Diagnostic Value of ^{18}F-FDG PET for Evaluation of Paraaortic Nodal Metastasis in Patients with Cervical Carcinoma: A Metaanalysis

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We assessed the diagnostic performance of ^{18}F-FDG PET in detecting paraaortic lymph node (PALN) metastasis in patients with cervical cancer. **Methods:** Through a search of MEDLINE and EMBASE (1980 to March 2009), we performed a random-effects metaanalysis. A summary receiver-operating-characteristic curve was constructed using hierarchical regression models. To identify other sources of heterogeneity, regression metaanalysis was performed. **Results:** Patients ($n = 385$) from 10 studies were analyzed. Although specificity of ^{18}F-FDG PET was consistent (97%; 95% confidence interval [CI], 93%−99%), sensitivity was low and heterogeneous among the studies (34%; 95% CI, 10%−72%). Although regression metaanalysis did not identify any source to which heterogeneity could be attributed, it revealed a trend of increasing sensitivity according to an increase in the prevalence of PALN metastasis ($P = 0.001$). In the 5 studies with prevalence greater than 15%, estimated sensitivity and specificity were 73% (95% CI, 53%−87%) and 93% (95% CI, 86%−97%), respectively. With the diagnostic performance, assuming the prevalence of 15%, the calculated false-positive and -negative rates were 35% and 5%, respectively. **Conclusion:** In detecting PALN metastasis, PET performs acceptably only in populations with a relatively high probability of PALN metastasis. Otherwise, we found no evidence to justify the evaluation of PALN based solely on PET in cervical cancer.

Key Words: cervical neoplasm; ^{18}F-FDG PET; lymph node staging; paraaortic metastasis; positron emission tomography; surgical staging

Cervical cancer is the second most common cause of cancer-related mortality in developing countries (*1*). The rate of paraaortic lymph node (PALN) metastasis is approximately 15%−30% in patients with locally advanced cervical cancer (*2–4*). Patients with PALN metastasis have lower overall survival, disease-free survival, and survival after recurrence (*2,3,5,6*). Because PALNs are beyond the standard radiation fields, accurate assessment of PALN metastasis is crucial for determining the extent of radiotherapy and improving patient survival (*7,8*). Unfortunately, clinical staging does not provide accurate information about tumor involvement of PALNs. Therefore, surgical staging has been suggested as a gold standard for the evaluation of PALN metastasis (*6,9*). However, the routine use of surgical staging before radiotherapy has been challenged because it has significant adverse effects and morbidities (*10–12*). In addition, some argue that only a small number of patients will benefit from surgical staging (*13,14*). Although there are many reports that address its feasibility and survival advantage (*15–17*), there are few randomized prospective trials indicating the efficacy of surgical staging. Therefore, to evaluate PALN metastasis without surgical intervention, researchers have explored the diagnostic value of imaging studies.

MRI or CT has been used to determine the extent of the disease. The recent metaanalysis indicates that both MRI and CT have low sensitivity (55.5% and 57.5%, respectively) (*18*). This low sensitivity seriously hampered the overall diagnostic performance in the detection of nodal metastasis. Both MRI and CT had a negative likelihood ratio (LR) greater than 0.5; thus, these tests cannot be used to confirm the absence of nodal metastasis. The functional imaging modalities, such as ^{18}F-FDG PET and PET/CT, have better performance. In the same metaanalysis, PET

showed a higher positive LR and lower negative LR (15.3 and 0.23, respectively) than did MRI and CT. On the basis of this evidence, a clinical guideline recommends PET/CT as a routine procedure in the initial work-up of cervical cancer (19).

However, the diagnostic value of PET for PALN metastasis has not been properly evaluated because many studies have focused on the assessment of the pelvic lymph nodes. Moreover, histologic diagnosis of PALN was not performed in many studies. Therefore, it is both timely and important to evaluate the diagnostic performance of PET for PALN metastasis in cervical cancer by reviewing the current evidence. Given this background, we performed a systematic review of the literature to assess the diagnostic performance of PET in the evaluation of PALN metastasis.

MATERIALS AND METHODS

Literature Search and Selection Criteria

We searched MEDLINE and EMBASE (1980 to March 2009) to identify studies evaluating the diagnostic value of PET and PET/CT in the detection of lymph node metastasis in cervical cancer. No language restriction was applied. All relevant studies including at least 10 patients were retrieved. The following search algorithm was used: "cervical neoplasm"; "PET" OR "PET-CT" OR "PET/CT" OR "positron" OR "positron emission tomography" OR "fluorodeoxyglucose" OR "FDG"; "lymph node" OR "metastasis" OR "para-aortic" OR "paraaortic"; and exclusion of "head and neck." If overlapping patient cohorts were used between multiple studies, only the latest or the largest study was included. Selection criteria were as follows: diagnostic performance of PET or PET/CT should be specified for PALN metastasis, and 2 × 2 tables can be derived from the provided data; the study should evaluate at least 10 patients; and histologic assessment should be applied as a reference standard. Because the current analysis aimed to evaluate the diagnostic performance of PET or PET/CT in the assessment of PALN but not its prognostic value, clinical follow-up or radiographic techniques were not accepted as a reference standard.

Data Extraction and Quality Assessment

Data were obtained for author, year of publication, study design, patient characteristics, reference standard, and diagnostic performance of PET or PET/CT. Data were extracted independently by 2 investigators, and discrepancies were resolved by a third investigator. Methodologic quality was assessed using the quality assessment of diagnostic accuracy studies (QUADAS) (20). We arbitrarily considered the study population as representative when the proportion of International Federation of Gynecology and Obstetrics stage III or IV disease ranged between 25% and 45% of the study participants, and patient inclusion was not restricted on the basis of prior imaging technique. The selection criteria were considered to be well described when age, stage, and other health conditions were defined. The interval between the index test and the reference standard was considered to be ideal if it was 4 wk or less. The description of the reference standard was considered acceptable when the extent of the dissected PALN was documented. The description of the index test was considered acceptable when the radiopharmaceuticals, administered activity, fasting before testing, and interval to image acquisition were all documented. The technical specification and quality of PET or PET/CT procedures were evaluated using recommended guidelines (21,22). The score of each component was set to 1 if the answer was yes and 0 if the answer was no or unclear. We performed a regression metaanalysis between test performance and individual QUADAS components.

Statistical Analysis

The sensitivity and specificity of the techniques assessed in a given study were extracted or calculated using 2 × 2 contingency tables. The histologic diagnosis of PALN was the only acceptable reference standard. A bivariate model was constructed to summarize sensitivity, specificity, and positive or negative LRs, and a hierarchic summary receiver-operating-characteristic (HSROC) curve was generated (23–25). Confidence intervals (CIs) were computed, assuming asymptotic normality after a log transformation for variance parameters and for LRs and a logit transformation for proportions. The formula for a positive LR is sensitivity/(1 − specificity), and the formula for a negative LR is (1 − sensitivity)/specificity. A clinically useful test was defined as having a positive LR greater than 5.0 and a negative LR less than 0.2 (26,27). The spectrum of pretest probability can give the spectrum of posttest probability. The posttest probability was graphically plotted according to pretest probability and referred to as a graph of conditional probability (GCP). The posttest probability was calculated by converting the pretest probability into pretest odds, defined as probability/(1 − probability). Posttest odds were calculated by multiplying the pretest odds and the LR. The posttest odds were converted into posttest probability using the following equation: posttest probability = odds/(odds + 1). As a single indicator of test performance, a diagnostic odds ratio was also calculated to compare the odds for sensitivity with the odds for specificity using the following equation: diagnostic odds ratio = positive LR/negative LR.

To determine the best predictor of diagnostic performance, univariate regression metaanalysis was performed according to each quality assessment component of QUADAS (28). Heterogeneity was assessed using Higgins I^2, which measures the percentage of the total variance across studies due to heterogeneity, rather than chance (29). Also, the correlation between sensitivity of each study and the prevalence of PALN metastasis was evaluated using regression metaanalysis. We also performed a Monte Carlo permutation test to determine the true significance of a positive finding in our regression metaanalysis (30). To test publication bias, a funnel plot method was used (31). All P values presented are 2-sided, and associations are considered significant if the P value was less than or equal to 0.050. All statistical analyses were performed using STATA (version 10.0; Stata Corp.).

RESULTS

An electronic search yielded 320 articles; 205 articles were excluded up front on the basis of their abstracts. We screened 115 articles in full-text. The selection process and reasons for exclusion are summarized in Figure 1. A total of 385 patients from 10 studies were analyzed (32–43). The characteristics of the 10 studies are presented in Table 1 and Supplemental Table 1 (supplemental materials are available online only at http://jnm.snmjournals.org). Among these studies, 2 enrolled only patients with early-stage disease (IA2–IIA). In these 2 studies, PALN was sampled only
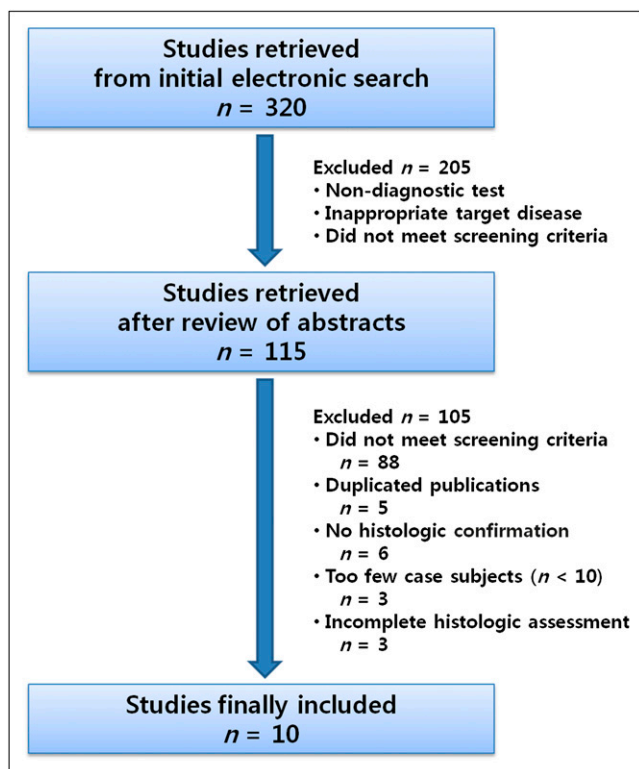
FIGURE 1. Flow chart of selection process for eligible studies.

when suspicion of metastasis was based on the surgeon's decision or palpation. Six studies enrolled patients with negative results for PALN on prior CT, MRI, or PET. Five studies applied masking for interpretation of PET or PET/CT findings. The summarized score for all QUADAS comments ranged from 7 to 12 (Supplemental Table 2). The mean was 9.1, with an SD of 1.5. Using regression metaanalysis, we explored whether each component affected the heterogeneity of diagnostic performance between studies. In univariate analysis, we found that no component of QUADAS significantly explained between-study vari-

ance (Table 2). Funnel plots were symmetric (Begg's $P = 0.881$, Egger's $P = 0.720$), showing an absence of publication bias.

The pooled prevalence of PALN metastasis was 14.2%. The diagnostic performance for all 10 studies is summarized in Table 3. The HSROC curve for the diagnostic performance of PET in the assessment of PALN metastasis is illustrated in Figure 2A. The negative LR was 0.60 (95% CI, 0.34–1.11), which suggests PET is not useful in ruling out disease. However, the positive LR was 13.69 (95% CI, 5.93–31.62), suggesting PET may be useful in confirming disease. Because reported sensitivity showed extreme heterogeneity, we hypothesized that partial verification bias may have been introduced into the studies with extremely low prevalence. Moreover, 2 studies excluded patients with negative index tests (32,41), which may also have impaired estimated sensitivity. Therefore, we restricted the analysis to the 5 studies with prevalence greater than 15% (Table 3), because the rate of PALN metastasis is known to be approximately 15%−30% in patients with locally advanced cervical cancer (2–4). None of the studies had prevalence rates of more than 30%. Interestingly, limiting the analysis to high-prevalence studies (>15%) increased sensitivity (73%; 95% CI, 53%−87%), although the specificity remained similar (93%; 95% CI, 86%−97%). Among the high-prevalence studies, the estimated positive and negative LRs were 10.62 (95% CI, 4.89–23.05) and 0.29 (95% CI, 0.15–0.55), respectively. Again, via regression metaanalysis we verified our hypothesis that prevalence influences the reported sensitivity. We observed a significant trend showing that the reported sensitivity increased as the prevalence increased (regression coefficient, 3.99; $P = 0.001$). Next, we tested whether parameters such as application of PET/CT, year of publication, sample size, prospective design, or masking method might have influenced the between-study difference of sensitivity (Table 4). The parameters were tested via regression metaanalysis, and standard errors of P value were obtained by Monte Carlo approach with 1,000 permutations. After permutation, the application of PET/

TABLE 1. Characteristics of 10 Studies Included in Metaanalysis

Author, year, and reference	n	Stage III/IV patients (%)	Design	Masking	Indication of node dissection	Prevalence	Technique	QUADAS score
Rose/1999 (40)	32	Included (81)	Prospective	NR	CT negative	25%	PET	10
Narayan/2001 (37)	26	Included (12)	Retrospective	Yes	CT negative*	19%	PET	7
Reinhardt/2001 (38)	12	Not included	Prospective	Yes	Palpable node	25%	PET	8
Lin/2003 (35)	50	Included (NR)	Prospective	No	CT negative	28%	PET	9
Roh/2005 (39)	28	Included (8)	Prospective	Yes	All patients	7%	PET	9
Wright/2005 (42)	45	Not included	Retrospective	NR	Surgeon's decision	9%	PET and PET/CT	8
Choi/2006 (33)	27	Included (11)	Prospective	Yes	All patients	11%	PET/CT	11
Boughanim/2008 (32)	38	Not included	Prospective	Yes	PET/CT negative	8%	PET/CT	9
Vergote/2008 (41)	85	Included (NR)	Prospective	NR	PET/CT negative	11%	PET and PET/CT	12
Yildirim/2008 (43)	16	Included (19)	Prospective	Yes	CT negative	25%	PET/CT	8

*Five of 26 patients had positive node on CT and received paraaortic nodal sampling.

NR = not reported.

TABLE 2. Association Between Possible Influences on Study Quality and Between-Study Heterogeneity of Diagnostic Performance

QUADAS component	Coefficient	95% CI	P	I-squared
Were selection criteria clearly described?	0	−3.0 to 3.1	0.989	9.6%
Is the time between reference standard and index test short enough?	−1.8	−5.3 to 1.8	0.256	0%
Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	−1.6	−4.3 to 1.0	0.171	0%
Was the execution of the index test described in sufficient detail to permit its replication?	−2.0	−8.1 to 4.0	0.405	1.8%
Was the execution of the reference standard described in sufficient detail to permit its replication?	−1.9	−7.6 to 3.7	0.423	0%
Were the index test results interpreted without knowledge of the results of the reference standard?	−1.5	−4.0 to 1.1	0.199	0%
Were withdrawals from the study explained?	−0.3	−3.9 to 3.2	0.826	9.2%

Component that shows same score in all studies was dropped because of colinearity.

CT and prevalence of PALN remained as provisional confounders. After multivariate analysis with or without permutation, we observed that the prevalence was the single significant confounder of sensitivity ($P = 0.022$ and 0.018). The HSROC curve in this cohort is illustrated in Figure 2B.

Among the studies, the observed prevalence of PALN metastasis was 14.2%. The observed false-positive and false-negative rates were 27.0% (95% CI, 14.4%−44.4%) and 8.0% (95% CI, 5.5%−11.5%), respectively. In the 5 studies that had a prevalence of PALN metastasis greater than 15%, the observed false-positive rate was 21.9% (95% CI, 9.9%−40.4%). Interestingly, the false-negative rate did not vary as a function of prevalence: it was 7.8% in the low-prevalence group and 8.7% (95% CI, 4.3%−16.2%) in the high-prevalence group.

DISCUSSION

The current review shows that PET or PET/CT is a highly specific diagnostic tool for the evaluation of PALN metastasis in cervical cancer. To date, there have been 3 metaanalyses of the diagnostic value of PET in lymph node evaluation in cervical cancer (18,44,45). Of these, 1 evaluated the diagnostic performance of PET for PALN metastasis across 4 studies (44). The authors reported that the pooled sensitivity and the specificity were 84% and 95%, respectively. Although the specificity was similar to our data, the high sensitivity found in the prior metaanalysis may have resulted from the small sample size of their analysis. For example, in 1 of the 4 studies, 81.3% of the patients studied had stage III–IV disease (40). In another, histologic evaluation was performed only when the enlarged node was palpable during surgery, resulting in no false-positive cases (38). In a third metaanalysis of 8 studies, the authors found that PET has a sensitivity of 75% in the evaluation of pelvic and paraaortic nodes in cervical cancers (18)—a sensitivity that corresponds to that we observed in the population with a high prevalence of PALN metastasis.

Our data revealed that the apparent between-study heterogeneity of sensitivity does not result from the quality of the study. Rather, the different nature of the cohorts, represented by the prevalence of PALN metastasis, contributed significantly to the heterogeneity. In a statistical sense, it is not reasonable that the sensitivity or specificity of a test can be influenced by disease prevalence. However, in a certain clinical setting, biologic variation in populations with a difference in prevalence may influence the sensitivity or specificity of the diagnostic test. Prevalence of PALN metastasis may represent characteristics of me-

TABLE 3. Diagnostic Performance of PET Using ^{18}F-FDG

Index	All studies (n = 10)	Studies with low prevalence (≤15%) of PALN metastasis (n = 5)	Studies with high prevalence (>15%) of PALN metastasis (n = 5)
Sensitivity	0.34 (0.10–0.72)	0.05 (0–0.55)	0.73 (0.53–0.87)
Specificity	0.97 (0.93–0.99)	0.99 (0.90–1.00)	0.93 (0.86–0.97)
Positive LR	12.49 (4.64–33.62)	9.15 (0.37–226.46)	10.62 (4.90–23.05)
Negative LR	0.68 (0.40–1.15)	0.95 (0.82–1.11)	0.29 (0.15–0.55)
Diagnostic odds ratio	18.49 (4.72–72.43)	9.60 (0.35–261.70)	36.80 (11.03–122.76)

Data in parentheses are 95% CIs.

FIGURE 2. HSROC curves of diagnostic performance of ^{18}F-FDG PET in evaluation of PALN metastasis. Size of circles indicates weight of each study. Each ellipsis represents region containing likely combinations of mean value of sensitivity and specificity. (A) HSROC curve for 10 studies. (B) HSROC curve for studies with PALN metastasis prevalence greater than 15%.
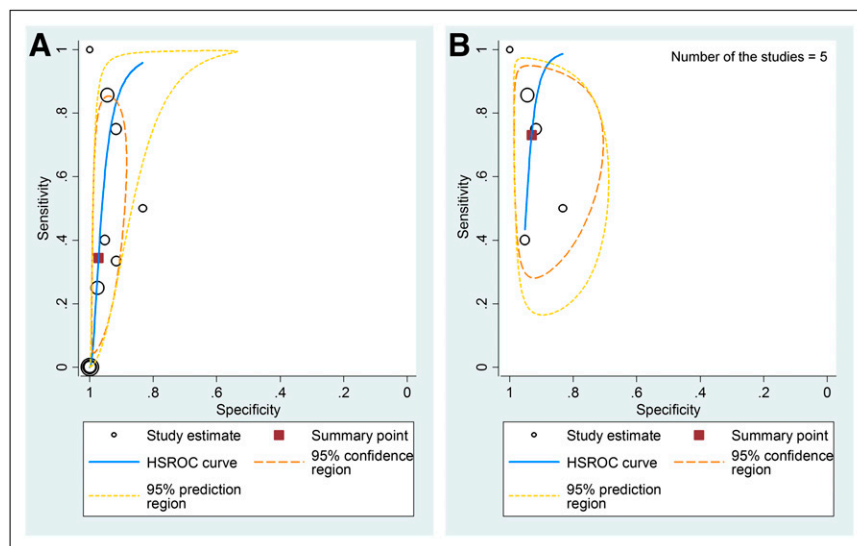
tastatic nodes in the population. A population with a high prevalence of PALN metastasis may consist of patients with a high proportion of stage III–IVA disease or with bulky nodes selected via palpation or imaging. Subsequently, that population may have more large-sized, conglomerated lymphadenopathy and show increased sensitivity. In contrast, a population with a low prevalence of PALN metastasis, such as patients with early-stage disease or negative prior imaging results, is more likely to have a smaller tumor deposit and show less sensitivity. Therefore, readers should be careful about the nature of the study population in interpreting publications describing the performance of PET or PET/CT.

Several concerns arise from our analysis. First, even in a population with a considerable prevalence of PALN metastasis, PET or PET/CT showed a false-positive rate of 21.9%. Because it is likely that a patient wrongfully diagnosed with PALN metastasis may be subjected to unnecessary extended-field radiotherapy, some may argue that the 21.9% false-positive rate of PET or PET/CT is not a negligible rate. However, when we integrate prior diagnostic testing, we may enhance the diagnostic proficiency of PET or PET/CT. We assume that the diagnostic perfor-

mance of PET or PET/CT is similar to that observed in the high-prevalence cohort that had a prevalence of PALN metastasis greater than 15% (sensitivity, 73%, and specificity, 93%). Using the estimated LRs, we translated the spectrum of pretest probability of PALN metastasis into posttest probability and used it for GCP construction (Fig. 3). Indeed, GCP indicates that there exists considerable false positivity when the prevalence decreases and that positive posttest probability ranges from 35% to 46% at the prevalence between 10% and 20%. In this case, the clinician should discuss with a patient the need to perform histologic confirmation to avoid unnecessary extended-field radiation, which may result in severe morbidity and deterioration of quality of life. However, when the PET or PET/CT is used in the population with a high risk of PALN metastasis, the case may be different. For example, we assumed that serum tumor biomarkers could identify the high-risk patients with the prevalence of 30% (46). If we put the positive posttest probability of the biomarker test in the GCP as pretest probability, we can obtain a high positive predictive value of 82%. Therefore, our data indicate that a PALN metastasis detected by PET or PET/CT may have strong diagnostic value when it is supported

TABLE 4. Univariate and Multivariate Regression Metaanalysis of Possible Confounders of Sensitivity

Possible confounder	Univariate				Multivariate		
	Coefficient	P without permutation	P with permutation	SE	Coefficient, P	P without permutation	P with permutation
Year of publication	−0.068	0.045	0.101	0.010			
Sample size (per 10 cases)	−0.079	0.190	0.215	0.013			
Application of PET/CT	−0.500	0.014	0.058	0.008	−0.164	0.386	0.380
Prospective design	0.415	0.085	0.130	0.011			
Prevalence of PALN	3.987	0.001	<0.001		3.260	0.018	0.022
Masking method	−0.129	0.602	0.554	0.016			

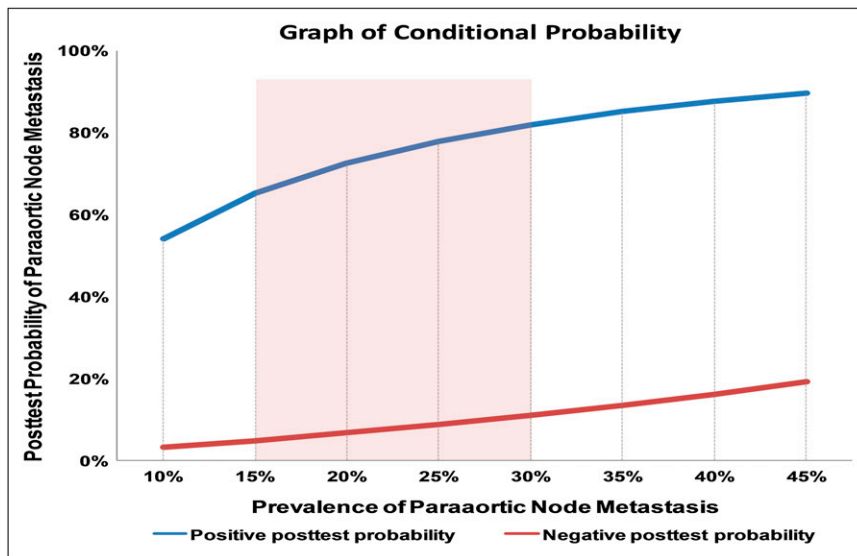1,000 permutations were performed via Monte Carlo approach.

FIGURE 3. GCP of PALN metastasis in cervical cancer based on diagnostic performance of PET or PET/CT in cohort with prevalence greater than 15%. *x*-Axis represents pretest probability, which can be translated into prevalence of disease.

by prior diagnostic tests or conditions increasing the probability of PALN metastasis. In the recent review by Magne et al., the authors proposed a decisional guideline based on PET/CT in the management of cervical cancer (*47*). They recommended that surgical evaluation may be omitted when both the PALN and the pelvic nodal uptake were present. Because the probability of PALN metastasis increases significantly when pelvic lymph node uptake is present (*34*), our data correspond to the proposed guideline.

Second, our data indicate that the false-negative rate of PET or PET/CT is about 8%–9%, which is fairly homogeneous across the studies, regardless of the prevalence in the samples. The homogeneity of the false-negative rate is not explained by the Bayesian theorem, because it indicates that a false-negative rate decreases according to prevalence. However, we also observed that the diagnostic performance of PET or PET/CT decreases according to prevalence. Therefore, the homogeneity can be explained by counterbalancing interaction between the diagnostic performance and the prevalence. It is highly disputable whether this false-negative rate should be permitted in clinical practice. Those opposed to surgical staging propose several reasons to allow the false-negative rate. Because false negativity is commonly attributed to the limited spatial resolution of PET/CT (*41,43*), it can be argued that these micrometastases can be eliminated with the help of concurrent chemoradiation. However, a recent study reported that a false-negative rate of 8% was observed even after the chemoradiation was administered (*32*). This suggests that concurrent chemoradiation is not enough to eradicate occult PALN metastasis. We expect that an ongoing collaborative study conducted by the American College of Radiology Imaging Network and Gynecologic Oncology Group could provide an answer to the question.

In addition, our data have a possible implication for the design of future clinical trials to test new treatments for PALN metastasis. Despite extended-field radiation and concurrent chemotherapy, the survival outcome for patients presenting with PALN metastasis is not satisfactory (*7,48*). Therefore, it is urgent that a potent chemotherapeutic agent or a new strategy should be developed and tested. However, if a trial permits PALN evaluation solely based on PET, the trial will suffer from considerable false-positive cases, especially when prior imaging indicates no evidence of PALN. Moreover, because inadequate sensitivity may result in the loss of a considerable number of candidates for treatment, the time and resources required to complete such a trial would increase.

The current analysis has several limitations. First, although there was no detectable contributor to the between-study heterogeneity in the regression metaanalysis, the small number of included studies might have provided insufficient power to accurately judge the cause of the heterogeneity. Thus, it is possible that the parameters such as use of PET/CT, retrospective study design, year of publication, or application of masking methods might have influenced the results. Therefore, readers should be aware that the current data only expresses that the prevalence of PALN influenced the reported sensitivities significantly. Especially, the current study did not answer whether PET/CT is better than PET. We provided the comparison of diagnostic performance between PET/CT and PET in Supplemental Table 3, and we observed no statistical difference of sensitivity between the 2 techniques. This finding corresponds to the recent metaanalysis describing that there was no statistically significant difference of performance between PET and PET/CT in the overall staging of cervical cancer (*45*). Second, the current analysis did not allow node-by-node or region-by-region comparison, which might have provided important information. Third, the frequencies of stage III–IV disease in most of the studies were less than 20% or more than 50%. This factor also might have played a role as a bias. Fourth, our Bayesian analysis was based on the assumption that diagnostic accuracy is independent of

prevalence. However, because the accuracy of PET varies according to the prevalence of the cohort, our conditional-probability model is not recommended for use in clinical settings for the purpose of estimating the probability of PALN metastasis.

CONCLUSION

It is evident that PET or PET/CT is useful in the management of cervical cancer. It can provide valuable prognostic information, guide the extent of radiotherapy, and also be useful in posttherapy surveillance (*47*). However, the current data indicate that the diagnostic performance of PET or PET/CT for the assessment of PALN metastasis is acceptable when it is performed in the population with a high prevalence of PALN metastasis (>15%). In the population with a low prevalence such as patients with stage I–II disease or negative prior test results, there is not enough evidence yet to convince clinicians to substitute PET or PET/CT for PALN node dissection. The limitations of PET in assessment of PALN metastasis should be seriously considered in designing future clinical trials for high-risk patients with locally advanced cervical cancer.

ACKNOWLEDGMENTS

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