, $P = .000$), and the HR for studies employing multivariate analyses was 1.42 (95% CI: 1.05–1.93, $P = .022$). For the subgroup analysis by TNM staging method, the HR for studies using I/II staging was 3.10 (95% CI = 1.86–5.15, $P = .000$), and the HR fur studies using III/IV staging was 1.67 (95% CI = 1.27–2.18, $P = .000$) (Table 4).

Table 4

Subgroup analyses of the associations between SUVmax and survival outcomes.

Endpoint	Volumetric parameters	Factor	No. of studies	Heterogeneity test (I2, P)	Effect model	HR	95% CI of HR	P value	Conclusion
OS	SUV max	Cutoff method							
		ROC	5	69.7	Random	1.38	0.92–2.09	P=.122	
		Others	10	6.3	Fixed	1.91	1.56–2.34	P=.000	Significant
		Threshold							
		≥5.1	6	26.9	Fixed	1.65	1.34–2.04	P=.000	Significant
		<5.1	9	75.3	Random	1.94	1.28–2.94	P=.002	Significant
		Analysis method							
		Univariate analysis	7	0	Fixed	2.12	1.69–2.66	P=.000	Significant
		Multivariate analysis	8	62.6	Random	1.42	1.05–1.93	P=.022	Significant
		TNM stage							
		I/II	3	31.5	Fixed	3.10	1.86–5.15	P=.000	Significant
		III/IV	5	10.9	Fixed	1.67	1.27–2.18	P=.000	Significant
EFS	SUV max	Cutoff method							
		ROC	5	51.7	Random	1.87	1.26–2.77	P=.002	Significant
		Others	8	64.9	Random	1.96	1.38–2.77	P=.000	Significant
		Threshold							
		≥5.1	5	65.2	Random	1.83	1.28–2.64	P=.001	Significant
		<5.1	8	61.0	Random	2.01	1.36–2.98	P=.000	Significant
		Analysis method							
		Univariate analysis	6	70.0	Random	2.17	1.50–3.14	P=.000	Significant
		Multivariate analysis	7	40.3	Fixed	1.50	1.18–1.91	P=.001	Significant
		TNM stage							
		I/II	4	79.2	Random	2.03	1.06–3.91	P=.034	Significant
		III/IV	4	0	Random	1.99	1.52–2.61	P=.000	Significant

CI = confidence interval, EFS = event-free survival, MTV = metabolic tumor volume, OS = overall survival, ROC = receiver operating characteristic curve, SUVmax = maximum standardized uptake value, TLG = total lesion glycolysis.

Table 5

Subgroup analyses of the associations between MTV/TLG and survival outcomes.

Endpoint	Volumetric parameters	Factor	No. of studies	Heterogeneity test (I2, P)	Effect model	HR	95% CI of HR	P value	Conclusion
OS	MTV	Cutoff method							
		ROC	4	81.6	Random	2.06	0.97–4.37	P=.059	
		Others	2	71.2	Random	2.09	0.56–7.81	P=.272	
		Tumour delineation							
		SUV 2.5	3	0	Fixed	2.76	1.66–4.57	P=.000	Significant
		Others	3	82.6	Random	1.17	0.89–1.54	P=.252	
		TNM stage							
		I/II	2	75.4	Random	1.88	0.70–5.03	P=.208	
		III/IV	3	77.8	Random	1.77	0.78–4.00	P=.173	
	TLG	Cutoff method							
		ROC	4	84.1	Random	2.22	0.99–5.02	P=.055	
		Others	4	71.8	Random	1.72	1.03–2.88	P=.040	Significant
		Tumour delineation							
		SUV 2.5	3	0	Fixed	2.90	1.75–4.80	P=.000	Significant
		Others	5	85.0	Random	1.37	1.02–1.84	P=.034	Significant
		TNM stage							
		I/II	2	65.3	Random	1.81	0.65–4.99	P=.254	Significant
		III/IV	5	83.6	Random	1.72	0.98–3.04	P=.060	Significant
EFS	MTV	Cutoff method							
		ROC	3	0	Fixed	2.42	1.59–3.69	P=.000	Significant
		Others	2	0	Fixed	1.25	1.07–1.46	P=.004	Significant
		Tumour delineation							
		SUV2.5	3	0	Fixed	2.42	1.59–3.69	P=.000	Significant
		Others	2	0	Fixed	1.25	1.07–1.46	P=.004	Significant
		TNM stage							
		I/II	2	71.5	Random	1.74	0.74–4.09	P=.208	
		III/IV	2	40.3	Fixed	1.83	1.09–3.08	P=.023	Significant
	TLG	Cutoff method							
		ROC	4	0	Fixed	2.09	1.49–2.94	P=.000	Significant
		Others	2	59.6	Random	1.50	0.82–2.75	P=.193	
		Tumour delineation							
		SUV2.5	3	0	Fixed	2.16	1.43–3.26	P=.000	Significant
		Others	3	55.4	Random	1.56	1.02–2.40	P=.041	Significant
		TNM stage							
		I/II	2	65.3	Random	1.65	0.71–3.84	P=.246	
		III/IV	3	0	Fixed	1.88	1.27–2.78	P=.002	Significant

EFS = event-free survival, MTV = metabolic tumor volume, OS = overall survival, ROC = receiver operating characteristic curve, TLG = total lesion glycolysis.
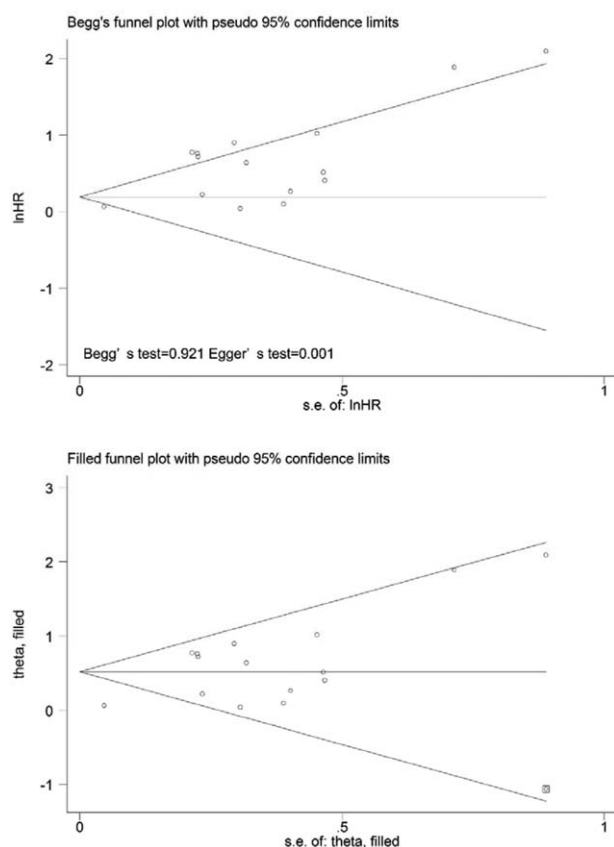
Figure 6. Funnel plots without (up column) and with (low column) trim and fill of SUVmax with overall survival. The pseudo 95% confidence interval (CI) is computed as part of the analysis that produced the funnel plot and corresponds to the expected 95% CI for a given standard error (SE). HR = hazard ratio, SUVmax = maximum standardized uptake value.
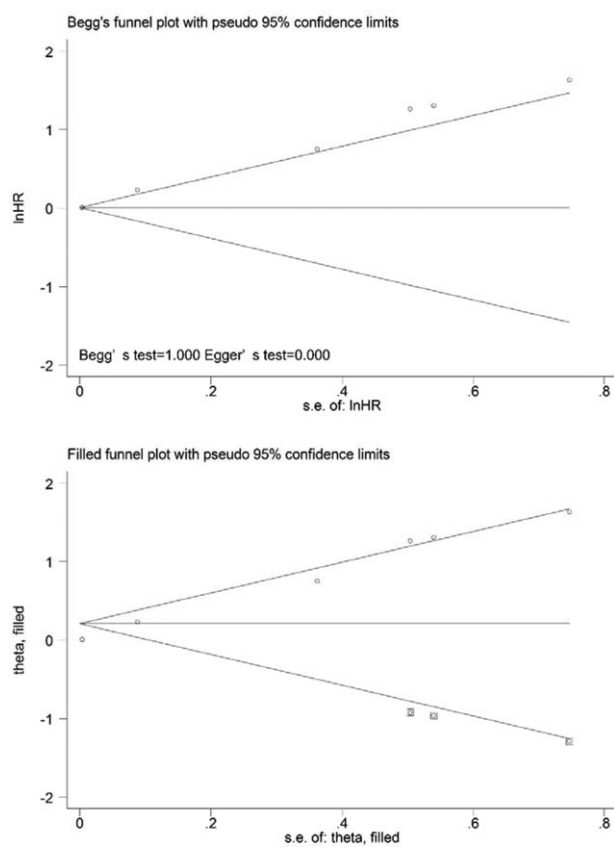

Figure 7. Funnel plots without (up column) and with (low column) trim and fill of MTV with overall survival. MTV = metabolic tumor volume.

Subgroup meta-analyses stratified by cut-off method, tumor delineation, and disease stage were conducted. Each subgroup analysis indicated the presence of a significant HR for death (Table 5).

4. Discussion

Of late, ^{18}F-FDG-PET/CT has been the imaging modality most commonly used for diagnosis, staging, evaluating response to treatment, and detecting postoperative recurrence and metastasis in PC.[37–41] Since the late 1980s, PET-derived quantitative SUV has been widely used, as this parameter is a robust indicator that can easily be calculated for the evaluation of PET data.[42] The potential role of FDG uptake values in the prediction of prognosis has been recently reported in several meta-analyses, high SUV values at diagnosis were more highly associated with poor survival than were low SUV values in a variety of cancers, such as head and neck cancer, hepatocellular carcinoma, and bone and soft tissue sarcoma.[43–45] MTV and TLG have been considered parameters for that are more reliable for predicting survival than SUVmax, as they reflect whole tumor burden.[46] Recent meta-analyses have also revealed that volumetric parameters, such as MTV and TLG, may serve as prognostic factors in non-small cell lung cancer and head and neck cancer.[20,47]

However, conflicting results have been published regarding the superiority or prognostic value of other quantitative methods derived from PET to SUVmax.[13,14,23,28,34] Although a previous

meta-analysis reported that the identification of high SUVmax values based on PET imaging in PC was associated with increased risk of poor survival.[10] One of the main problems is that these studies only assessed a relatively small number of patients, resulting in limited statistical power. Therefore, we conducted a comprehensive meta-analysis to derive more robust estimates regarding the predictive performance of SUVmax. The results of our meta-analysis, which was conducted using the data from the largest number of patients with PC yet, indicated that SUVmax was a prognostic factor for the outcomes of interesting, suggesting that at diagnosis, ^{18}F-FDG-PET/CT imaging may serve as an important imaging tool that plays a predictive role for patients with PC.

After pooling data from the available studies, we found that high SUVmax values were significantly correlated with poor prognosis, including poor EFS and OS. However, the association between SUVmax and survival outcomes may be affected by several confounding factors; therefore, a subgroup analysis was conducted by statistical analysis method to validate the parameters as independent prognostic factors. Multivariate analysis may also serve as an effective method when evaluating potential prognostic factors, and the Cox proportional hazards model or logistic regression model may be used to reduce biases resulting from major confounders.[48] In our study, SUVmax proved to be significantly associated with survival in both the univariate and multivariate analyses; therefore, one could presume that SUVmax might be an independent prognostic factor for survival outcomes.

To evaluate the effects of the methods utilized by each study (Table 1), we performed subgroup analyses by cut-off method, threshold, analysis method, and analysis method. For example, in
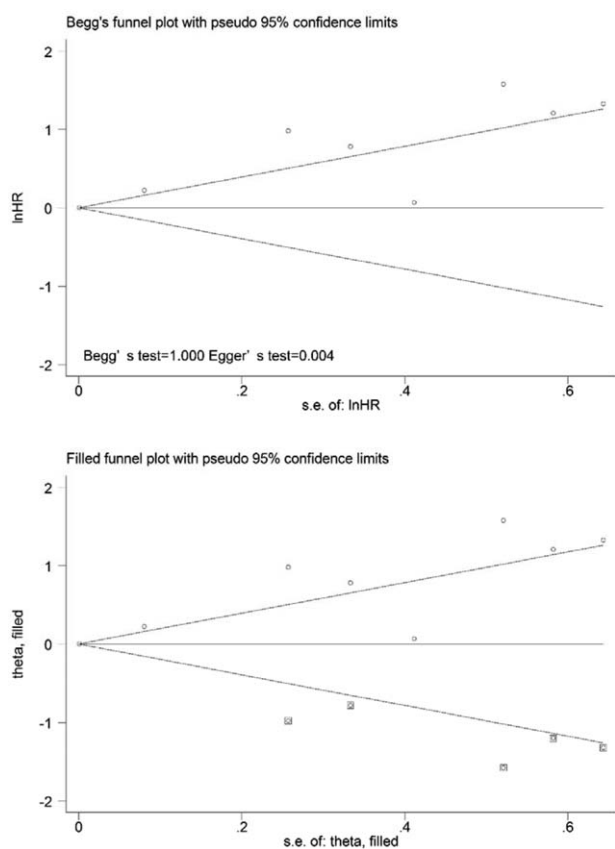
Figure 8. Funnel plots without (up column) and with (low column) trim and fill of TLG with overall survival. TLG = total lesion glycolysis.

the cut-off values analysis, we evaluate the methods used to determine cut-off values in the included studies, and specifically assessed the ROC curve and median value methods. In our meta-analysis, 5 articles used receiver operating characteristic curves to determine the optimal cut-off point,[13,23,26–28] which has been reported to be a more reasonable method for cut-off calculation. Therefore, subgroups stratified by the methods were created to evaluate the effect of using different cut-off values. The results of the subgroup analyses showed small and acceptable variations in the HRs for EFS associated with SUVmax (1.50–3.10) despite the wide range of SUVmax values observed (3.4–6.8). In the current meta-analysis, the cut-off value used for SUVmax varied in each study because SUV can be significantly influenced by measurement errors that are associated with both true biological changes and technological factors that cannot be entirely controlled, such as weight composition, diet, fasting state, scanner method, and reconstruction parameters.[49,50]

The question of whether traditional imaging technique can predict PC patient survival remains controversial because previous studies have focused on tumor size. While MTV and TLG, which are a combination of volumetric and metabolic parameters, may be utilized in metabolic analyses of radiotracer activity, reflecting both properties of the tumor tissues. Our findings confirm previous findings suggesting that high volumetric parameter values indicated poor EFS and OS, suggesting that ^{18}F-FDG-PET/CT has vast prospects for predicting survival outcomes in PC patients. Although an SUVmax threshold of 2.5 was used tumor delineation in 3 of the 6 studies included in this meta-analysis, Abelson et al[51] found that an SUVmax threshold

of 7 may be a better standard for volume of interest delineation in their patient population. Therefore, the identification of the cut-off values for MTV and TLG values most highly associated with worse OS and PFS should be the subject of further research, the methods used for SUV measurement and tumor delineation should be normalized and standardized, and controversies regarding the most appropriate segmentation method should be resolved. Currently, various commercially available tools for the measurement of volumetric parameters are being developed and disseminated, which may enable faster and easier tumor analysis.[48] Although the methods used for determining optimal cut-off MTV and TLG values or tumor delineation may have affected the MTV or TLG values reported in each study, high MTV and TLG values were associated with increased probability of disease progression and/or death. To assess the effects of the methods used in each included study, we also performed additional subgroup analyses by cut-off method, tumor delineation, and disease stage, the results of which showed there to be acceptable variations of the HRs for EFS and OS. Further prospective studies are in need to validate the findings.

Our meta-analysis had some limitations. Although all included studies were evaluated by NOS scores and considered high quality, we only included 1 prospective study, and most of the studies were retrospective in nature, which may have caused them to be more prone to potential biases. More prospective studies are needed to support and validate our meta-analysis results. Second, significant heterogeneity was observed across the included studies for both OS and EFS. Many possible factors could have caused the observed heterogeneity, such as differences in histology type, TNM stage, study region, treatment method, cut-off value, and HR estimation method. After the sensitivity analyses, the prognostic values of the parameters were not decreased. Second, we only included the English articles, and reviews, conference papers, and editorial materials were excluded; this may have resulted in a language bias and publication bias. However, the results of the Begg tests did not suggest clear evidence of bias. The results of the trim and fill sensitivity analysis further supported the prognostic role of ^{18}F-FDG-PET/CT parameters in PC patients after potentially missing studies were included, which demonstrated that our analysis was reliable.

5. Conclusion

The results of this meta-analysis demonstrated that ^{18}F-FDG-PET/CT parameters, such as SUVmax, MTV, or TLG, may serve as significant prognostic factors for predicting outcomes in PC patients. Despite the clinical and methodological heterogeneity observed across studies, the ^{18}F-FDG-PET/CT parameters may be used to stratify patient risk in terms of disease control and survival and aid in the selection of appropriate treatment strategies for individual patients. Additional large multicenter studies are in need to validate our findings and explore the applicability of other prognostic variables associated with ^{18}F-FDG-PET/CT in efforts to prolong survival of PC patients.

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