Prognostic impact of pretreatment FDG PET parameters in locally advanced cervical cancer treated with concomitant chemoradiotherapy: A systematic review and meta-analysis

Lu Han[1], Qi Wang[2], Lanbo Zhao[3], Kailu Zhang[1], Yiran Wang[1], Xue Feng[1], Yuliang Zou[2], and Qiling Li[4]

[1]the First Affiliated Hospital of Xi'an Jiaotong University
[2]Department of Obstetrics and Gynecology, First Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, China
[3]Xi'an Jiaotong University
[4]Xian Jiaotong University

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Abstract

Background More evidence has shown FDG PET/CT parameters might be associated with survival of patients with locally advanced cervical cancer (LACC) treated with concurrent chemo-radiotherapy (CCRT). Objectives To perform this meta-analysis to investigate the prognostic value of pretreatment FDG PET/CT parameters. Search strategy PubMed and Embase. Selection criteria Studies that met the following criteria were enrolled: patients treated with CCRT for LACC; FDG PET/CT scans performed before or during treatment; and relationship between the parameters of FDG PET/CT and the prognosis of patients were investigated. Data collection and analysis Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were used to estimate overall survival (OS) or event-free survival (EFS). Main results Higher primary tumor TLG (HR = 1.843, 95% CI = 1.100–3.086, P = 0.02) and MTV (HR = 2.06, 95% CI, 1.21–3.51, P = 0.007) were significantly associated with shorter EFS. Patients with high SUVmax have a shouter OS than those with low SUVmax (HR = 2.582, 95% CI 1.936–3.443, P <0.001). Primary tumor SUVmax (HR = 1.938, 95% CI, 1.203–3.054, P = 0.004) and nodal SUVmax (HR = 3.478, 95% CI = 2.006-6.029, P <0.001) were significantly correlated with EFS with relatively high heterogeneity (I2 = 84%, I2 = 69.4%, respectively). Nodal SUVmax (HR = 2.095, 95% CI = 2.027–2.166, P <0.001) were significantly correlated with OS with relatively high heterogeneity (I2 = 54.1%, P = 0.140). Other parameters had no detected association with survival. Conclusions Pretreatment FDG PET/CT parameters serve as a prognostic predictor.

Introduction

Cervical cancer is a common gynecological malignancy with around 569,847 new cases and 311,365 deaths annually worldwide, and a significant proportion of patients are diagnosed at a locally advanced stage.[1] For locally advanced cervical cancer (LACC), concurrent chemoradiotherapy (CCRT), using cisplatin-based chemotherapy in association with pelvic external-beam radiotherapy and subsequent brachytherapy is considered the standard treatment.[2] Although the contribution of CCRT toward an improvement in survival outcomes and reduction in recurrence has been well confirmed, the complete clinical response of these patients is 70%–90%, and about one-third of patients with CC experience recurrence.[3, 4]

Accurate prediction of recurrence is of great significance. Several traditional clinical and pathological factors are identified as poor prognostic factors, which include advanced International Federation of Gynecology and Obstetrics (FIGO) stage, presence of lymph node metastasis, parametrial invasion, histological tumor

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type, and a large tumor diameter.[5-7] However, there are still no satisfactory parameters sufficient to predict prognosis accurately.

Computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose positron emission CT (FDG PET/CT) are the most commonly used imaging modalities. Compared to CT or MRI, FDG PET/CT could show metabolic information on tumors and more accurate assessment of lymph node involvement, distant metastasis, and recurrent disease.[8] Therefore, FDG PET/CT has been widely used in staging, therapeutic strategy, and treatment response assessment of patients with CC.[9]

With the technology developed, imaging has provided the potential of a prognostic biomarker.[10] Except for the aforementioned roles, quantitative parameters derived from FDG-PET/CT, including maximum standardized uptake value (SUV_{max}), average SUV (SUV_{mean}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), have recently been proposed as prognostic biomarkers for patients with LACC who are treated with CCRT, but the results of studies show some extent differences. For example, Im et al. detected that the patients with high SUV_{max} measurement on tumor tissue had a higher risk of recurrence or progression than those with low SUV_{max} (HR= 2.14, 95%CI=1.08-4.22, P=0.029) ,[11] but Chong et al. draw the opposite conclusion (HR=0.673, 95%CI=0.5-4.0, P=0.412) .[12]Therefore, we performed this meta-analysis to synthetize the relevance of FDG PET/CT parameters as prognostic biomarkers for patients with LACC who are treated with CCRT.

Methods

Literature search and selection criteria

Embase and Pubmed (from inception to May 2020) were systematically searched, using the appropriate terminology as described in**Table S1** . Besides, the reference lists of the articles reviewed as full texts were also searched manually. The inclusion criteria in the meta-analysis were as follows: patients treated with CCRT for LACC; FDG PET/CT scans performed before or during treatment; and relationship between the parameters of FDG PET/CT and the prognosis of patients was detected. Studies meeting the following criteria were excluded: publication type other than original research articles (i.e., review articles, conference abstracts, and editorial), patients treated with surgery at any point in treatment, patients treated with chemotherapy or radiotherapy alone, and patients lacking important information for analysis (i.e., articles reporting hazard ratios [HRs], using Cox proportional hazards modeling with parameters as a continuous variable). Two authors conducted the searches and screening independently. Any discrepancies were resolved by consensus with another reviewer.

Data extraction

The following information was extracted using a standardized form: surname of first author, year of publication, country, design (prospective or retrospective), patients' characteristics (including patients' number, tumor node metastasis [TNM] staging, histology, radiotherapy technique, the schedule of systemic therapy, and follow-up period), and outcomes.

Statistical analysis

The primary outcome, progression event-free survival (EFS), was defined as the date from initiating therapy to recurrence or metastasis. In some included studies, disease-free survival (DFS) or progression-free survival (PFS) was obtained as the primary outcome, but they were all redefined as EFS in this meta-analysis. The secondary outcome was overall survival (OS), defined as the date from initiating therapy until death. The effect sizes of the prognostic values of SUV_{max}, SUV_{mean}, MTV, and TLG were measured in terms of HR. An HR greater than 1 implied worse survival for patients with a high SUV_{max}, SUV_{mean}, MTV, or TLG. The most adjusted estimate of hazard ratio (HR) was extracted directly from each study, if provided by the authors. Otherwise, the HR estimate and its variance were extracted from Kaplan-Meier curves by Engauge Digitizer, version 3.0 (http://digitizer.sourceforge.net). Heterogeneity was assessed with the Q test and I^2 statistic, and$P$ value less than 0.05 or I^2 values higher than 50% indicated significant heterogeneity. The fixed-effects model was used to estimate the cases with homogeneity and the random-effects model was used

for the cases with significant heterogeneity. Publication bias of the studies was visually displayed by the asymmetry of an inverted funnel plot, and quantitatively evaluated by Egger's tests with the P value less than 0.05 suggesting the significant publication bias. Sensitivity analyses were conducted to assess the stability of the meta-analysis results. All statistical analysis was conducted with STATA 14.0 (STATA Corporation, College Station, TX, USA) software.

Results

Study selection

We picked up 721 potentially eligible articles in the electronic search. 78 articles were removed for duplication, and 628 articles were excluded after the reviewers read the titles and abstracts. In total, 14 eligible studies with a total of 1313 patients were included in this meta-analysis after reviewing the full text (**Figure 1**) .

Patient characteristics and treatment features

The median age of patients included in the studies was 51.5-58 years (range from 21 to 89 years). Only 12 of the 14 studies provided information about histology, and89.14% patients had a squamous cell carcinoma (1076/1205)(**Table 1**) . The largest stage subgroup was FIGO stage IIB, which contained 64.66% (846/1313) of patients. The median follow-up for all patients was 22-60 months (range from 3 to 129 months) (**Table 2**) . No information on the radiotherapy technique used was available in three studies, and most patients of the other studies were treated with 3D-conformal radiotherapy. The widely adopted external beam radiotherapy regimen consisted of conventional fractionation of 1.8 Gy per fraction (8/9 studies) for a total dose of 45-50.4 Gy. The intracavitary brachytherapy regimen used in majority of patients consisted of fractionation of 7 Gy per fraction (6/10 studies) with four cycles (4/9 studies). The adopted concurrent chemotherapy regimen was standard weekly 40 mg/m^2 cisplatin in most patients (10/13 studies) (**Table 3**) .

Primary outcome: EFS

Night articles about SUV_{max} measuring on tumor tissue were included in the study.[11-19] The combined HR for EFS of higher SUV_{max} was 1.938 (95% CI, 1.203-3.054, P = 0.004) (**Figure S1A**) , which meant the patients with high SUV_{max} measurement on tumor tissue had a higher risk of recurrence or progression than those with low SUV_{max}. However, significant heterogeneity existed between the articles (I^2 = 84%, P = 0.000). The publication bias was significant based on the funnel graph (**Figure S1B**) and Egger's test (P = 0.015). The results obtained through sensitivity analysis was relatively stable (**Figure S1C**) .

Four articles about primary tumor SUV_{mean} were included in the study.[15-17, 20] Due to no significant heterogeneity (I^2 = 0%, P = 0.938), the fixed-effects model was performed. The synthesized results showed that patients with high SUV_{mean} had a moderately higher risk of recurrence or progression than those with low SUV_{mean}, but without statistically significant (HR = 1.182, 95% CI = 0.899-1.544, P = 0.230)(**Figure S2A**) . Begg's funnel plot and Egger's test indicated no publication bias (P = 0.345), and sensitivity analysis showed that the analysis was relatively stable (**Figure S2B-C**) .

Three articles about MTV, measuring tumor tissue, were included in the study.[12, 15, 17] With no significant heterogeneity (I^2 = 20.9%, P = 0.282), the combined HR for EFS with higher MTV was 2.06 (95% CI, 1.21-3.51, P = 0.007) (**Figure 2A**). It indicated thatpatients with high MTV had a higher risk of recurrence or progression than those with low MTV. Because the data was limited, publication bias was not performed.

Four articles about primary tumor TLG were included in the study.[15, 17, 20, 21] In the absence of significant heterogeneity (I^2 = 0%, P = 0.552), the fixed-effects model was applied. The synthesized results showed that patients with high TLG had a significantly higher risk of recurrence or progression than those with low TLG (HR = 1.843, 95% CI = 1.100–3.086, P = 0.02)(**Figure 2B**) . Begg's funnel plot and Egger's test indicated no publication bias (P = 0.261), and sensitivity analysis showed analysis was relatively stable (**Figure 2C-D**) .

Five articles about nodal SUV_{max} were included in the study.[13, 19, 21-23] For significant heterogeneity (I^2 = 69.4%, P = 0.011), the random-effects model was applied. The synthesized results showed that patients

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with higher nodal SUV_{max} had a significantly higher risk of recurrence or progression than those with lower nodal SUV_{max} (HR = 3.478, 95% CI = 2.006-6.029, P <0.001) **(Figure S3A)** . The publication bias was significant based on the funnel graph**(Figure S3B)** and Egger's test (P = 0.04). Sensitivity analysis proved that the results was relatively stable **(Figure S3C)** .

Second outcome: OS

Seven articles about SUV_{max} measurement of tumor tissue were included in the study.[11, 13, 14, 18, 19, 24, 25]For moderate heterogeneity (I^2 = 36.2%, P = 0.151), the fixed-effects model was applied when pooling HR. The combined HR was 2.582 (95% CI 1.936-3.443, P <0.001), which meant patients with high SUV_{max} had a shorter survival time than those with low SUV_{max} **(Figure 3A)** . Begg's funnel plot and Egger's test indicated no publication bias (P = 0.113), and sensitivity analysis showed that the analysis was relatively stable**(Figure 3B-C)** .

Two articles about primary tumor SUV_{mean} were included in the study.[14, 20] For no heterogeneity (I^2 = 0.0%, P = 0.893), the fixed-effects model was applied when pooling HR. The synthesized results showed that patients with high SUV_{mean} had a shorter survival time than those with low SUV_{mean}, but there was no statistical significance (HR = 1.523, 95% CI = 0.764–3.038, P = 0.232)**(Figure S4A)** . Because of the limited data, publication bias and sensitivity analysis were not performed.

Two articles about TLG measurement of tumor tissue were included in the study.[14, 20] In the absence of heterogeneity (I^2 = 0.0%, P = 0.672), the fixed-effects model was applied when pooling HR. The synthesized results showed that patients with high TLG had a shorter survival time than those with low TLG, but the result had no statistical significance (HR = 1.371, 95% CI = 0.681-2.759, P = 0.377) **(Figure S4B)** . Because of the limited data, publication bias and sensitivity analysis were not performed.

Two articles about nodal SUV_{max} were included in the study.[19, 22] For no heterogeneity (I^2 = 54.1%, P = 0.140), the fixed-effects model was applied when pooling HR. The synthesized results showed that patients with high nodal SUV_{max} had a shorter survival time than those with low nodal SUV_{max} (HR = 2.095, 95% CI = 2.027-2.166, P <0.001) **(Figure S4C)** . Because of the limited data, publication bias and sensitivity analysis were not performed.

Discussion

In this meta-analysis, the results revealed that MTV and TLG measurement of tumor tissue showed potential as a biomarker for EFS. The results about primary tumor SUV_{max} and nodal SUV_{max} were significantly correlated with EFS with relatively high heterogeneity. Besides, primary tumor SUV_{max} could be a biomarker for OS, and nodal SUV_{max} was significantly related to OS with relatively high heterogeneity. Other FDG PET/CT parameters were found to have no significant association with prognosis.

This meta-analysis focused on the FDG PET/CT parameters as a categorical variable, but the results of articles interesting in FDG PET/CT parameters as a continuous variable exhibited extreme discrepancy among different studies. For example, Carpenter et al. reported that primary tumor MTV and primary tumor TLG were significantly associated with OS in the univariate analyses, whereas only primary tumor TLG were significantly correlated with OS in the multivariate analyses.[26] Calles-Sastre et al. found that primary-tumor MTV and primary-tumor TLG showed a significant association with OS and with RFS in the univariate analyses.[27]Scher et al. detected primary-tumor MTV and primary-tumor TLG were correlated with OS and DFS in the univariate analyses, whereas primary-tumor TLG was the only FDG PET parameter significantly correlated with OS and DFS in the multivariate analyses.[24] In addition, Liu et al. confirmed that primary-tumor MTV was a significant predictor of OS in the univariate analyses.[28] Chong et al. reported that primary-tumor SUV_{max}, primary tumor MTV, and primary tumor TLG were significant prognostic factors for DFS in univariate analysis, but none of them was significant in the multivariate analyses **(Table S2)** .[23]

Apart from pretreatment FDG PET/CT parameters, some studies focused on the prognostic value of during-treatment FDG PET/CT parameters. Carpenter et al. reported that primary-tumor MTV and primary-

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tumor TLG during treatment were significantly associated with OS and DFS.[26] Liu et al. found that primary-tumor MTV during treatment was significantly associated with OS.[28]Krhili et al. confirmed that not only primary-tumor MTV and primary-tumor TLG but also SUV_{max} during treatment were significant prognostic factors for OS and DFS (**Table S3**) .[29] Besides, changes between pre- and intra-treatment FDG-PET/CT parameters also were confirmed to be prognostic factors in some studies. Park et al. confirmed that the percentage changes of SUV_{max} have a prognostic value for predicting DFS.[30] Oh et al. showed that a decrease of SUV_{max} was a statistically significant predictor of PFS.[31] However, Carpenter et al. reported no correlation among the changes in primary-tumor SUV_{max}, SUV_{mean}, MTV, TLG, and survival.[26]

Except for the pretreatment FDG PET/CT parameter, during-treatment FDG PET/CT parameter, and changes between pre- and intra-treatment FDG-PET/CT parameters, the one-two punch, using various types of prognostic factors to create a prognosis-predicting model, was a new orientation. For example, Hong et al. suggested a simple prognosis prediction model, using pretreatment FDG PET/CT and human papillomavirus (HPV) genotyping in patients with LACC treated with CCRT.[32] Lee et al. constructed a nomogram based on these six (including age, nodal SUV_{max}, primary-tumor SUV_{max}, size, stage, and SCC) and seven (including age, nodal SUV_{max}, primary-tumor SUV_{max}, size, stage, SCC, and high-risk HPV status) independent risk factors for two-year DFS and five-year OS.[19] Besides, radiomics is a new frontier to predict the prognosis of patients with LACC. For example, Lucia et al. found that in LACC treated with CCRT, radiomics features such as Grey Level Non-uniformity GLRLM from PET are independent predictors of recurrence and loco-regional control with significantly higher prognostic power than usual clinical parameters.[16] The predictive tool-enrolled FDG PET/CT parameter still needs more study.

Our study has some noteworthy limitations. First, all studies enrolled in the meta-analysis were retrospective, which might add selective bias. Second, significant heterogeneity existed in the results of this meta-analysis, and no subgroup analysis was performed for the limited studies. The potential resource of the heterogeneity was probably from four aspects. Patients in each study had different FIGO stages, different histologic subtypes, different treatment strategies, and different follow-up endpoints (**Table 1-3**) . Besides this, the different PET/CT technique and image analysis were existed in each study, which might cause the heterogeneity in this analysis (**Table S4**) . Third, the cut-off values for FDG PET/CT metabolic parameters were different in each study. Last, the HR used in this meta-analysis was directly extracted from a Cox proportional hazards model (multivariate analysis and univariate analysis) or indirectly estimated from Kaplan-Meier curves. By ignoring this discrepancy, the potential heterogeneity was exposed after synthesizing the results of all included studies. Considering these limitations, future large-scale prospective studies are needed to confirm the prognostic values of FDG PET metabolic parameters further. Despite these limitations, our study is the first meta-analysis to evaluate the prognostic value of FDG PET/CT metabolic parameters in LACC treated with CCRT and offers some significant findings.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contributions to authorship

QLL and YLZ conceived and designed the study. LH and QW extracted and analysed data. LH, LBZ and QW were the statisticians who confirmed the analysis of this study. LH, KLZ and YRW wrote the manuscript. QLL, YLZ and XF critically revised the manuscript. All authors reviewed and approved the final manuscript.

Details of ethics approval

Not applicable.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Results for primary SUVmax for DFS. (A) Forest plots of the HRs for SUVmax. (B) Begg's funnel plot for SUVmax. (C) Sensitivity analysis of the influence of each individual study on the pooled HR for SUVmax.

Figure S2. Results for nodal SUVmax for DFS. (A) Forest plots of the HRs. (B) Begg's funnel plot. (C) Sensitivity analysis of the influence of each individual study on the pooled HR.

Figure S3. Results for primary SUVmax for OS. (A) Forest plots of the HRs. (B) Begg's funnel plot. (C) Sensitive analysis of the influence of each individual study on the pooled HR.

Figure S4. Results for primary SUVmean, TLG and nodal SUVmax, and for OS. (A) Forest plots of the HRs with primary SUVmean. (B) Forest plots of the HRs with primary TLG. (C) Forest plots of the HRs with nodal SUVmax.

Table S1. Searching strategy.

Table S2. Summary of prognostic results about pretreatment FDG PET parameters as a continuous variable

Table S3. Summary of prognostic results about FDG PET parameters during treatment.

Table S4. Information about PET/CT technique and image analysis

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Figure legends

Figure 1. Flow chart of the literature search.

Figure 2. Results for primary MTV and TLG for DFS (A) Forest plots of the HRs for DFS with MTV. (B) Forest plots of the HRs for DFS with TLG. (C) Begg's funnel plot for TLG. (D) Sensitivity analysis of the influence of each individual study on the pooled HR for TLG.

Figure 3. Results for primary SUV_{max} for OS. (A) Forest plots of the HRs. (B) Begg's funnel plot. (C) Sensitivity analysis of the influence of each individual study on the pooled HR.

Table 1. Basic information and patient characteristics.

Surname of first author	Year	Country	Study design	No. of patients	Age	Age	Histology	Histology
					Median	Range	SSC	ACa
Yilmaz	2018	Turkey	Retrospective	44	54.6	28–78	NS	NS
Yildirim	2018	Turkey	Retrospective	63	58	21–86	NS	NS
Cima	2017	Switzerland	Retrospective	92	57	30-89	71	14
Guler	2018	Turkey	Retrospective	129	57	22–83	119	10
Lucia	2018	France	Retrospective	69	58	29–90	54	9
Hong	2016	Korea	Retrospective	56	57	32–81	49	7
Herrera	2016	Switzerland	Retrospective	38	52.5	26–83	33	5
Chong	2015	Korea	Retrospective	56	51.5	NS	50	6
Onal	2015	Korea	Retrospective	93	58	30–89	87	6
Im	2014	Korea	Retrospective	145	55	22-88	131	10
Onal	2013	Turkey	Retrospective	149	58	21-86	138	11
Chong	2017	Korea	Retrospective	93	53.1	NS	85	5
Lee	2020	Korea	Retrospective	270	NS	NS	243	NS
Vercellino	2012	France	Retrospective	16	57	32-69	15	1

SSC, squamous cell carcinoma; AC, adenocarcinoma, NS, not stated

Table 2 Disease features: stage and follow-up

Surname of first author	Stage	Stage	Stage	Stage	Stage	Stage		Follow-up	Fo up
	IB	IIA	IIB	IIIA	IIIB	IV		Median	Ra
Yilmaz	7	2	27	1	3	4		22	8-5
Yildirim	4	4	38	8	9	-		60	3-1
Cima	-	-	78	3	4	7		31	6-8
Guler	16	4	52	13	36	8		30	3.7 94.
Lucia	10	4	36	1	9	9		36	6-7
Hong	-	-	38	3	6	9		NS	NS
Herrera	6	10	15	2	4	1		52.5	26-
Chong (2015)	-	-	44	7	5	-		42	6-9
Onal	9	2	49	10	21	2		29	3-7
Im	19	8	90	5	20	3		NS	NS
Onal	16	7	84	15	24	3		29	3-7
Chong (2017)	-	-	75	12	5	1		55	9-1
Lee	-	-	215	NS	NS	NS		49.5	3-1
Vercellino	1	1	8	3	3	3			

NS, not stated

Table 3 Treatment-related features.

Surname of first author	EBRT	EBRT	EBRT	ICR	ICR	ICR	Co ch ap
	Type	Total dose Median(range)	Fraction (Gy)	Fraction (Gy)	Number	Number	Ty
Yilmaz	3D-CRT	50.4	1.8	6	6	5	We 40r m2 cis
Yildirim	3D-CRT	50.4	1.8	7	7	4	We 40r m2 cis
Cima	3D-CRT	NS	NS	NS	NS	NS	We 40r m2 cis
Guler	3D-CRT	50.4	1.8	7	7	4	We 40r m2 cis
Lucia	3D-CRT/IMRT	45-50.4	NS	7	7	3–4	We 40r m2 cis
Hong	NS	54	2	3.5	3.5	8	We 30r cis or tri pa 13 an ca
Herrera	IGRT	45(45-50.4)	NS	7	7	3–4	We 40r m2 cis
Chong (2015)	3D-CRT	45	1.8	-	-	-	We 40r cis
Onal	3D-CRT	50.4	1.8	7	7	4	We 40r m2 cis
Im	NS	NS	NS	NS	NS	NS	We cis

Surname of first author	EBRT	EBRT	EBRT	ICR	ICR	ICR		Co ch ap
Onal	3D-CRT	50.4	1.8	7	7	4		We 40... m2... cis...
Chong (2017)	3D-CRT	45	1.8	6	6	NS		We 40... cis...
Lee	3D-CRT	45	1.8	NS	NS	NS		We 40... m2... cis...
Vercellino	NS	NS	NS	NS	NS	NS	NS	NS

EBRT, External Beam Radiotherapy; ICR Intracavitary Brachytherapy IGRT, Image Guided Radiation Therapy; 3D-CRT, 3D Conformal Therapy; IMRT, Intensity-Modulated Radiation Therapy; NS, not stated

A.

Study ID		HR (95% CI)	% Weight
Chong (2015)		2.17 (0.80, 5.60)	29.68
Hong (2016)		6.20 (1.35, 28.48)	12.10
Guler (2018)		1.60 (0.80, 3.21)	58.22
Overall (I-squared = 20.9%, p = 0.282)		2.06 (1.21, 3.51)	100.00

.0351   1   28.5

B.

Study ID		HR (95% CI)	% Weight
Chong (2015)		2.29 (0.80, 5.60)	28.09
Hong (2016)		1.82 (1.52, 91.96)	6.31
Herrera (2016)		3.17 (0.34, 29.21)	5.39
Yilmaz (2018)		4.17 (1.01, 16.13)	13.82
Guler (2018)		1.19 (0.55, 2.50)	46.39
Overall (I-squared = 0.0%, p = 0.552)		1.84 (1.10, 3.09)	100.00

.0109   1   92

C.

Funnel plot with pseudo 95% confidence limits

D.

Meta-analysis estimates, given named study is omitted

Lower CI Limit ○ Estimate	Upper CI Limit
Yilmaz (2018)	
Guler (2018)	
Hong (2016)	
Herrera (2016)	
Chong (2015)	

-0.08   0.10   0.61   1.13   1.69

A.

Study ID		HR (95% CI)	% Weight
Vercellino (2012)		5.87 (1.18, 29.29)	3.21
Onal (2013)		6.41 (2.81, 14.62)	12.18
Im (2014)		2.14 (1.08, 3.87)	20.34
Scher (2017)		8.02 (1.63, 39.34)	3.27
Cima (2017)		1.96 (0.93, 4.15)	14.81
Yildirim (2018)		1.98 (0.82, 4.75)	10.74
Lee (2020)		2.14 (1.32, 3.47)	35.46
Overall (I-squared = 36.2%, p = 0.152)		2.58 (1.94, 3.44)	100.00

.0254   1   39.3

B.

Funnel plot with pseudo 95% confidence limits

C.

Meta-analysis estimates, given named study is omitted

Lower CI Limit ○ Estimate	Upper CI Limit
Yildirim (2018)	
Scher (2017)	
Cima (2017)	
Im (2014)	
Onal (2013)	
Lee (2020)	
Vercellino (2012)	

0.52   0.63   1.02   1.41   1.62

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