Prognostic Implications of the SUVmax of Primary Tumors and Metastatic Lymph Node Measured by ^{18}F-FDG PET in Patients With Uterine Cervical Cancer

A Meta-analysis

Azmal Sarker, MD, Hyung-Jun Im, MD,*† Gi Jeong Cheon, MD, PhD,*‡ Hyun Hoon Chung, MD, PhD,‡§ Keon Wook Kang, MD, PhD,*‡ June-Key Chung, MD, PhD,*‡ E. Edmund Kim, MD, PhD,†|| and Dong Soo Lee, MD, PhD*†‡*

Purpose: We conducted a meta-analysis to evaluate the prognostic value of the SUVmax measured in pretreatment primary lesions and metastatic lymph nodes (LNs) on ^{18}F-FDG PET scans in patients with uterine cervical cancer.

Methods: A systematic search of EMBASE and MEDLINE was performed using the keywords "positron emission tomography (PET)," "uterine cervical cancer," and "prognosis." Event-free survival and overall survival were evaluated as outcomes. The impact of SUVmax on survival was measured by the effect size of the hazard ratio (HR).

Results: Fourteen eligible studies including 1150 patients were analyzed. Patients with a high primary SUVmax showed a worse prognosis, with an HR of 2.66 (95% confidence interval [CI], 1.90–3.74; $P < 0.00001$) for adverse events and an HR of 2.45 (95% CI, 1.74–3.45; $P < 0.00001$) for death. Patients with high SUVmax in metastatic pelvic LN (PLN) showed a worse prognosis, with an HR of 2.92 (95% CI, 1.94–4.39; $P < 0.00001$) for adverse events and an HR of 2.66 (95% CI, 1.60–4.43; $P = 0.0002$) for SUVmax in PLN for death. In addition, high SUVmax in metastatic para-aortic LN was associated with a worse prognosis, with an HR of 4.41 (95% CI, 2.32–8.38; $P < 0.00001$) for death.

Conclusions: Patients with uterine cervical cancer and a high SUVmax primary lesion, PLN, or para-aortic LN are at higher risk of adverse events or death.

Key Words: FDG PET, prognosis, SUVmax, uterine cervical cancer

(*Clin Nucl Med* 2016;41: 34–40)

Uterine cervical cancer is the third most common cancer in women worldwide and the second most common in developing countries.[1] An estimated 528,000 new cases occurred worldwide in 2012, and 85% of the cases are occurring in developing countries. Worldwide deaths from this disease were estimated to be 266,000 in 2012, accounting for 7.5% of all female cancer deaths and 87% of the cases occurring in developing countries.[2] Conventional prognostic factors for clinical workup include the International Federation of Gynecology and Obstetrics (FIGO) stage, tumor volume, lymph node (LN) metastasis, parametrial invasion, lymphovascular space invasion, and age of the patient.[3]

PET using ^{18}F-FDG has been accepted as a noninvasive tool for staging, assessing the disease response to chemotherapy and radiotherapy, restaging, and predicting prognosis in variable types of malignancy including uterine cervical cancer.[4–7] Among various parameters of FDG PET, the SUVmax of a tumor or metastatic LN reflects the highest metabolic activity of the lesion and is the most widely used semiquantitative measurement in oncologic PET. SUVmax has been used for differential diagnosis of malignancy,[8,9] predicting response to systemic treatment[10] and predicting prognosis in many types of cancer.[7,11,12] However, there are several conflicting data on the prognostic value of SUVmax.[13,14]

Several authors have suggested that PET positivity or high SUVmax of a primary uterine cervical cancer tumor is a surrogate for an adverse outcome.[15–18] In addition, a meta-analysis[19] reported that FDG PET positivity in primary cervical cancer is related to a worse prognosis. However, the degree of FDG uptake or the quantitative value was not considered in the previous meta-analysis. SUV of a metastatic LN is also a significant prognostic factor in patients with uterine cervical cancer.[20] Thus, the present meta-analysis was performed to determine the prognostic implications of SUVmax, which is the most widely used and accepted measurement to assess metabolism of both primary tumor and LN metastasis in patients with uterine cervical cancer.[21]

MATERIALS AND METHODS

Data Search and Study Selection

We performed a systematic search of EMBASE and MEDLINE (inception to March 2014) for English publications using the keywords "cervical cancer" or "cervical malignancy" or "cervical carcinoma" and "positron" or "pet/ct" or "pet-ct" or "fluorodeoxyglucose or "FDG" and "prognosis" or "disease free" or "disease specific" or "prognostic," or "survival." All searches were limited to human studies. Inclusion criteria were ^{18}F-FDG PET or PET/CT used as an imaging tool before or after undergoing surgery, chemotherapy, or radiotherapy with curative or palliative intent, uterine cervical cancer of any histological type; SUV measurements of primary lesions or metastatic pelvic lymph nodes (PLNs) or para-aortic LNs (PALNs); and survival data with a cutoff SUVmax.

Reviews, abstracts, and editorial materials were excluded. Two authors conducted the searches and screening independently. Any discrepancies were resolved by consensus.

Data Extraction and Quality Assessment

Data were extracted from the publications independently by the 2 reviewers, and the following information was recorded: first

Received for publication May 5, 2015; revision accepted September 10, 2015.
From the *Department of Nuclear Medicine, Seoul National University Hospital; †Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy; ‡Cancer Research Institute, Seoul National University Hospital; and §Department of Obstetrics and Gynecology, College of Medicine, Seoul National University, Seoul, Korea; and ||Department of Radiological Science, University of California at Irvine, CA.
A.S. and H.-J.I. contributed equally to this work.
Conflicts of interest and sources of funding: none declared.
Correspondence to: Gi Jeong Cheon, MD, PhD, Department of Nuclear Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 110-744, Korea. E-mail: larrycheon@gmail.com.
Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.nuclearmed.com).

ISSN: 0363-9762/16/4101–0034
DOI: 10.1097/RLU.0000000000001049

author, year of publication, country, study design, number of patients, TNM stage, treatment, and end points. Three reviewers scored each publication on a quality scale, based on that used in previous studies.[7,22] This quality scale was grouped into 4 categories: scientific design, generalizability, analysis of results, and PET reports (Supplementary Table 1, http://links.lww.com/CNM/A27). A value between 0 and 2 was attributed to each item. Each category had a maximum score of 10 points.

Statistical Analysis

The primary outcome was event-free survival (EFS). Disease-free survival, recurrence-free survival, and progression-free survival were measured as the primary outcomes and redefined as EFS, which was measured from the date of initiating therapy to recurrence or metastasis. The secondary end point was overall survival (OS), defined as the date from initiating therapy until death by any cause.[23,24] The impact of SUVmax primary lesion, SUVmax PLN, or SUVmax PALN on survival was measured by the effect size of the hazard ratio (HR). Survival data were extracted using the methodology suggested by Parmar et al.[25] We extracted a univariate HR estimate and 95% confidence intervals (CIs) directly from each study, if provided by the authors. Otherwise, P values for the log-rank test, 95% CI, number of events, and number at risk were extracted to estimate the HR indirectly. Survival rates on Kaplan-Meier curves were read by the Engauge Digitizer version 3.0 (http://digitizer.sourceforge.net) to reconstruct the HR estimate and its variance, assuming that patients were censored at a constant rate during the follow-up. An HR of greater than 1 implied a worse survival for patients with a high SUVmax, whereas an HR of less than 1 implied a survival benefit for patients with a high SUVmax. Heterogeneity among studies was assessed by the χ^2 test and I^2 statistics, as described by Higgins et al.[26] We also extracted SUVmax survival data from the same studies included in this meta-analysis, as mentioned previously. $P < 0.05$ was considered statistically significant. Data from each study were analyzed using Review Manager (RevMan, version 5.3; Copenhagen, Denmark: The Nordic Cochrane Center, The Cochrane Collaboration; 2012).

RESULTS

Study Characteristics

The electronic search identified 105 articles. Sixty-four studies were excluded, which did not meet the inclusion criteria based on the title and abstract. Reviewing the full text of the remaining

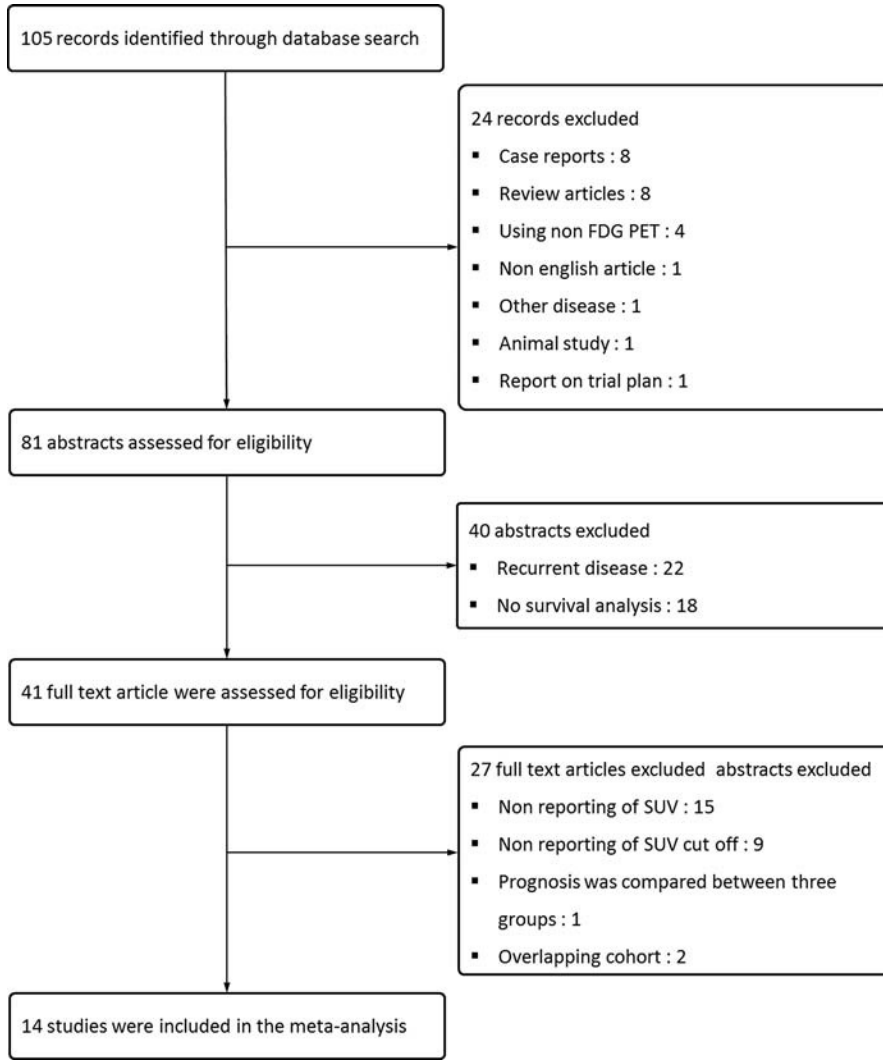

FIGURE 1. Flowchart to identify eligible studies.

41 articles, 14 studies that included 1150 patients were eligible for this study (Fig. 1). Nine studies were designed retrospectively and 5 prospectively. Event-free survival was measured according to the primary lesion SUVmax in 6 studies. Among these, HR of EFS was reported in 2 studies[3,20] and calculated from the event rate in the other 4 studies.[27–30] The HR of OS based on the primary lesion SUVmax was calculated from death rate in 6 studies.[15,27,29,31–33] The HR of EFS based on the PLN SUVmax was reported in 2 studies[20,34] and calculated from event rate in the other 2 studies.[35,36] The HR of OS based on PLN SUVmax was reported in 1 study[34] and was calculated from death rate in other 2 studies.[35,36] The HR of EFS and OS based on PALN SUVmax were reported in 1 study,[34] whereas the HR of OS based on PALN SUVmax was calculated from death rate in 1 study.[37]

In each study, patients were divided into 2 groups (high and low SUV) according to cutoff values. Each group of researchers determined different cutoffs for their respective studies to demonstrate discrepancies in survival among patient groups with higher and lower SUVmax. Receiver operating characteristic analysis was applied in 4 studies to determine the cutoff level,[29,32,36,37] a log-rank test was applied in 2 studies,[3,20,28] and the median value was applied in 2 studies.[15,27] Other methods of cutoff determination were logistic likelihood ratio,[35] the mean value,[31] successive arbitrary cutoff,[30] tertile categorization for PLN SUVmax, and dichotomization for PALN SUVmax.[34] Method of cutoff determination was not described in 1 study.[33] The cutoff values were 5.3 to 15.6 for primary SUVmax, 2.1 to 4.5 for PLN SUVmax, and 3.3 to 6.5 for PALN SUVmax. The study characteristics are summarized in Tables 1 and 2.

Primary Outcome—EFS

Event-free survival according to primary SUVmax was analyzed in the 6 studies.[3,20,27–30] The combined HR (Fig. 2) for adverse events was 2.66 (95% CI, 1.90–3.74; $P < 0.00001$). No significant evidence of heterogeneity was detected ($\chi^2 = 4.31$; $P = 0.51$; $I^2 = 0\%$). Four PLN SUVmax studies were included in the EFS analysis.[20,34–36] The pooled HR using a random-effects model (Fig. 3) was 2.92 (95% CI, 1.94–4.39; $P < 0.00001$; $I^2 = 0\%$). One study was found that reported HR for EFS based on SUVmax PALN,[34] which was 3.47 (95% CI, 1.41–8.56; $P = 0.007$).

Secondary Outcome—OS

Overall survival according to primary SUVmax was analyzed in the 6 studies.[15,27,29,31–33] The combined HR for death was 2.45 (95% CI, 1.74–3.45; $P < 0.00001$) (Fig. 4). The heterogeneity test result was not significant ($\chi^2 = 4.41$; $P = 0.49$; $I^2 = 0\%$). Three PLN SUVmax studies[34–36] were included in the OS analysis. The pooled HR (Fig. 5) for death was 2.66 (95% CI, 1.60–4.43; $P = 0.0002$). No evidence of significant heterogeneity was detected ($\chi^2 = 0.59$; $P = 0.75$, $I^2 = 0\%$). Two PALN SUVmax studies[34,37] were included in the OS analysis. The pooled HR for death (Fig. 6) was 4.41 (95% CI, 2.32–8.38; $P < 0.00001$). No evidence of heterogeneity was detected ($\chi^2 = 0.02$; $P = 0.88$, $I^2 = 0\%$).

DISCUSSION

In the present meta-analysis, the prognostic value of SUVmax on ^{18}F-FDG PET in patients with uterine cervical cancer was evaluated by analyzing the HRs of EFS and OS in patients with high primary lesion, PLN, or PALN SUVmax compared with those with low SUVmax. Patients with high primary SUVmax had a 2.66-fold higher risk of an adverse event, according to pooled results, or a 2.45-fold higher risk of death than did those with a low primary SUVmax. In addition, the risk of adverse effects was 2.92-fold higher and the risk of death was 2.66-fold higher in patients with a high PLN SUVmax, compared with those with a low PLN

TABLE 1. Studies Included in the Meta-analysis

Authors	Year of Publication	Country	Study Design	Quality Score, %	No. of Patients	TNM Staging	Treatment	End Points	Tumor Delineation (Thresholds)	Primary SUVmax		PLN SUVmax		PALN SUVmax	
										Method of Determination	Cut off	Method of Determination	Cut off	Method of Determination	Cut off
Chao et al[37]	2008	Taiwan	P	81.6	47	I-IV	RTx/CCRT	PFS/OS	SUVmax PALN	—	—	—	—	ROC	6.5
Chou et al[32]	2010	Taiwan	R	81.6	83	IB1-IIB	Op/Op + RTx or CCRT	OS	SUVmax prim	ROC	5.3	—	—	—	—
Chung et al[20]	2014	Korea	R	78.9	130	IB1-IIA	Op/CCRT/CTx	PFS	SUVmax prim and SUVmax PLN	Log-rank test	7.10	Log-rank test	2.36	—	—
Im et al[3]	2014	Korea	R	89.5	145	IB1-IVA	CCRT	PFS	SUVmax prim	Log-rank test	15.6	—	—	—	—
Kidd et al[18]	2010	USA	P	73.68	83	IB1-IIIB	RTx/CCRT	RFS/OS	SUVmax PLN	—	—	Logistic likelihood ratio	4.3	—	—
Lee et al[30]	2009	Korea	P	78.9	44	IB1-IIA	Op/Op + RTx or CCRT	RFS	SUVmax prim	Successive arbitrary cut off	13.4	—	—	—	—
Nakamura et al[31]	2010	Japan	R	68.4	52	IB1-IVA	RTx/CCRT	OS	SUVmax prim	mean	15.6	—	—	—	—
Nakamura et al[36]	2014	Japan	R	73.7	80	IB1-IVA	RTx/CCRT	DFS/OS	SUVmax PLN			ROC	2.1(D) & 2.2 (O)	—	—
Onal et al[29]	2013	Turkey	R	84.2	149	IB2-IVA	RTx/CCRT	DFS/OS	SUVmax prim	ROC	15.6	—	—	—	—
Pan et al[15]	2012	China	R	84.2	82	IA-IVB	RTx/Op/Op + RTx/PT	OS	SUVmax prim	median	11.2	—	—	—	—
Vercellino et al[33]	2012	France	P	73.7	16	IB2-IVB	CCRT	OS	SUVmax prim	ND	14.9	—	—	—	—
Xue et al[27]	2006	USA	R	84.2	96	IB1-IVB	RTx/CCRT	DFS/OS	SUVmax prim	median	10.2	—	—	—	—
Yen et al[34]	2008	Taiwan	P	92.1	70	I-IV	RTx/CCRT	RFS/OS	SUVmax PLN and SUVmax PALN	—	—	Categorized tertile	4.5	Dichotomized	3.3
Yoo et al[28]	2012	Korea	R	84.2	73	I-IV	Op/Op + CCRT/RTx/CCRT	EFS	SUVmax prim	Log-rank test	7.5	—	—	—	—

CCRT indicates concurrent chemoradiotherapy; CTx, chemotherapy; D, for DFS; DFS, disease-free survival; ND, not described; O, for OS; Op, operation; OS, overall survival; P, prospective; prim, primary tumor; PT, palliative treatment; R, retrospective; RTx, radiotherapy.

TABLE 2. PET Protocols of the Included Studies

Authors	SUV Normalization	BST, mg/dL	Duration of Fasting, h	Post Injection Interval, min	Scan Time, min/bed	SUV Formula	Reconstruction Method	Attenuation Correction	Dose, MBq
Chao et al[37]	ND	ND	6	40–50	3	ND	OSEM	CT	333–407
Chou et al[32]	ND	<200	6	50	3	ND	OSEM	CT	370
Chung et al[20]	BW	ND	4	60	2.5	D	RAMLA	CT	5.55/kg
Im et al[3]	BW	ND	8	60	3	D	OSEM	CT	444–740
Kidd et al[18]	BW	68–198	ND	41–128	ND	D	ND	ND	ND
Lee et al[30]	BW	ND	6	45	5	ND	ND	TS	370
Nakamura et al[31]	BW	<150	5	90	2.4	D	OSEM	CT	3.7/kg
Nakamura et al[36]	BW	ND	ND	90	2.4	D	OSEM	CT	3.7/kg
Onal et al[29]	ND	<150	6	60	3	ND	ND	CT	370–555
Pan et al[15]	BW	<180	6	60	3	D	OSEM	CT	7.4/kg
Vercellino et al[33]	ND	ND	ND	60–120	2	ND	LOR-RAMLA	CT	5/kg
Xue et al[27]	BW	54–193	4	40–195	ND	D	OSEM	CT	555–740
Yen et al[34]	BW	ND	6	40	ND	D	AMLR	TS	370
Yoo et al[28]	BW	<200	6	45	ND	ND	OSEM	TS	370

AMLR indicates accelerated maximum likelihood reconstruction; BST, blood sugar test; BW, normalized by body weight; D, described/defined; LOR, line of response; ND, not described; OSEM, ordered subset expectation maximization; RAMLA, row-action maximum likelihood algorithm; TS, transmission scan.

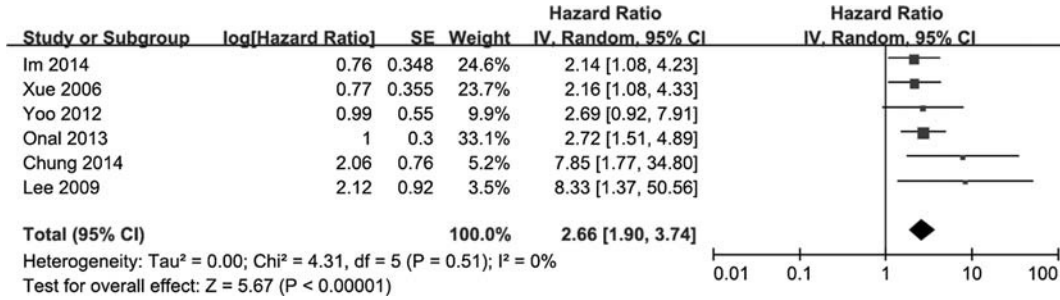

FIGURE 2. Forest plots of the HRs for events with primary SUVmax. Hazard ratios for events with primary lesion SUVmax in individual studies and the pooled results are shown. Error bars indicate the 95% CIs.

SUVmax. Accordingly, the risk of adverse effects was 3.47-fold higher and the risk of death was 4.41-fold higher in patients with a high PALN SUVmax, compared with those with a low PALN SUVmax.

The primary tumor SUVmax before treatment is a prognostic factor in various types of malignant tumors including uterine cervical cancer.[6–8] Although conflicting results exist for other types of cancer, such as esophageal and lung,[13,14] all uterine cervical cancer studies included in the present meta-analysis showed a significantly worse prognosis associated with higher SUVmax. However, SUVmax was not a significant independent prognostic factor in the multivariate analyses conducted in each study in the present meta-analysis, except in 2 studies.[29,30] Onal et al[29] show an HR of 7.29 (95% CI, 3.5–15.17), whereas Lee et al[30] show an HR of 36.3 (95% CI, 1.73–761.5) for EFS. The probable reason is that primary tumor SUVmax is related to other prognostic factors, such as FIGO stage, parametrial invasion, LN metastasis, and tumor

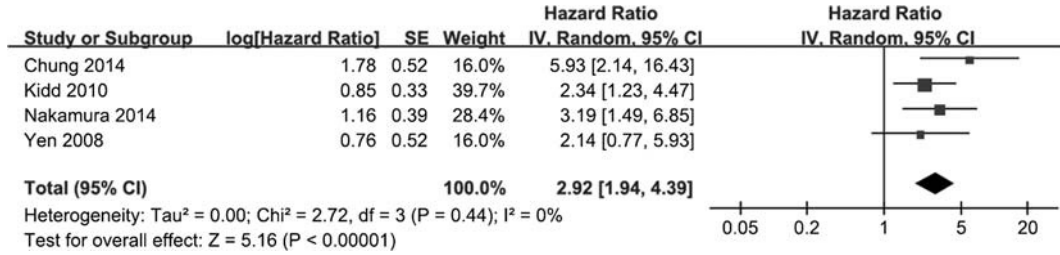

FIGURE 3. Forest plots of the HRs for events with PLN SUVmax. Hazard ratios for events with PLN SUVmax in individual studies and the pooled results are shown. Error bars indicate the 95% CIs.

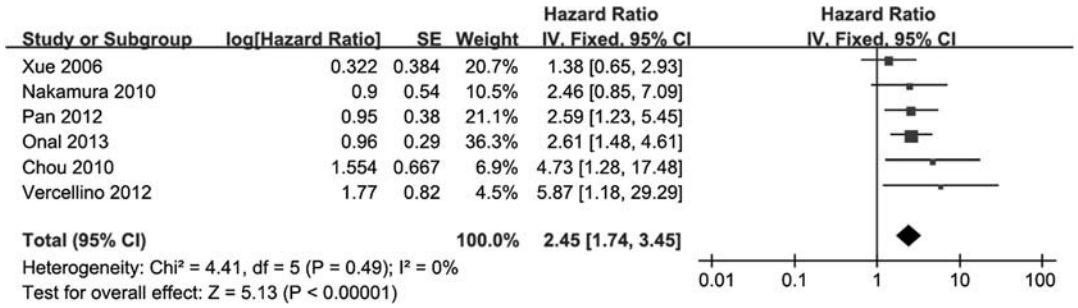

FIGURE 4. Forest plots of HRs for OS with primary SUVmax. Hazard ratios for OS with primary SUVmax of individual studies and pooled results are shown. Error bars indicate the 95% CIs.

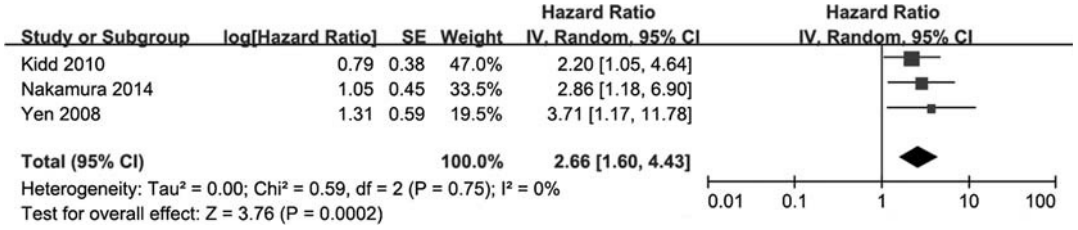

FIGURE 5. Forest plots of HRs for OS with PLN SUVmax. Hazard ratios for OS with PLN SUVmax of individual studies and the pooled results are shown. Error bars indicate the 95% CIs.

size.[9] Actually, these 2 studies[29,30] included patients with relatively low stages (I-II). Also, another study by Chung et al[20] evaluating patients with low-stage disease (IBI-IIA) reported that the primary tumor SUVmax was almost an independent prognostic factor as suggested by multivariate analysis, with an HR of 5.06 (95% CI, 0.97–26.42; $P = 0.055$). Xue et al[27] have also found FIGO stage I to be a borderline significant ($P = 0.058$) predictor of disease-free survival. Thus, primary tumor SUVmax could be an independent prognostic factor for EFS in patients with lower-stage uterine cervical cancer.

Previous reports have designated abnormal uptake of FDG into LNs on PET images as an independent prognostic factor in patients with uterine cervical cancer.[16–18] An increased risk of recurrence with higher uptake in LN metastasis has also been reported.[18] In the present meta-analysis, there were 2 studies that conducted multivariate analysis including PLN SUVmax. The 2 studies[20,36] reported that the PLN SUVmax is a significant independent prognostic factor for EFS. There was only 1 study[34] that conducted multivariate analysis including PALN SUVmax in the present meta-analysis, and the study showed that PALN SUVmax is a significant independent prognostic factor, with an HR of 3.47 (95% CI, 1.41–8.56; $P = 0.007$). Although very limited studies are available, the metastatic LN SUVmax could be an independent prognostic factor in patients with uterine cervical cancer.

Among studies that were excluded after full-text review, 15 studies reported survival statistics without SUV, and there were 9 studies that did not report any cutoff value of SUV. There were 11 articles regarding prognostic value of primary FDG uptake; among those, 6 studies have found pretreatment primary tumor uptake of FDG or SUVmax primary as predictor of survival, whereas no uptake or lower SUVmax was associated with better outcome,[16,17,38–41] whereas 5 studies could not find FDG uptake in primary tumor or primary tumor SUVmax to be associated with prognosis or as a predictor of survival.[42–46] Meanwhile, 2 studies investigated the predictive role of the ratio of pretreatment and posttreatment SUVmax of primary tumor and found it as a predictor of survival, prognosis,[47] and treatment response.[48] There were 13 articles regarding the prognostic value of PLN or PALN FDG uptake; among them are 10 studies that found pretreatment PLN or PALN uptake of FDG as a predictor of survival, whereas a negative uptake was associated with better outcome,[16,17,38,42,49–54] and 3 studies could not find abnormal FDG uptake in PLN or PALN as a significant predictor of survival.[46,48,55] Meanwhile, pretreatment SUVmax of PLN and PALN was also reported to be higher in patients who were

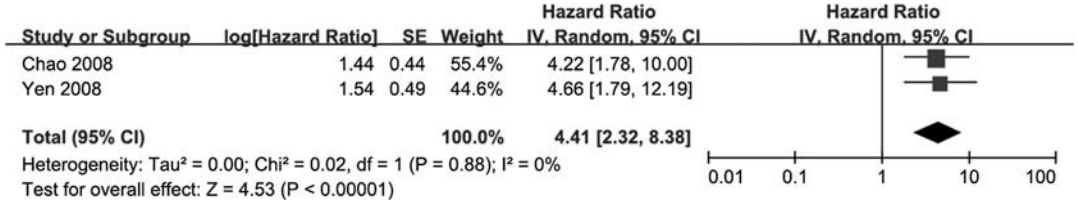

FIGURE 6. Forest plots of the HRs for OS with PALN SUVmax. Hazard ratios for OS with PALN SUVmax in individual studies and the pooled results are shown. Error bars indicate the 95% CIs.

nonresponders to treatment compared with patients who responded well.[42] Also, several studies showed that patients with progressive echelon of LN involvement (PLN, PALN, supraclavicular lymph node) were found to be prone of disease recurrence and worse survival.[17,18,56]

One article[57] that almost met the inclusion criteria was excluded from our meta-analysis because the investigators reported survival by comparing among 3 prognostic groups; thus, we could add the data for calculating summed HR. However, they found an increased pretreatment primary tumor SUVmax to be a predictor of death and cause specific survival where higher SUVmax primary was associated with poor survival, persistent disease, recurrence of disease, and LN metastases. We found 3 articles from Seoul National University, all meeting inclusion criteria of our meta-analysis. However, to avoid the overlapping of cohort, 2 articles[58,59] were excluded, whereas the one[20] that had the largest patient cohort and also the most recently published was included. Both these excluded articles have explored that the pretreatment primary tumor SUVmax was a significant predictor of EFS, whereas a poor survival and metastasis to LNs were significantly associated with a higher primary lesion SUVmax.

SUV varies according to blood glucose levels, fasting duration, uptake duration, and method of attenuation correction and reconstruction. We reviewed these factors in the included studies using a quality assessment form (Table 1). Five studies scored 8/8, 6 scored 7s/8 (87.5%), and the other 3 scored 6/8 (75%) in PET reports for the quality assessment category. Seven studies reported that blood sugar level testing and imaging were performed in patients with blood sugar levels of less than 150 to 200 mg/dL. Fasting durations, ranging from 4 to 8 hours, were well documented in all studies, except in 3.[33,35,36] In addition, uptake durations, ranging from 40 to 90 minutes, after injecting ^{18}F-FDG were well reported in all studies (Table 2), except in 3 studies reporting a duration of up to 195 minutes.[27,33,35] Regulations for measuring SUV were acceptable, except in those 3 studies[27,33,35] because of the relatively long and wide range of the uptake period; however, the pooled HR was similar to the original result even after those studies were excluded.

Our meta-analysis results demonstrated that the risks of an event and survival are distributed along a cutoff for the pretreatment SUVmax of both primary tumor and metastatic LN. Although there was a discrepancy in the SUVmax cutoff among studies, and each study applied a different method to identify a specific SUVmax cutoff for worse prognosis, the association between a greater risk of an event and a higher SUVmax was unanimous. Also, heterogeneity was not detected in the present meta-analysis. Although cutoff SUVmax of primary tumor to predict worse outcome had a wide range in the present meta-analysis, which is from 5.3 to 15.6, SUVmax cutoff of primary tumor for worse outcome might be suggested differently according to FIGO stage of the patients. The studies that enrolled patients with low FIGO stage (stages I and II) had relatively low SUVmax cutoffs, which were 5.3 (Chou et al[32]), 7.1 (Chung et al[20]), and 13.4 (Lee et al[30]). On the other hand, the studies that enrolled patients with high FIGO stage as well (stages I-IV) had generally higher SUVmax cutoffs, which are 7.5 (Yoo et al[28]), 10.2 (Xue et al[27]), 11.2 (Pan et al[15]), 15.6 (Im et al[3]), 15.6 (Nakamura et al[31]), and 15.6 (Onal et al[29]).

This is the first meta-analysis to evaluate the prognostic value of the SUVmax in patients with uterine cervical cancer; however, there were several limitations. We were unable to propose an optimal cutoff value to categorize primary, PLN, or PALN SUVmax values as high or low. A different cutoff delineation and strategy were applied, because study patients of different FIGO stages and different histological findings were enrolled in each study, which may have affected the events occurring over time and the survival. Further studies with individual patient data are needed to propose cutoff standards and delineation methods to predict a prognosis using SUVmax. Although we found that patients with high SUVmax had a higher risk of adverse events or death than did those with low SUVmax, there was difficulty interpreting the HRs for SUVmax, which was caused by an unknown incidence rate for the events. Further prospective studies utilizing incidence rates are needed. Most of the included studies were designed retrospectively[3,15,20,27–29,31,32,36]; thus, inference was underpowered. However, 5 studies were designed prospectively.[30,33–35,37] Publication bias could not be excluded. In addition, the potential impact of language bias could have existed, because non-English articles were excluded. In addition, even though 2 reviewers independently extracted the data from each study, complete data accuracy could not be ensured.

CONCLUSIONS

SUVmax measured by ^{18}F-FDG PET is a significant prognostic factor of outcome in patients with uterine cervical cancer. Patients with a high preoperative primary lesion, metastatic PLN, and/or PALN SUVmax are at higher risk of adverse events or death.

REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin*. 2011;61:69–90.
2. Ferlay J SI, Ervik M, Dikshit R, et al. *GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11* [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at: http://globocan.iarc.fr. Accessed September 13, 2014.
3. Im HJ, Yoon HJ, Lee ES, et al. Prognostic implication of retrocrural lymph node involvement revealed by (18)F-FDG PET/CT in patients with uterine cervical cancer. *Nucl Med Commun*. 2014;35:268–275.
4. Mirpour S, Mhlanga JC, Logeswaran P, et al. The role of PET/CT in the management of cervical cancer. *AJR Am J Roentgenol*. 2013;201:W192–W205.
5. Herrera FG, Prior JO. The role of PET/CT in cervical cancer. *Front Oncol*. 2013;3:34.
6. Fletcher JW, Djulbegovic B, Soares HP, et al. Recommendations on the use of ^{18}F-FDG PET in oncology. *J Nucl Med*. 2008;49:480–508.
7. Berghmans T, Dusart M, Paesmans M, et al. Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non–small cell lung cancer (NSCLC): a systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. *J Thorac Oncol*. 2008;3:6–12.
8. Hu SL, Yang ZY, Zhou ZR, et al. Role of SUV(max) obtained by ^{18}F-FDG PET/CT in patients with a solitary pancreatic lesion: predicting malignant potential and proliferation. *Nucl Med Commun*. 2013;34:533–539.
9. Gould MK, Maclean CC, Kuschner WG, et al. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. *JAMA*. 2001;285:914–924.
10. Kong CB, Byun BH, Lim I, et al. ^{18}F-FDG PET SUVmax as an indicator of histopathologic response after neoadjuvant chemotherapy in extremity osteosarcoma. *Eur J Nucl Med Mol Imaging*. 2013;40:728–736.
11. Rizk N, Downey RJ, Akhurst T, et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography standardized uptake values predict survival after esophageal adenocarcinoma resection. *Ann Thorac Surg*. 2006;81:1076–1081.
12. Nakamura K, Hongo A, Kodama J, et al. The measurement of SUVmax of the primary tumor is predictive of prognosis for patients with endometrial cancer. *Gynecol Oncol*. 2011;123:82–87.
13. Sugawara Y, Quint LE, Iannettoni MD, et al. Does the FDG uptake of primary non–small cell lung cancer predict prognosis? A work in progress. *Clin Positron Imaging*. 1999;2:111–118.
14. Rizk NP, Tang L, Adusumilli PS, et al. Predictive value of initial PET-SUVmax in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. *J Thorac Oncol*. 2009;4:875–879.
15. Pan L, Cheng J, Zhou M, et al. The SUVmax (maximum standardized uptake value for F-18 fluorodeoxyglucose) and serum squamous cell carcinoma antigen (SCC-ag) function as prognostic biomarkers in patients with primary cervical cancer. *J Cancer Res Clin Oncol*. 2012;138:239–246.
16. Unger JB, Lilien DL, Caldito G, et al. The prognostic value of pretreatment 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography scan in women with cervical cancer. *Int J Gynecol Cancer*. 2007;17:1062–1067.

17. Narayan K, Fisher RJ, Bernshaw D, et al. Patterns of failure and prognostic factor analyses in locally advanced cervical cancer patients staged by positron emission tomography and treated with curative intent. *Int J Gynecol Cancer*. 2009;19:912–918.
18. Kidd EA, Siegel BA, Dehdashti F, et al. Lymph node staging by positron emission tomography in cervical cancer: relationship to prognosis. *J Clin Oncol*. 2010;28:2108–2113.
19. Zhao Q, Feng Y, Mao X, et al. Prognostic value of fluorine-18-fluorodeoxyglucose positron emission tomography or PET–computed tomography in cervical cancer: a meta-analysis. *Int J Gynecol Cancer*. 2013;23:1184–1190.
20. Chung HH, Cheon GJ, Kang KW, et al. Preoperative PET/CT FDG standardized uptake value of pelvic lymph nodes as a significant prognostic factor in patients with uterine cervical cancer. *Eur J Nucl Med Mol Imaging*. 2014;41:674–681.
21. Rahim MK, Kim SE, So H, et al. Recent trends in PET image interpretations using volumetric and texture-based quantification methods in nuclear oncology. *Nucl Med Mol Imaging*. 2014;48:1–15.
22. Pan L, Gu P, Huang G, et al. Prognostic significance of SUV on PET/CT in patients with esophageal cancer: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol*. 2009;21:1008–1015.
23. Pak K, Cheon GJ, Nam HY, et al. Prognostic value of metabolic tumor volume and total lesion glycolysis in head and neck cancer: a systematic review and meta-analysis. *J Nucl Med*. 2014;55:884–890.
24. Im HJ, Pak K, Cheon GJ, et al. Prognostic value of volumetric parameters of (18)F-FDG PET in non–small-cell lung cancer: a meta-analysis. *Eur J Nucl Med Mol Imaging*. 2015;42:241–251.
25. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med*. 1998;17:2815–2834.
26. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–560.
27. Xue F, Lin LL, Dehdashti F, et al. F-18 fluorodeoxyglucose uptake in primary cervical cancer as an indicator of prognosis after radiation therapy. *Gynecol Oncol*. 2006;101:147–151.
28. Yoo J, Choi JY, Moon SH, et al. Prognostic significance of volume-based metabolic parameters in uterine cervical cancer determined using ^{18}F-fluorodeoxyglucose positron emission tomography. *Int J Gynecol Cancer*. 2012;22:1226–1233.
29. Onal C, Reyhan M, Parlak C, et al. Prognostic value of pretreatment ^{18}F-fluorodeoxyglucose uptake in patients with cervical cancer treated with definitive chemoradiotherapy. *Int J Gynecol Cancer*. 2013;23:1104–1110.
30. Lee YY, Choi CH, Kim CJ, et al. The prognostic significance of the SUVmax (maximum standardized uptake value for F-18 fluorodeoxyglucose) of the cervical tumor in PET imaging for early cervical cancer: preliminary results. *Gynecol Oncol*. 2009;115:65–68.
31. Nakamura K, Okumura Y, Kodama J, et al. The predictive value of measurement of SUVmax and SCC-antigen in patients with pretreatment of primary squamous cell carcinoma of cervix. *Gynecol Oncol*. 2010;119:81–86.
32. Chou HH, Chang HP, Lai CH, et al. (18)F-FDG PET in stage IB/IIB cervical adenocarcinoma/adenosquamous carcinoma. *Eur J Nucl Med Mol Imaging*. 2010;37:728–735.
33. Vercellino L, Groheux D, Thoury A, et al. Hypoxia imaging of uterine cervix carcinoma with (18)F-FETNIM PET/CT. *Clin Nucl Med*. 2012;37:1065–1068.
34. Yen TC, See LC, Lai CH, et al. Standardized uptake value in para-aortic lymph nodes is a significant prognostic factor in patients with primary advanced squamous cervical cancer. *Eur J Nucl Med Mol Imaging*. 2008;35:493–501.
35. Kidd EA, Siegel BA, Dehdashti F, et al. Pelvic lymph node F-18 fluorodeoxyglucose uptake as a prognostic biomarker in newly diagnosed patients with locally advanced cervical cancer. *Cancer*. 2010;116:1469–1475.
36. Nakamura K, Joja I, Nagasaka T, et al. Maximum standardized lymph node uptake value could be an important predictor of recurrence and survival in patients with cervical cancer. *Eur J Obstet Gynecol Reprod Biol*. 2014;173:77–82.
37. Chao A, Ho KC, Wang CC, et al. Positron emission tomography in evaluating the feasibility of curative intent in cervical cancer patients with limited distant lymph node metastases. *Gynecol Oncol*. 2008;110:172–178.
38. Kidd EA, El Naqa I, Siegel BA, et al. FDG-PET–based prognostic nomograms for locally advanced cervical cancer. *Gynecol Oncol*. 2012;127:136–140.
39. Onal C, Reyhan M, Guler OC, et al. Treatment outcomes of patients with cervical cancer with complete metabolic responses after definitive chemoradiotherapy. *Eur J Nucl Med Mol Imaging*. 2014;41:1336–1342.
40. Schwarz JK, Payton JE, Rashmi R, et al. Pathway-specific analysis of gene expression data identifies the PI3K/Akt pathway as a novel therapeutic target in cervical cancer. *Clin Cancer Res*. 2012;18:1464–1471.
41. Schwarz JK. Translating imaging results into tumor biology: FDG-PET and the response to chemoradiation in human cervical carcinoma. *Radiat Res*. 2013;180:223–230.
42. Akkas BE, Demirel BB, Dizman A, et al. Do clinical characteristics and metabolic markers detected on positron emission tomography/computerized tomography associate with persistent disease in patients with in-operable cervical cancer? *Ann Nucl Med*. 2013;27:756–763.
43. Crivellaro C, Signorelli M, Guerra L, et al. ^{18}F-FDG PET/CT can predict nodal metastases but not recurrence in early stage uterine cervical cancer. *Gynecol Oncol*. 2012;127:131–135.
44. Kim BS, Kim IJ, Kim SJ, et al. The prognostic value of the metabolic tumor volume in FIGO stage IA to IIB cervical cancer for tumor recurrence: measured by F-18 FDG PET/CT. *Nucl Med Mol Imaging*. 2011;45:36–42.
45. Kidd EA, Grigsby PW. Intratumoral metabolic heterogeneity of cervical cancer. *Clin Cancer Res*. 2008;14:5236–5241.
46. Shim SH, Lee SW, Park JY, et al. Risk assessment model for overall survival in patients with locally advanced cervical cancer treated with definitive concurrent chemoradiotherapy. *Gynecol Oncol*. 2013;128:54–59.
47. Kunos C, Radivoyevitch T, Abdul-Karim FW, et al. ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography standard uptake value ratio as an indicator of cervical cancer chemoradiation therapeutic response. *Int J Gynecol Cancer*. 2011;21:1117–1123.
48. Oh D, Lee JE, Huh SJ, et al. Prognostic significance of tumor response as assessed by sequential ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography during concurrent chemoradiation therapy for cervical cancer. *Int J Radiat Oncol Biol Phys*. 2013;87:549–554.
49. Akkas BE, Demirel BB, Vural GU. Clinical impact of ^{1} F-FDG PET/CT in the pretreatment evaluation of patients with locally advanced cervical carcinoma. *Nucl Med Commun*. 2012;33:1081–1088.
50. Grigsby PW, Zighelboim I, Powell MA, et al. In vitro chemoresponse to cisplatin and outcomes in cervical cancer. *Gynecol Oncol*. 2013;130:188–191.
51. Beriwal S, Kannan N, Sukumvanich P, et al. Complete metabolic response after definitive radiation therapy for cervical cancer: patterns and factors predicting for recurrence. *Gynecol Oncol*. 2012;127:303–306.
52. Schwarz JK, Siegel BA, Dehdashti F, et al. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA*. 2007;298:2289–2295.
53. Miller TR, Grigsby PW. Measurement of tumor volume by PET to evaluate prognosis in patients with advanced cervical cancer treated by radiation therapy. *Int J Radiat Oncol Biol Phys*. 2002;53:353–359.
54. Grigsby PW, Siegel BA, Dehdashti F. Lymph node staging by positron emission tomography in patients with carcinoma of the cervix. *J Clin Oncol*. 2001;19:3745–3749.
55. Tsai CS, Lai CH, Chang TC, et al. A prospective randomized trial to study the impact of pretreatment FDG-PET for cervical cancer patients with MRI-detected positive pelvic but negative para-aortic lymphadenopathy. *Int J Radiat Oncol Biol Phys*. 2010;76:477–484.
56. Singh AK, Grigsby PW, Dehdashti F, et al. FDG-PET lymph node staging and survival of patients with FIGO stage IIIB cervical carcinoma. *Int J Radiat Oncol Biol Phys*. 2003;56:489–493.
57. Kidd EA, Siegel BA, Dehdashti F, et al. The standardized uptake value for F-18 fluorodeoxyglucose is a sensitive predictive biomarker for cervical cancer treatment response and survival. *Cancer*. 2007;110:1738–1744.
58. Chung HH, Kim JW, Han KH, et al. Prognostic value of metabolic tumor volume measured by FDG-PET/CT in patients with cervical cancer. *Gynecol Oncol*. 2011;120:270–274.
59. Chung HH, Nam BH, Kim JW, et al. Preoperative [^{18}F]FDG PET/CT maximum standardized uptake value predicts recurrence of uterine cervical cancer. *Eur J Nucl Med Mol Imaging*. 2010;37:1467–1473.