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Prognostic value of post-treatment 18F-fluorodeoxyglucose positron emission tomography in uterine cervical cancer patients treated with radiotherapy: a systematic review and meta-analysis

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ABSTRACT

Objectives: To perform a systematic review and meta-analysis of the prognostic value of post-treatment 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) in uterine cervical cancer patients treated with radiotherapy (RT) with or without chemotherapy.

Methods: PubMed and Embase databases were searched up to July 22, 2018, for studies which evaluated the response outcomes of 18F-FDG PET following RT, and their prognostic significance in uterine cervical cancer was assessed with overall survival (OS) or progression-free survival (PFS) as endpoints. Hazard ratios (HRs) were meta-analytically pooled using the random-effects model.

Results: Eleven studies with 12 patient cohorts including 1,104 patients were included. For a quantitative synthesis of OS, 7 cohorts were included. Two cohorts which reported disease-specific survival instead of OS were also included with flexibility. Pooled HR of complete metabolic response (CMR) compared to partial metabolic response (PMR) was 0.19 (95% confidence interval [CI]=0.11–0.31). Pooled HR of CMR compared to progressive metabolic disease (PMD) was more evident at 0.07 (95% CI=0.04–0.12), and that of CMR compared to both PMR and PMD was 0.20 (95% CI=0.12–0.34). Quantitative synthesis for PFS was performed with a total of 8 cohorts. Pooled HR of CMR was 0.17 (95% CI=0.10–0.29) compared to PMR, 0.02 (95% CI=0.01–0.06) compared to PMD and 0.12 (95% CI=0.07–0.19) compared to both PMR and PMD.

Conclusion: Response results of post-RT 18F-FDG PET were significant prognostic factors in patients with uterine cervical cancer, and 18F-FDG PET could be a reasonable follow-up imaging modality.

Keywords: Positron Emission Tomography; Uterine Cervical Neoplasms; Radiotherapy; Survival

INTRODUCTION

Uterine cervical cancer is the fourth most common malignancy in women worldwide, and accounts for 7.5% of all female cancer-related deaths with estimated 266,000 deaths in 2012 [1]. Definitive concurrent chemoradiotherapy (CCRT) is a standard therapy for locally advanced cervical cancer at stages IIB–IVA according to the International Federation of Gynecology and Obstetrics (FIGO) [2]. At earlier stages (FIGO stage IB–IIA), radiotherapy (RT) with or without chemotherapy has shown survival outcomes comparable to those following radical surgery, with a lower risk of complications [3]. Thus, RT has been one of the standard treatment options for uterine cervical cancer.

Although the significance of residual disease after RT remains undefined, a previous study reported that uterine cervical cancer which does not regress promptly (post-treatment 1 to 3 months) was likely to recur. However, they only used physical examination or biopsy without imaging, and the timing of evaluation was varied [4]. A recent retrospective study demonstrated that 10% of the patients with FIGO stage IB2–IVA who received CCRT showed the presence of residual tumor based on magnetic resonance imaging (MRI) checked at 3 months after therapy [5]. They reported that residual tumor size of ≤2 cm was a significantly good prognostic factor for overall survival (OS) (hazard ratio [HR]=0.26; 95% confidence interval [CI]=0.08–0.86; p=0.027), and local progression-free survival (PFS) (HR=0.10; 95% CI=0.03–0.39; p=0.001). Although MRI is more effective than computed tomography (CT) in evaluating the response after CCRT [6], MRI assessment is still challenging with the limitation of false positives detected due to post-treatment changes [7]. Also, false-positive results might cause unnecessary repeated imaging and salvage treatments.

The ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) which measures the metabolic viable disease can be a better choice as the follow-up modality after RT in uterine cervical cancer patients [8]. A number of prospective and retrospective studies have evaluated the use of ^{18}F-FDG PET to assess the response and predict survival following RT in uterine cervical cancer. However, the significance of post-RT ^{18}F-FDG PET response evaluation has not been well-established, and the procedure is not routinely performed in clinical settings. Therefore, we performed a systematic review and meta-analysis to evaluate the prognostic value of post-treatment ^{18}F-FDG PET in patients with uterine cervical cancer who received definitive RT with or without chemotherapy.

METHODS

This systematic review and meta-analysis were done in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [9]. The protocol was registered to the International Prospective Register of Systematic Reviews (registration No. CRD42018104860). The research question of the present meta-analysis was as below: "Could response evaluation using post-RT ^{18}F-FDG PET predict the survival outcomes in patients with cervical cancer?"

1. Literature search

PubMed and Embase databases were searched up to July 22, 2018. Search queries included synonyms of "uterine cervical cancer," "^{18}F-FDG PET," and "radiotherapy" as the following (uterus OR uterine) AND (cervix OR cervical) AND (FDG OR fluorodeoxyglucose) AND (PET

OR "positron emission tomography") AND (radiation OR chemoradiation OR radiotherapy OR chemoradiotherapy). There was no language restriction. To find the additional relevant studies, the references of retrieved articles were also checked.

The inclusion criteria was based on the Patient/Intervention/Comparator/Outcome/Study design criteria [9]: 1) "patients" with uterine cervical cancer; 2) response outcomes of post-treatment ^{18}F-FDG-PET as "intervention"; 3) no "comparator" on this study; 4) OS or PFS as "outcome"; and 5) "study design" as original articles or brief report. The exclusion criteria were as follows: 1) not in the field of interest; 2) insufficient survival information; 3) inclusion of recurrent cases; and 4) overlapping study population.

2. Data extraction and quality assessment

The characteristics of study, clinicopathological factors, and ^{18}F-FDG PET were extracted using a standardized form: 1) study characteristics: first author, year of publication, institution, enrollment period, number of patients, and design (prospective or retrospective/ consecutive enrollment); 2) clinicopathological characteristics: age, stage, pathology, treatment, interval between the date of therapy and ^{18}F-FDG PET, response, endpoint, and follow-up period; and 3) ^{18}F-FDG PET characteristics: vendor, model, injected dose, uptake time, scan time, reconstruction methods, and attenuation methods. There was a study which reported disease-specific survival instead of OS, it was also included for OS analysis with flexibility [10].

The methodological quality of included studies was assessed using Quality in Prognostic Studies (QUIPS) tool [11]. Two independent reviewers performed literature selection, data extraction, and quality assessment. If there was any discrepancy, it was resolved via discussion.

3. Statistical analysis

Primary endpoint was OS, and secondary endpoint was PFS. As an effect size of prognostic value, HRs from comparisons amongst response groups (i.e. complete metabolic response [CMR], partial metabolic response [PMR], stable metabolic disease [SMD], and progressive metabolic disease [PMD]) were used. HRs with 95% CIs from univariate Cox regression were extracted. If not available, CIs were indirectly calculated based on p-values from log-rank test [12]. When Kaplan-Meier curves were presented, HRs and their CIs were extracted using Engauge Digitizer version 10.4 (http://markummitchell.github.io/engauge-digitizer/) and methodology by Tierney et al [13]. Of note, we included 2 studies having suspected overlapping study population, as they reported HRs from the comparison of different response groups [10,14].

The HRs were meta-analytically pooled using the random-effects model. Heterogeneity was evaluated with Higgins I^2 [15]. Assessment of publication bias was not feasible, because of the paucity of studies in each subgroup [16]. Statistical analyses were done with Review Manager (version 5.3.5; The Cochrane Collaboration, London, UK). The p-value <0.05 was considered statistically significant.

RESULTS

1. Study characteristics

Fig. 1 describes the study selection process. Initial literature search retrieved 853 articles, of which 26 articles were considered potentially eligible. After full-text review, 15 articles were excluded as following: No survival analysis (n=8), overlap in study population (n=5), or inclusion of recurrent cases (n=2). Ultimately, 11 original articles with 1,104 patients were included [10,14,17-25]. The characteristics of the study, clinicopathological factors, and PET are summarized in **Tables 1** and **2**. Since Schwarz et al. [10] included 2 study populations (retrospective and prospective cohorts) and reported results from each, we pooled their results separately in all synthesis. To avoid confusion, we specified the number of study cohorts (a total of 12) instead of the number of studies (a total of 11). Among the 12 cohorts, 4 were prospectively enrolled. The FIGO stages ranged from I to IV. The median interval between the end of treatment and PET ranged from 1.0 to 5.0 months. The metabolic responses were classified as CMR, PMR, or PMD upon visual assessment (qualitative) in 10 cohorts. Except 2 studies which used their own scoring system [20,23], the rest defined CMR as the absence of abnormal FDG uptake noted on the pre-treatment ^{18}F-FDG PET, and PMR was defined as any persistent abnormal uptake at these sites. PMD was defined as new foci of
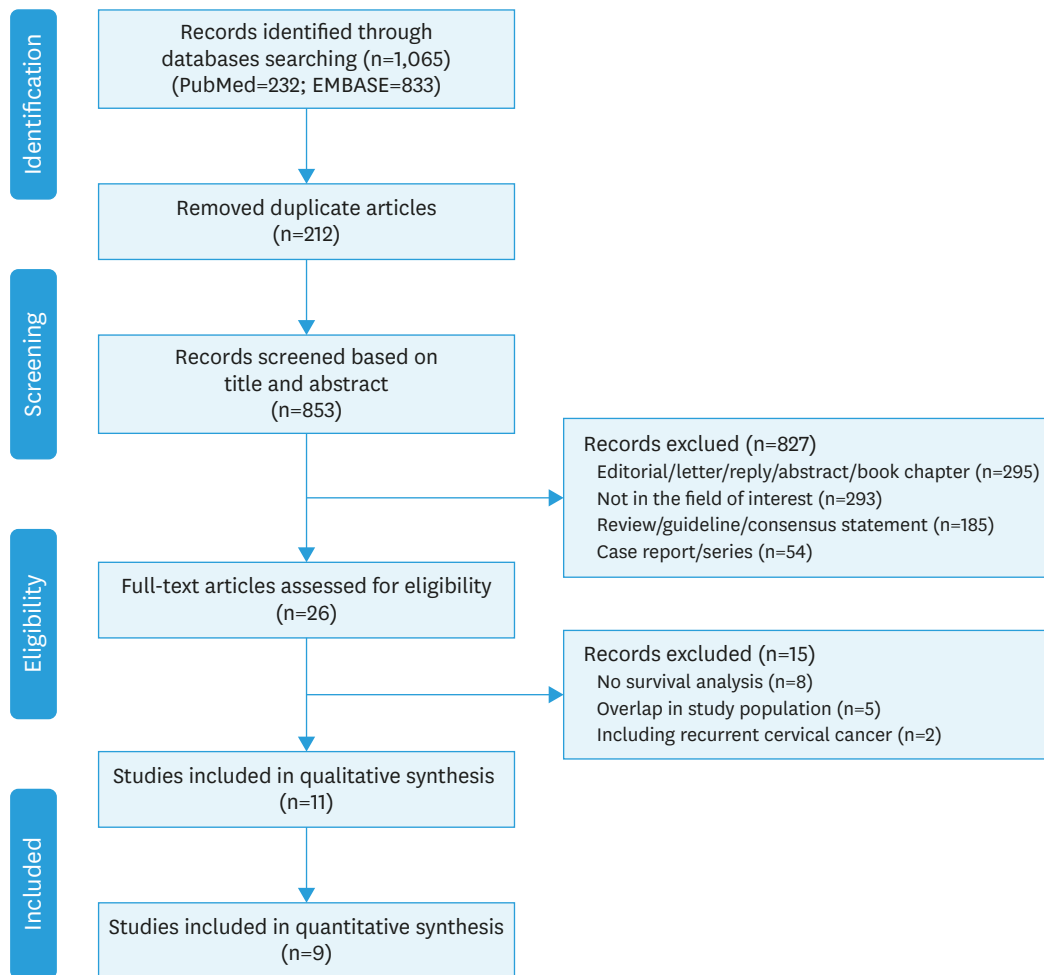
Fig. 1. Flow diagram showing the study selection process.

Records identified through databases searching (n=1,065) (PubMed=232; EMBASE=833)

Removed duplicate articles (n=212)

Records screened based on title and abstract (n=853)

Records excluded (n=827)
  Editorial/letter/reply/abstract/book chapter (n=295)
  Not in the field of interest (n=293)
  Review/guideline/consensus statement (n=185)
  Case report/series (n=54)

Full-text articles assessed for eligibility (n=26)

Records excluded (n=15)
  No survival analysis (n=8)
  Overlap in study population (n=5)
  Including recurrent cervical cancer (n=2)

Studies included in qualitative synthesis (n=11)

Studies included in quantitative synthesis (n=9)

Identification | Screening | Eligibility | Included

Table 1. Study and clinicopathological characteristics of studies included in meta-analysis

First author	Year	Institution	Enrollment period	No. of patients	Study design	Median age (yr)	Stage	Pathology	Tx	Median interval (Tx-PET, mo)	Response (%)	Compare		Endpoint	Median f/u (mo)
Chong et al. [17]	2015	Kyungpook National University Medical Center	2005–2014	56	R	51.5*	IIB–IIIB	SqCC, AC	CCRT	5.0	CMR (66) PMR (30) PMD (4)	CMR	PMR/PMD	PFS	42.0
Grigsby et al. [14]	2003	Washington University School of Medicine	1998–2001	76	R	50.0*	IA2–IVB	SqCC, AC, ASC, SCC	CCRT/RT	Range, 2.4–10.4	CMR (82) PMR/PMD (18)	CMR	PMR/PMD	PFS	21.3
Herrera et al. [18]	2016	Lausanne University Hospital	2007–2014	38	R	52.5	IB1–IVA	SqCC, AC	CCRT	3.0	CMR (76) PMR (24)	CMR	PMR	PFS, OS	37.0
Kunos et al. [19]	2011	Case Comprehensive Cancer Center	2004–2009	51	R	49.0	IB2–IVA	SqCC, AC, ASC	CCRT	2.6	Post/Pre-Tx SUV ratio >0.33 (29) <0.33 (71)	>0.33	<0.33	PFS	15.0
Liu et al. [20]	2018	Chang Gung Memorial Hospital	2009–2013	55	P	56.0	I–IIIA	SqCC	CCRT	Range, 2–3.0	CMR (60) Equivocal (24) PMR/PMD (16)	CMR	PMR/PMD	OS	81.0
Oh et al. [21]	2013	Samsung Medical Center	2009–2010	59	P	53.5	IB1–IVA	SqCC, AC	CCRT	1.0	CMR (73) PMR (20) PMD (7)	CMR	PMR/PMD	PFS	25.0
Onal et al. [22]	2014	Baskent University Faculty of Medicine	2006–2012	152	R	CMR group: 58.0 PMR/PMD group: 57.0	IB2–IVA	SqCC, AC	CCRT	3.9	CMR (80) PMR (15) PMD (5)	CMR	PMR/PMD	PFS, OS	28.7
Scarsbrook et al. [23]	2017	Leeds Teaching Hospitals NHS Trust	2011–2014	96	R	47.0*	IB1–IVA	SqCC, AC, ASC, NEC	CCRT	3.3*	CMR (42) Indeterminate (25) PMR (18) PMD (15)	CMR / CMR	PMR / PMD	PFS, OS	Range 18–54.0
Schwarz et al. [10]	2007	Washington University School of Medicine	1998–2006	152	R	49.0	IB1–IVA	SqCC, AC, CCC	CCRT	NR	CMR (75) PMR (12.5) PMD (12.5)	CMR / CMR	PMR / PMD	PFS, DSS	Range 28–70
Schwarz et al. [10]	2007	Washington University School of Medicine	2003–2006	92	P	51.0	IB1–IVA	SqCC, AC, CCC	CCRT	3.1*	CMR (70) PMR (16) PMD (13)	CMR / CMR	PMR / PMD	PFS, DSS	25*
Siva et al. [24]	2015	Peter MacCallum Cancer Centre	2002–2007	105	P	54.0	IB–III	SqCC, AC, Others	CCRT	Range, 3–6.0	CMR (70) PMR (9) PMD (21)	CMR / CMR	PMR / PMD	OS	62.3
Yoon et al. [25]	2016	Yonsei University College of Medicine	2005–2013	172	R	55.0	IB1–IVA	SqCC, AC, SCC	CCRT/RT	1.5	CMR (11) PMR (72) SMD (12) PMD (5)	CMR/ PMR	SMD/PMD	PFS, OS	NR

AC, adenocarcinoma; ASC, adenosquamous carcinoma; CCC, clear cell carcinoma; CCRT, concurrent chemoradiotherapy; CMR, complete metabolic response; DSS, disease-specific survival; f/u, follow-up; NR, not reported; OS, overall survival; P, prospective; PET, positron emission tomography; PFS, progression-free survival; PMD, progressive metabolic disease; PMR, partial metabolic response; R, retrospective; RT, radiotherapy; SCC, small cell carcinoma; SMD, stable metabolic disease; SqCC, squamous cell carcinoma; SUV, standardized uptake value; Tx, treatment.
*Data reported as mean values.

Table 2. Characteristics of PET

First author	Vendor	Model	Dose (MBq)	Uptake time (min)	Scan time (min/bed)	Reconstruction	Attenuation correction	PET/CT	Methods of response evaluation
Chong et al. [17]	GE/CTI	Reveal RT-HiREZ/ Discovery STE	8.1/kg	60	3	OSEM	CT	Yes	Qualitative
Grigsby et al. [14]	Siemens/CTI	ECAT EXACT	NR	NR	NR	NR	NR	PET alone	Qualitative
Herrera et al. [18]	GE	Discovery 690FX/TOF	3.5/kg	60	NR	NR	CT	Yes	Qualitative
Kunos et al. [19]	Phillips	Gemini TF/GXL	370–444	60	1–3	NR	CT	Yes	Quantitative (SUV ratio)
Liu et al. [20]	GE/Siemens	Discovery ST16/ Biograph mCT	370 ± 10%	50	NR	OSEM	CT	Yes	Qualitative
Oh et al. [21]	GE	Discovery STE	5.0/kg	60	2.5	OSEM	CT	Yes	Qualitative, Quantitative (SUV difference)
Onal et al. [22]	GE	Discovery STE 8	370–555	60	3	NR	CT	Yes	Qualitative
Scarsbrook et al. [23]	Phillips	Gemini TF 64	400	60	NR	OSEM	CT	Yes	Qualitative
Schwarz et al. [10]	NR	NR	NR	NR	NR	NR	NR	PET alone	Qualitative
Schwarz et al. [10]	Siemens	Biograph LSO 2	555–740	45–60	2–4	OSEM	CT	Yes	Qualitative
Siva et al. [24]	GE	Discovery LS/STE	370	NR	NR	NR	CT	Yes	Qualitative
Yoon et al. [25]	GE	Discovery LS/ST	5.5/kg	60	3	OSEM	CT	Yes	Quantitative (EORTC)

CT, computed tomography; EORTC, European Organisation for Research and Treatment of Cancer; NR, not reported; OSEM, ordered subset expectation maximization; PET, positron emission tomography; SUV, standardized uptake value.

abnormal FDG uptake. One used quantitative assessment based on European Organization for Research and Treatment of Cancer (EORTC) criteria. Kunos et al. [19] stratified treatment response based on standardized uptake value (SUV) ratio or difference between pre- and post-RT (**Table 2**).

2. Quality assessment

Fig. 2 presents risk of bias assessment using the QUIPS tool. Two different study cohorts in Schwarz et al. [10] were separately assessed. For selection bias, 6 cohorts including the retrospective cohorts of Schwarz et al. [10] had a moderate risk, as the study populations were enrolled retrospectively and not consecutively [14,17,19,25]. All the included cohorts had a low-risk of attrition bias. Regarding prognostic factor measurement, 9 cohorts had a moderate risk of bias as it was not clearly mentioned whether image analyses were done in a blind manner [14,17,18,20-24]. For outcome measurement, 10 cohorts had a moderate risk of bias, because it is unclear whether the outcome was measured without knowledge of prognostic factors or the methods for outcome measurement was not clearly reported [14,17-19,21-25]. In regard to confounding bias, 2 cohorts had a high-risk as no or incomplete multivariate analysis was performed [22,23]. Regarding statistical analysis, all the studies had a low-risk of bias.
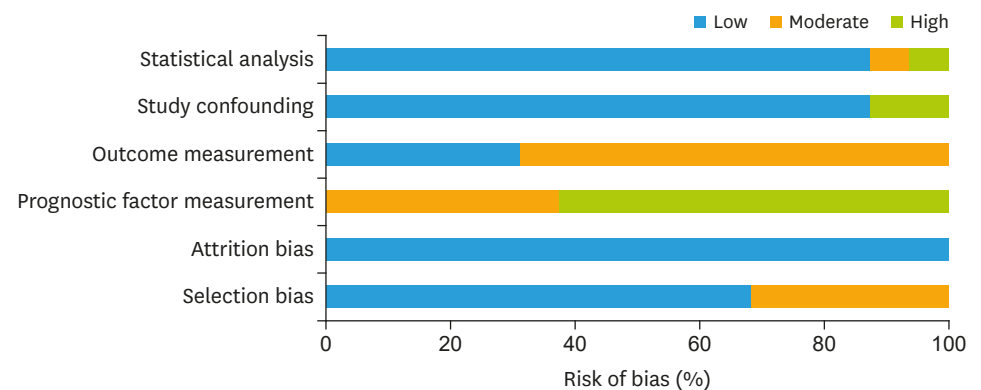

Fig. 2. Assessment of risk of bias using the QUIPS tool.
QUIPS, Quality in Prognostic Studies.

3. OS

The prognostic value of ^{18}F-FDG PET response for OS or disease-specific survival was assessed in 8 cohorts. Most cohorts (7/8) compared CMR to PMR and/or PMD. However, Yoon et al. [25] compared responders (CMR and PMR) to non-responders (SMD and PMD) so that the study was not included for quantitative synthesis. The study reported that maximum SUV responders demonstrated significantly low HRs in OS (HR=0.01; 95% CI=0.00–0.17; p=0.002) and PFS (HR=0.07; 95% CI=0.01–0.60; p=0.016) compared to non-responders in multivariate analysis. As a result, a total of 7 cohorts were included for OS quantitative synthesis, and 3 subgroup analyses were possible according to the pattern of comparison as follows: 1) CMR vs. PMR, 2) CMR vs. PMD, and 3) CMR vs. PMR/PMD (**Fig. 3**).

Pooled HR of CMR compared to PMR was 0.19 (95% CI=0.11–0.31) in 5 cohorts. Moderate heterogeneity was found (I^2=50%). Pooled HR of CMR compared to PMD was more evident at 0.07 (95% CI=0.04–0.12) in 4 cohorts, and pooled HR of CMR compared to both PMR and PMD was 0.20 (95% CI=0.12–0.34) in 2 cohorts without significant heterogeneity (I^2=0%).

A

First author	Log[HR]	SE	Weight (%)	HR IV, Random, 95% CI	HR IV, Random, 95% CI
Herrera et al.[18]	−1.20	0.34	24.1	0.30 (0.15–0.59)	
Scarsbrook et al. [23]	−1.51	0.35	23.5	0.22 (0.11–0.44)	
Schwarz et al. [10] (P)	−1.90	0.55	14.4	0.15 (0.05–0.44)	
Schwarz et al. [10] (R)	−1.43	0.34	24.1	0.24 (0.12–0.47)	
Siva et al. [24]	−2.97	0.56	14.0	0.05 (0.02–0.15)	
Total (95% CI)			100.0	**0.19 (0.11–0.31)**	

Heterogeneity: τ^2=0.16; χ^2=7.98, df=4 (p=0.09); I^2=50%
Test for overall effect: Z=6.49 (p<0.001)

0.01 0.1 1 10 100
CMR PMR

B

First author	Log[HR]	SE	Weight (%)	HR IV, Random, 95% CI	HR IV, Random, 95% CI
Scarsbrook et al. [23]	−3.00	0.84	12.8	0.05 (0.01–0.26)	
Schwarz et al. [10] (P)	−2.21	0.50	36.3	0.11 (0.04–0.29)	
Schwarz et al. [10] (R)	−2.81	0.83	13.2	0.06 (0.01–0.31)	
Siva et al. [24]	−2.97	0.49	37.7	0.05 (0.02–0.13)	
Total (95% CI)			100.0	**0.07 (0.04–0.12)**	

Heterogeneity: τ^2=0.00; χ^2=1.40, df=3 (p=0.70); I^2=0%
Test for overall effect: Z=8.89 (p<0.001)

0.01 0.1 1 10 100
CMR PMD

C

First author	Log[HR]	SE	Weight (%)	HR IV, Random, 95% CI	HR IV, Random, 95% CI
Liu et al. [20]	−2.12	0.91	9.2	0.12 (0.02–0.71)	
Onal et al. [22]	−1.56	0.29	90.8	0.21 (0.12–0.37)	
Total (95% CI)			100.0	**0.20 (0.12–0.34)**	

Heterogeneity: τ^2=0.00; χ^2=0.34, df=1 (p=0.56); I^2=0%
Test for overall effect: Z=5.83 (p<0.001)
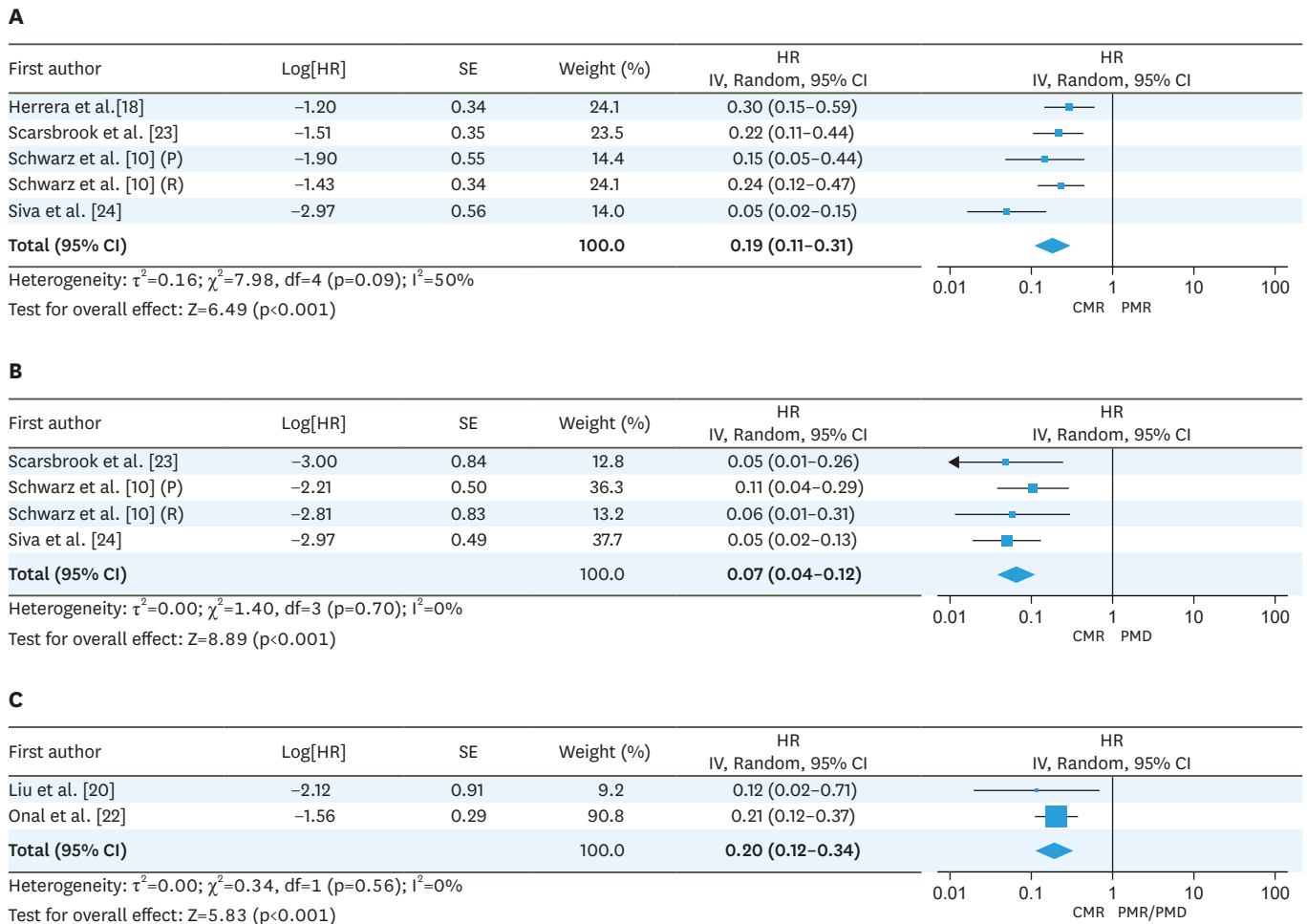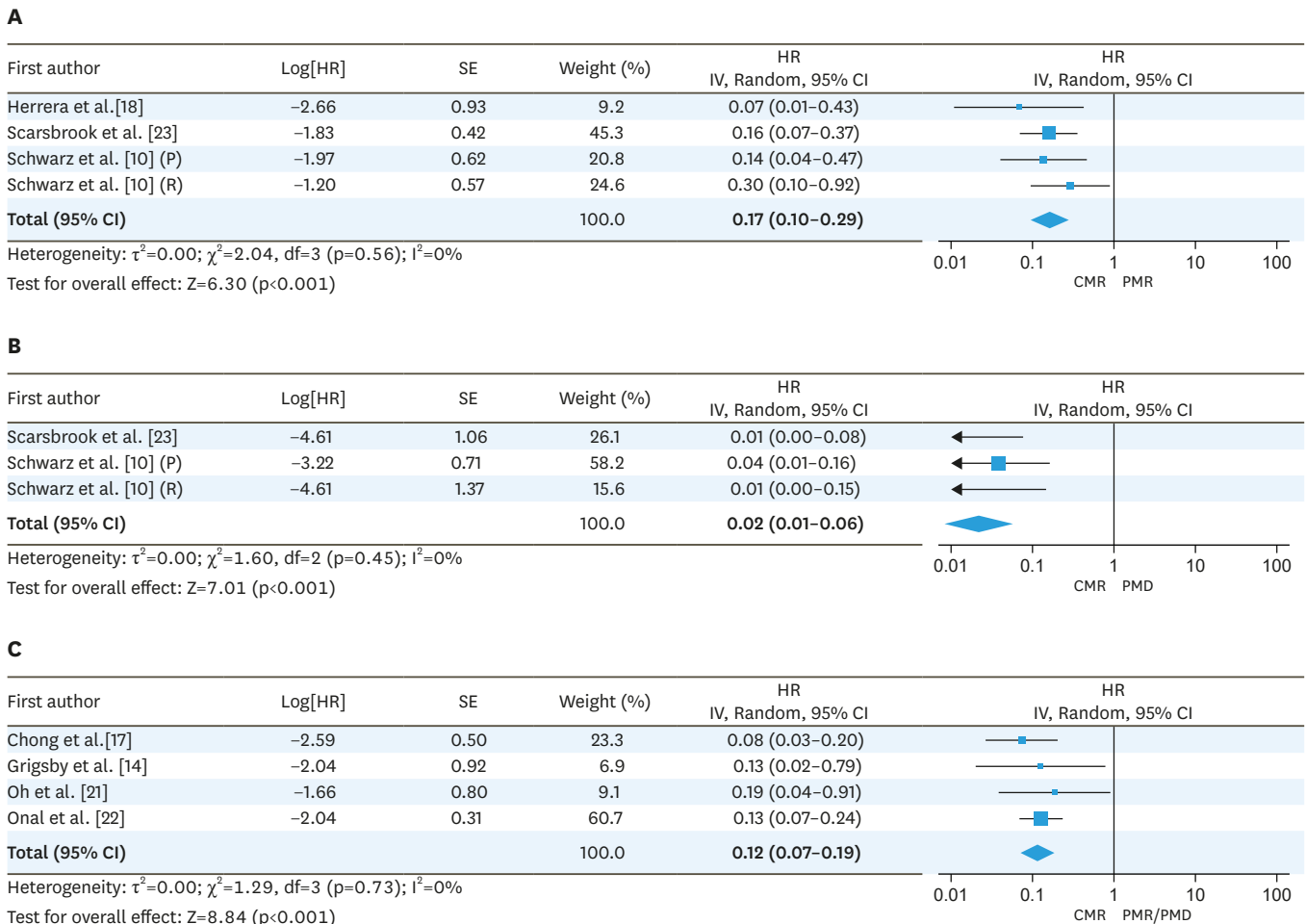
0.01 0.1 1 10 100
CMR PMR/PMD

Fig. 3. Forest plots for HRs of OS comparing (A) CMR to PMR, (B) CMR to PMD, and (C) CMR to PMR/PMD.
CI, confidence interval; CMR, complete metabolic response; HR, hazard ratio; OS, overall survival; PMD, progressive metabolic disease; PMR, partial metabolic response; SE, standard error.

A

First author	Log[HR]	SE	Weight (%)	HR IV, Random, 95% CI	HR IV, Random, 95% CI
Herrera et al.[18]	−2.66	0.93	9.2	0.07 (0.01–0.43)	
Scarsbrook et al. [23]	−1.83	0.42	45.3	0.16 (0.07–0.37)	
Schwarz et al. [10] (P)	−1.97	0.62	20.8	0.14 (0.04–0.47)	
Schwarz et al. [10] (R)	−1.20	0.57	24.6	0.30 (0.10–0.92)	
Total (95% CI)			100.0	**0.17 (0.10–0.29)**	

Heterogeneity: τ^2=0.00; χ^2=2.04, df=3 (p=0.56); I^2=0%
Test for overall effect: Z=6.30 (p<0.001)

B

First author	Log[HR]	SE	Weight (%)	HR IV, Random, 95% CI	HR IV, Random, 95% CI
Scarsbrook et al. [23]	−4.61	1.06	26.1	0.01 (0.00–0.08)	
Schwarz et al. [10] (P)	−3.22	0.71	58.2	0.04 (0.01–0.16)	
Schwarz et al. [10] (R)	−4.61	1.37	15.6	0.01 (0.00–0.15)	
Total (95% CI)			100.0	**0.02 (0.01–0.06)**	

Heterogeneity: τ^2=0.00; χ^2=1.60, df=2 (p=0.45); I^2=0%
Test for overall effect: Z=7.01 (p<0.001)

C

First author	Log[HR]	SE	Weight (%)	HR IV, Random, 95% CI	HR IV, Random, 95% CI
Chong et al.[17]	−2.59	0.50	23.3	0.08 (0.03–0.20)	
Grigsby et al. [14]	−2.04	0.92	6.9	0.13 (0.02–0.79)	
Oh et al. [21]	−1.66	0.80	9.1	0.19 (0.04–0.91)	
Onal et al. [22]	−2.04	0.31	60.7	0.13 (0.07–0.24)	
Total (95% CI)			100.0	**0.12 (0.07–0.19)**	

Heterogeneity: τ^2=0.00; χ^2=1.29, df=3 (p=0.73); I^2=0%
Test for overall effect: Z=8.84 (p<0.001)

Fig. 4. Forest plots for HRs of PFS comparing (A) CMR to PMR, (B) CMR to PMD, and (C) CMR to PMR/PMD.
CI, confidence interval; CMR, complete metabolic response; HR, hazard ratio; PFS, progression-free survival; PMD, progressive metabolic disease; PMR, partial metabolic response; SE, standard error.

4. PFS

The HRs of ^{18}F-FDG PET response regarding PFS was evaluated in 9 cohorts. Since Kunos et al. [19] reported the outcome in a different way using the ratio of post-therapy to pre-therapy SUVs, it was excluded for quantitative synthesis. They presented that the post-therapy/pre-therapy SUV ratio <0.33 was associated with a 35% improvement in 6-month PFS (p=0.004).

With a total of 8 cohorts included in quantitative synthesis, 3 subgroup analyses were performed same as OS analyses (**Fig. 4**). The pooled HR of CMR was 0.17 (95% CI=0.10–0.29) compared to PMR in 4 cohorts, 0.02 (95% CI=0.01–0.06) compared to PMD in 3 cohorts and 0.12 (95% CI=0.07–0.19) compared to both PMR and PMD in 4 cohorts. No heterogeneity was present in all subgroup analyses (I^2=0%).

DISCUSSION

The present study demonstrated that response evaluation using post-RT ^{18}F-FDG PET could be a strong prognostic factor for both OS and PFS in uterine cervical cancer patients. Patients

who resulted in CMR showed significantly lower risk of progression and death compared to populations with PMR or PMD. The HR of CMR compared to PMR was 0.19, and it was more prominent compared to PMD with HR of 0.07 in OS analyses. Although HR comparing CMR to both PMR and PMD (0.20) was higher than that of CMR compared to PMR, we speculated that the small number of included studies was susceptible for bias of sampling error.

About one-third of cervical cancer patients experience recurrence mostly within the first 2 years after RT [26], and majority of them might have been presented with PMD or PMR, if they had undergone post-treatment ^{18}F-FDG PET evaluation. Early intervention could be considered for patients who expect poor prognosis, with PMR or PMD detected using post-RT ^{18}F-FDG PET to improve their survival. Several previous studies failed to show the benefit of surgery following CCRT compared to definitive CCRT [27]. However, a considerable proportion of patients presented with pathological complete response (range, 38%–86%), and these patients may have concealed the benefit of surgery for cases of residual tumor. Response evaluation using post-RT ^{18}F-FDG PET could be valuable in identifying appropriate candidates for surgery after CCRT. Furthermore, the decision of a surgical salvage heavily depends on the location and extent of failure. The extent of hysterectomy also affects survival, as Sun et al. [28] reported significantly better OS among patients who received extrafascial hysterectomy than those who treated with extended hysterectomy after CCRT for advanced cervical cancer (5-year OS, 53.5% vs. 40.7%; p<0.05). This made the role of post-RT imaging more crucial.

The traditional response evaluation tool was Response Evaluation Criteria in Solid Tumors (RECIST) criteria using the diameter of the tumor [25]. However, size measurement is often difficult in the tumors with obscure margins, cystic lesions, and scar tissue. Sometimes, tumors do not shrink but are stabilized with necrotic and cystic changes without viability. Although CT or MRI has been more commonly used for post-treatment imaging than ^{18}F-FDG PET in the clinical setting, CT or MRI using RECIST criteria inevitably could not reflect these phenomena. On the other hand, ^{18}F-FDG PET allowed measurement of tumor response even in the absence of anatomical changes, by evaluating metabolic activity of the residual tumor [8]. Yoon et al. [25] reported that ^{18}F-FDG PET parameters were better prognostic markers compared to RECIST criteria, although CT which has lower diagnostic value than MRI was used. Their findings also suggested that the tumor diameter itself may not decrease due to fibrotic changes, inflammation or necrosis, and the more important factor seemed to be glucose metabolism. Post-treatment ^{18}F-FDG PET is generally not advocated due to lack of definite evidence [2]. However, National Comprehensive Cancer Network (NCCN) guidelines recommends ^{18}F-FDG PET/CT as a preferred follow-up modality owing to its detection ability for both locoregional and distant recurrences [29].

Few studies reported the accuracy of ^{18}F-FDG PET in detecting residual tumor compared to pathologic results. There was a single prospective trial comparing the diagnostic performances of MRI and ^{18}F-FDG PET/CT in predicting pathologically assessed residual disease after neoadjuvant CCRT [30]. Although there was no difference in overall accuracy (MRI, 84.6% vs. PET/CT, 85.0%; p=0.900), sensitivity was higher for MRI (62.8%) than for PET/CT (47.1%, p<0.001), while specificity was higher for PET/CT (96.5%) than for MRI (91.2%, p<0.001). To improve the accuracy of post-RT response evaluation, combination of MRI and ^{18}F-FDG PET has emerged with promising predictive power through combining advanced anatomical information and tumor metabolic information. A pilot study demonstrated an increase in diagnostic confidence in 80%–90% of the patients who received

CCRT. Also, change of opinion was observed in 70% and change of policy in 50%, especially in the group with residual tumor [31]. Although there is still a lack of strong evidence regarding the benefit of assessing treatment response, PET/MRI demonstrated an improved diagnostic performance during initial staging workup with accuracy of 83.3% for cervical tumor staging, which was better than that of PET/CT (53.3%, p=0.008) [32], and detection of lymph node metastasis [33].

Although the timing of imaging can considerably affect the results of response evaluation, optimal timing of post-treatment imaging is still undefined. Despite using ^{18}F-FDG PET is still difficult to discriminate treatment-related changes from residual tumors. Therefore ^{18}F-FDG PET was examined 3 months after the completion of CCRT [34]. Most studies included in the present analysis also reported their median interval between the completion of RT and ^{18}F-FDG PET around 3 months. However, the overall timing was varied, ranging from 1.0 to 10.4 months. CMR rate at 3 months post-RT was ~70% (**Table 1**). Oh et al. [21] which obtained ^{18}F-FDG PET at l month as per protocol, reported similar response outcomes with CMR of 73% similar to the results of PET at 3 months, while Yoon et al. [25] with a median interval of 1.5 month reported CMR of only 11%. Due to the conflicting response results and concern of treatment-related metabolic response, recommended timing of post-treatment ^{18}F-FDG PET appeared to be 3 months. However, with the advent of combined imaging modalities such as PET/MRI, further studies analyzing the effectiveness of shortened interval between end of treatment and imaging are needed.

Absence of objective response criteria is another issue. All studies included in quantitative synthesis in the present report qualitatively assessed the metabolic response (**Table 2**). Except 2 studies, the rest of 7 studies utilized same definition for response assessment. However, qualitative evaluation had fundamental limitation of inter-observer variation. To resolve the challenge on lack of uniformity, quantitative approaches such as EORTC or PET response criteria in solid tumors (PERCIST) criteria has been widely adopted [35]. The pooled HRs in the present study might not be directly applied to the quantitative response evaluation tools. Yoon et al. [25] was the only study which utilized EORTC criteria, and there was no study using PERCIST rule. However, considering the fair agreement of visual versus quantitative assessment [36], introduction of EORTC or PERCIST criteria to post-RT ^{18}F-FDG PET in uterine cervical cancer may be of significant clinical value, and could provide reproducible response outcomes and improved prognostic power.

There were several limitations in this meta-analysis. First of all, majority of the studies included were retrospective trials so that there might be a tendency toward overestimation of pooled HRs. Secondly, the number of studies for quantitative synthesis was small. In addition, due to the different patterns of reporting, the studies were divided into 3 subgroups with small number of study cohorts included. Furthermore, 1 subgroup analysis comparing CMR and PMR/PMD included only 2 cohorts [20,22], and one of them weighed more than 90% [22]. As described previously, this could be vulnerable to sampling error. Thirdly, study and clinicopathological characteristics were varied in most studies (**Table 1**) and it might be a bias for survival. Meta-regression analysis could evaluate the impact of these factors. However, it was impossible in the present study due to the paucity of the number of studies in each subgroup. Despite the disadvantages, the present study is the first systematic review and meta-analysis of the role of ^{18}F-FDG PET evaluation in patients with uterine cervical cancer who received RT.

In conclusion, patients with cervical cancer which resulted in CMR during post-RT ^{18}F-FDG PET were at considerably lower risk of death or progression. As ^{18}F-FDG PET has the advantage of detecting metabolic activity of the tumor, ^{18}F-FDG PET could be a reasonable follow-up modality after RT for cervical cancer. Future studies to find the most optimal modality, timing, and assessment criteria for evaluating post-treatment response and prognosis are warranted.

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