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

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Uterine cervical cancer is the third most common cancer in women worldwide and the second most common in developing countries. 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. Conventional 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. 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, predicting response to systemic treatment and predicting prognosis in many types of cancer. Several authors have suggested that PET positivity or high SUVmax of a primary uterine cervical cancer tumor is a surrogate for an adverse outcome. In addition, a meta-analysis 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. 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.

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” or “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
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. 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. 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. 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 $\chi^2$ test and $I^2$ statistics, as described by Higgins et al. 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

![Flowchart to identify eligible studies](http://digitizer.sourceforge.net)

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<sup>32,33</sup> and calculated from the event rate in the other 4 studies. The HR of OS based on the primary lesion SUVmax was calculated from death rate in 6 studies.<sup>27,29,31–33</sup> The HR of EFS based on the PLN SUVmax was reported in 2 studies<sup>20,34</sup> and calculated from event rate in the other 2 studies.<sup>35,36</sup> The HR of OS based on PLN SUVmax was reported in 1 study,<sup>34</sup> whereas the HR of OS based on PALN SUVmax was calculated from death rate in 1 study.<sup>37</sup>

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<sup>29,32,36,37</sup> a log-rank test was applied in 2 studies<sup>20,28</sup> and the median value was applied in 2 studies.<sup>35,36</sup> Other methods of cutoff determination were logistic likelihood ratio,<sup>35</sup> the mean value,<sup>30</sup> successive arbitrary cutoff,<sup>29,30</sup> tertile categorization for PLN SUVmax, and dichotomization for PALN SUVmax.<sup>34</sup> Method of cutoff determination was not described in 1 study.<sup>33</sup> 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<sup>20,27,30–36</sup> 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<sup>20,34–36</sup>. The pooled HR using a random-effects model (Fig. 3) was 2.92 (95% CI, 1.94–4.39; P < 0.0001; $I^2 = 0\%$). One study was found that reported HR for EFS based on SUVmax PALN,<sup>34</sup> 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.<sup>15,27,29,31–33</sup> 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<sup>34–36</sup> 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<sup>34,37</sup> 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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of Publication</th>
<th>Country</th>
<th>Design</th>
<th>No. of Patients</th>
<th>Study Quality</th>
<th>Tumor Staging (TNM)</th>
<th>Method of Primary SUVmax</th>
<th>Method of PLN SUVmax</th>
<th>Method of PALN SUVmax</th>
<th>End Points</th>
<th>Tumor Delineation (Thresholds)</th>
<th>Statistic Test</th>
<th>Cut off</th>
<th>Categorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>2008</td>
<td>Taiwan</td>
<td>P</td>
<td>81.6</td>
<td>47</td>
<td>18F-HB</td>
<td>ROC</td>
<td>PALN</td>
<td>PALN</td>
<td>PFS/OS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>7.10</td>
<td>Log-rank test</td>
</tr>
<tr>
<td>Chung et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2010</td>
<td>Taiwan</td>
<td>R</td>
<td>81.6</td>
<td>83</td>
<td>IB-10</td>
<td>ROC</td>
<td>PLN</td>
<td>PLN</td>
<td>PFS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>4.3</td>
<td>Log-rank test</td>
</tr>
<tr>
<td>Im et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2014</td>
<td>Korea</td>
<td>R</td>
<td>76.9</td>
<td>130</td>
<td>IB-18</td>
<td>Logistic likelihood ratio</td>
<td>PLN</td>
<td>PLN</td>
<td>PFS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>15.6</td>
<td>Categorized tertile</td>
</tr>
<tr>
<td>Kidd et al&lt;sup&gt;18&lt;/sup&gt;</td>
<td>2010</td>
<td>USA</td>
<td>P</td>
<td>73.68</td>
<td>83</td>
<td>IB-10</td>
<td>ROC</td>
<td>PLN</td>
<td>PLN</td>
<td>RFS/OS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>2.36</td>
<td>Log-rank test</td>
</tr>
<tr>
<td>Lee et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>2009</td>
<td>Korea</td>
<td>P</td>
<td>78.9</td>
<td>44</td>
<td>IB-10</td>
<td>ROC</td>
<td>PLN</td>
<td>PLN</td>
<td>OS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>15.6</td>
<td>Log-rank test</td>
</tr>
<tr>
<td>Nakamura et al&lt;sup&gt;31&lt;/sup&gt;</td>
<td>2010</td>
<td>Japan</td>
<td>R</td>
<td>68.4</td>
<td>82</td>
<td>IB-18</td>
<td>ND</td>
<td>PALN</td>
<td>PALN</td>
<td>OS</td>
<td>SUVmax</td>
<td>ROC</td>
<td>2.1(D &amp; O) &amp; 2.2(O)</td>
<td></td>
</tr>
<tr>
<td>Onal et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2013</td>
<td>Turkey</td>
<td>R</td>
<td>84.2</td>
<td>149</td>
<td>IB-18</td>
<td>ROC</td>
<td>PLN</td>
<td>PLN</td>
<td>DFS/OS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>7.5</td>
<td>Log-rank test</td>
</tr>
<tr>
<td>Pan et al&lt;sup&gt;6&lt;/sup&gt;</td>
<td>2014</td>
<td>China</td>
<td>R</td>
<td>75.7</td>
<td>82</td>
<td>IB-18</td>
<td>ROC</td>
<td>PLN</td>
<td>PLN</td>
<td>DFS/OS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>15.6</td>
<td>Log-rank test</td>
</tr>
<tr>
<td>Poccia et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2010</td>
<td>Italy</td>
<td>R</td>
<td>84.2</td>
<td>16</td>
<td>IB-18</td>
<td>ROC</td>
<td>PLN</td>
<td>PLN</td>
<td>DFS/OS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>7.5</td>
<td>Log-rank test</td>
</tr>
<tr>
<td>Sarker et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>2008</td>
<td>Taiwan</td>
<td>P</td>
<td>92.1</td>
<td>70</td>
<td>IB-10</td>
<td>ROC</td>
<td>PALN</td>
<td>PALN</td>
<td>OS</td>
<td>SUVmax</td>
<td>Log-rank test</td>
<td>7.5</td>
<td>Log-rank test</td>
</tr>
</tbody>
</table>

*Note: ND = not described; D = disease-free survival; O = overall survival; R = retrospective; E = early stage; P = primary tumor, PI = palliative treatment; ROC = receiver operating characteristic; CT = computed tomography; MRI = magnetic resonance imaging; CTx = chemotherapy; RTx = radiotherapy.*

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SUV\textsubscript{max}. 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 SUV\textsubscript{max}, compared with those with a low PALN SUV\textsubscript{max}.

The primary tumor SUV\textsubscript{max} before treatment is a prognostic factor in various types of malignant tumors including uterine cervical cancer.

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

TABLE 2. PET Protocols of the Included Studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>SUV Normalization</th>
<th>BST, mg/dL</th>
<th>Duration of Fasting, h</th>
<th>Post Injection Interval, min</th>
<th>Scan Time, min/bed</th>
<th>SUV Formula</th>
<th>Reconstruction Method</th>
<th>Attenuation Correction</th>
<th>Dose, MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao et al\textsuperscript{37}</td>
<td>ND</td>
<td>ND</td>
<td>6</td>
<td>40–50</td>
<td>3</td>
<td>ND</td>
<td>OSEM</td>
<td>CT</td>
<td>333–407</td>
</tr>
<tr>
<td>Chou et al\textsuperscript{32}</td>
<td>ND</td>
<td>&lt;200</td>
<td>6</td>
<td>50</td>
<td>3</td>
<td>ND</td>
<td>OSEM</td>
<td>CT</td>
<td>370</td>
</tr>
<tr>
<td>Chung et al\textsuperscript{20}</td>
<td>BW</td>
<td>ND</td>
<td>4</td>
<td>60</td>
<td>2.5</td>
<td>D</td>
<td>RAMLA</td>
<td>CT</td>
<td>5.55/kg</td>
</tr>
<tr>
<td>Im et al\textsuperscript{3}</td>
<td>BW</td>
<td>ND</td>
<td>8</td>
<td>60</td>
<td>3</td>
<td>D</td>
<td>OSEM</td>
<td>CT</td>
<td>444–740</td>
</tr>
<tr>
<td>Kidd et al\textsuperscript{18}</td>
<td>BW</td>
<td>68–198</td>
<td>ND</td>
<td>41–128</td>
<td>ND</td>
<td>D</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Lee et al\textsuperscript{30}</td>
<td>BW</td>
<td>ND</td>
<td>6</td>
<td>45</td>
<td>5</td>
<td>ND</td>
<td>OSEM</td>
<td>CT</td>
<td>370</td>
</tr>
<tr>
<td>Nakamura et al\textsuperscript{16}</td>
<td>BW</td>
<td>&lt;150</td>
<td>5</td>
<td>90</td>
<td>2.4</td>
<td>D</td>
<td>OSEM</td>
<td>CT</td>
<td>3.7/kg</td>
</tr>
<tr>
<td>Nakamura et al\textsuperscript{31}</td>
<td>BW</td>
<td>ND</td>
<td>ND</td>
<td>90</td>
<td>2.4</td>
<td>D</td>
<td>OSEM</td>
<td>CT</td>
<td>3.7/kg</td>
</tr>
<tr>
<td>Onal et al\textsuperscript{29}</td>
<td>ND</td>
<td>&lt;150</td>
<td>6</td>
<td>60</td>
<td>3</td>
<td>ND</td>
<td>ND</td>
<td>CT</td>
<td>370–555</td>
</tr>
<tr>
<td>Pan et al\textsuperscript{15}</td>
<td>BW</td>
<td>&lt;180</td>
<td>6</td>
<td>60</td>
<td>3</td>
<td>ND</td>
<td>OSEM</td>
<td>CT</td>
<td>7.4/kg</td>
</tr>
<tr>
<td>Vercellino et al\textsuperscript{33}</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>60–120</td>
<td>2</td>
<td>ND</td>
<td>LOR-RAMLA</td>
<td>CT</td>
<td>5/kg</td>
</tr>
<tr>
<td>Xue et al\textsuperscript{27}</td>
<td>BW</td>
<td>54–193</td>
<td>4</td>
<td>40–195</td>
<td>ND</td>
<td>D</td>
<td>OSEM</td>
<td>CT</td>
<td>555–740</td>
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<tr>
<td>Yen et al\textsuperscript{34}</td>
<td>BW</td>
<td>ND</td>
<td>6</td>
<td>40</td>
<td>ND</td>
<td>D</td>
<td>AMLR</td>
<td>TS</td>
<td>370</td>
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<tr>
<td>Yoo et al\textsuperscript{28}</td>
<td>BW</td>
<td>&lt;200</td>
<td>6</td>
<td>45</td>
<td>ND</td>
<td>ND</td>
<td>OSEM</td>
<td>TS</td>
<td>370</td>
</tr>
</tbody>
</table>

AMLIR 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 SUV\textsubscript{max}. Hazard ratios for events with primary lesion SUV\textsubscript{max} in individual studies and the pooled results are shown. Error bars indicate the 95% CIs.

SUV\textsubscript{max}. 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 SUV\textsubscript{max}, compared with those with a low PALN SUV\textsubscript{max}.

The primary tumor SUV\textsubscript{max} before treatment is a prognostic factor in various types of malignant tumors including uterine cervical cancer.\textsuperscript{6–8} Although conflicting results exist for other types of cancer, such as esophageal and lung,\textsuperscript{3,14} all uterine cervical cancer studies included in the present meta-analysis showed a significantly worse prognosis associated with higher SUV\textsubscript{max}. However, SUV\textsubscript{max} was not a significant independent prognostic factor in the multivariate analyses conducted in each study in the present meta-analysis, except in 2 studies.\textsuperscript{29,30} Onal et al\textsuperscript{29} show an HR of 7.29 (95% CI, 3.5–15.17), whereas Lee et al\textsuperscript{30} show an HR of 36.3 (95% CI, 1.73–761.5) for EFS. The probable reason is that primary tumor SUV\textsubscript{max} 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 SUV\textsubscript{max}. Hazard ratios for events with PLN SUV\textsubscript{max} in individual studies and the pooled results are shown. Error bars indicate the 95% CIs.
size. Actually, these 2 studies included patients with relatively low stages (I-II). Also, another study by Chung et al evaluating patients with low-stage disease (IBT-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 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. An increased risk of recurrence with higher uptake in LN metastasis has also been reported. In the present meta-analysis, there were 2 studies that conducted multivariate analysis including PLN SUVmax. The 2 studies reported that the PLN SUVmax is a significant independent prognostic factor for EFS. There was only 1 study 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 studies that did not report any cutoff value of SUV. There were 11 articles regarding prognostic value of primary FDG uptake; among these, 6 studies have found pretreatment primary tumor uptake of FDG or SUVmax primary as predictor of survival, whereas no uptake or lower SUV was associated with better outcome, 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. 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, and treatment response. 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, and 3 studies could not find abnormal FDG uptake in PLN or PALN as a significant predictor of survival. Meanwhile, pretreatment SUVmax of PLN and PALN was also reported to be higher in patients who were...
nonespondeers to treatment compared with patients who responded well.\textsuperscript{17,18,56} Also, several studies showed that patients with progressive echelon of LN involvement (PLN, PALN, suprachlavicular lymph node) were found to be prone of disease recurrence and worse survival.\textsuperscript{17,18,56}

One article\textsuperscript{27} 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 SUV\textsubscript{max} to be a predictor of death and cause specific survival where higher SUV\textsubscript{max} 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\textsuperscript{15,59} were excluded, whereas the one\textsuperscript{22} 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 SUV\textsubscript{max} was a significant predictor of EFS, whereas a poor survival and metastasis to LN were significantly associated with a higher primary lesion SUV\textsubscript{max}.

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 7/8 (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,\textsuperscript{33,35,36} In addition, uptake durations, ranging from 40 to 90 minutes, after injecting 18\textsuperscript{F}-FDG were well reported in all studies (Table 2), except in 3 studies reporting a duration of up to 195 minutes.\textsuperscript{27,33,35} Regulations for measuring SUV were acceptable, except in those 3\textsuperscript{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 SUV\textsubscript{max} of both primary tumor and metastatic LN. Although there was a discrepancy in the SUV\textsubscript{max} cutoff among studies, and each study applied a different method to identify a specific SUV\textsubscript{max} cutoff for worse prognosis, the association between a greater risk of an event and a higher SUV\textsubscript{max} was unanimous. Although cutoff SUV\textsubscript{max} measured by 18\textsuperscript{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 SUV\textsubscript{max} are at higher risk of adverse events or death.

CONCLUSIONS

SUV\textsubscript{max} measured by 18\textsuperscript{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 SUV\textsubscript{max} are at higher risk of adverse events or death.

REFERENCES


