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REVIEW

# Diagnostic accuracy of preoperative $^{18}$F-FDG PET or PET/CT in detecting pelvic and para-aortic lymph node metastasis in patients with endometrial cancer: a systematic review and meta-analysis

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## Abstract

**Purpose** The aim of this study was to assess the diagnostic accuracy of preoperative $^{18}$F-FDG PET or PET/CT in detecting pelvic lymph node (PLN) and para-aortic lymph node (PALN) metastasis in patients with endometrial cancer (EC) in systematic review and meta-analysis format.

**Methods** A comprehensive search was performed on PubMed, Cochrane Library, EMBASE, Web of science, SpringerLink and Science Direct for studies reporting the diagnostic value of preoperative $^{18}$F-FDG PET or PET/CT in detecting PLN and PALN metastasis had been published up to August 8, 2018. Studies were included if enough data could be extracted for calculation of diagnostic accuracy indices.

**Results** Nineteen studies (1431 patients in total) were included in the analysis. On a lymph node basis, the overall pooled sensitivity, specificity, AUC and overall diagnostic accuracy ($Q^*$ index) of $^{18}$F-FDG PET or PET/CT in detecting total lymph node metastasis were 0.68 (95% CI 0.63–0.73), 0.96 (95% CI 0.96–0.97), 0.82, and 0.75, respectively. The corresponding indices for detecting PLN metastasis were 0.61 (95% CI 0.52–0.69), 0.96 (95% CI 0.95–0.97), 0.79, and 0.73, respectively. And the corresponding value for detection of PALN were 0.70 (95% CI 0.58–0.79), 0.92 (95% CI 0.9–0.94), 0.84, and 0.77, respectively. Data based on patients also performed well.

**Conclusions** $^{18}$F-FDG PET and PET/CT both have excellent diagnostic performance for detecting lymph node metastasis, including PLN and PALN metastasis, in patients with endometrial cancer preoperatively. Though the utility of this method is limited due to its moderate sensitivity, it can help surgeons make better-tailored surgical decision for its high specificity.

**Keywords** Endometrial cancer · PET · PET/CT · Pelvic lymph node metastasis · Para-aortic lymph node metastasis

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## Background

Endometrial cancer (EC) is the second common cancer of the female genital tract and the 6th most common malignancy with estimated 319,600 new cases and 76,200 deaths occurring in women worldwide in 2017 [1]. As the disease is frequently symptomatic at an early stage, 5-year overall survival rate of EC patients with localized lesions is 95% [2]. However, the 5-year overall survival rate decreases to 60–70% in patients with pelvic lymph node (PLN) metastasis, and 30–40% in those with para-aortic lymph node (PALN) metastasis [3]. Therefore, it is vital to detect if there is metastasis in PLN and PALN.

Although preoperative staging, including evaluation about status of lymph nodes, is performed through conventional imaging such as transvaginal ultrasonography, computed tomography (CT) and magnetic resonance imaging

(MRI), results of these assessments are not ideal enough to detect micro-morphologic changes before measurable anatomic tumors forming in EC [4, 5]. Therefore, current definite stages of EC still heavily depend on histopathologic findings during primary surgery, which includes hysterectomy, bilateral salpingo-oophorectomy abdominal exploration, peritoneal cytology washing from pelvis, and lymphadenectomy in selected patients who are presumed to be in high risk of metastasis [6]. However, routine systemic pelvic lymphadenectomy in patients of early-stage EC and in poor health is controversial with unnecessary postoperative complications and unproven benefit for overall survival [7]. Herein, development of effective and noninvasive imaging methods enables more accurate detection of the preoperative condition of lymph nodes, which may facilitate better-tailored surgical decision making.

Positron emission tomography (PET) and PET/CT, using metabolic tracer such as radio-labeled glucose analogue 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose ($^{18}$F-FDG), have been exploited as such kinds of noninvasive functional imaging to successfully recognize tumor lesions and lymph nodes metastasis in several cancers [8–12]. $^{18}$F-FDG PET/CT, which combines PET and CT in a single device, overcomes the limitation of morphologic imaging alone since functional changes usually precede anatomical changes assessed by conventional CT or MRI [13]. Though some researchers have demonstrated the value of $^{18}$F-FDG PET or PET/CT in preoperative assessment, diagnostic accuracy of it in detecting PLN and PALN metastasis, respectively, in patients with EC has not been systematically evaluated yet [14, 15]. Considering this background, we reviewed the available literature on this topic and presented the results in systematic review and meta-analysis format.

## Materials and methods

### Literature search

The PRISMA guidelines were followed for performing the current systematic review and meta-analysis. Since the study was not conducted on patients, no informed consent or ethical committee approval was needed. PubMed, Cochrane Library, EMBASE, Web of science, SpringerLink and Science Direct were all searched from inception to August 8, 2018 using the following keywords: ("endometrial neoplasm" or "endometrial carcinoma" or "endometrial cancer" or "endometrium cancer" or "endometrium carcinoma" or "cancer of the endometrium" or "carcinoma of endometrium" or "uterine neoplasm" or "corpus uteri cancer" or "uterine cancer" or "uterine carcinoma") and ("positron emission tomography computed tomography" or "positron emission tomography" or PET or "PET imaging"). Also, we searched "endometrial neoplasm" and "positron emission tomography computed tomography", respectively, in Mesh database as a supplement. References reported in all retrieved articles were also extensively checked to find any other possible relevant publications.

### Inclusion criteria

Studies on $^{18}$F-FDG PET or PET/CT that met the following criteria were included: (1) evaluated patients were diagnosed with EC in any stage; (2) $^{18}$F-FDG was used as tracer; (3) a dedicated device was performed to assess the status of lymph nodes; (4) the data were sufficient to construct or reconstruct a 2 × 2 contingency table to assess the diagnostic accuracy of $^{18}$F-FDG PET or PET/CT; (5) at least ten patients were included; (6) pathological results were used as the gold standard; (7) studies belonged to prospective or retrospective studies. Studies on animals and in vitro studies, not available in full text or not written in English, and unoriginal articles (e.g., reviews, letter to editors, legal cases, interviews, case reports) were excluded in this review. But meeting abstracts with enough information to abstract valid data were also included.

### Data abstraction

One physician and one statistician reviewed each retrieved article independently to determine the eligibility for inclusion and abstracted data from the studies finally selected. Data on the first author, publication year, number of patients analyzed, study design, mean or median age, percentage of endometrioid adenocarcinoma, International Federation of Gynecology and Obstetrics (FIGO) staging, percentage of patients with lymph node metastasis, imaging methods, interval time between performance of $^{18}$F-FDG PET or PET/CT and pathological biopsy, and blindness were recorded. To get more precise results, both lymph node-based and patient-based data on lymph nodal involvement were analyzed in the final analysis. All differences were settled by consensus. Methodological quality of each included article was assigned using QUADAS-2 which comprises four domains: patient selection, index test, flow and timing, and gold standard. Each domain was assessed in terms of risk of bias, and the first three domains were also assessed in terms of concerns regarding applicability [16].

### Statistical analysis

Statistical analysis was performed according to the guideline of diagnostic meta-analysis provided by Deville et al. [17]. Statistical pooling of diagnostic accuracy indices (sensitivity, specificity, positive [LR +] and negative [LR−] likelihood ratios, and diagnostic odds ratio [DOR]) with 95%

confidence intervals (CIs) were analyzed using a random effects model. When estimation of sensitivity, specificity, LR + and LR − for individual study provided at least one zero cell, a correction of 1/2 was added to every cell in that study to ensure estimates could be obtained.

Further, the summary receiver-operating characteristics curve (SROC) was conducted, and the area under the SROC curve (AUC) was determined. Maximum joint sensitivity and specificity ($Q^*$ index), measuring overall diagnostic accuracy, were estimated. $Q^*$ index represented the point at which the sensitivity and specificity were equal. I-square index was used to quantify the heterogeneity. Heterogeneity due to a threshold effect was investigated using the Spearman correlation coefficient. Univariate regression meta-analysis of possible confounders of sensitivity was also performed to find the source of heterogeneity. Deeks' Funnel plots asymmetry test was used for evaluating publication bias.

Statistical analyses were done using Meta-Disc (version 1.4), Stata12.0, and Review Manager (version 5.3) [18].

## Results

### Literature search results

PRISMA flowchart of the study is shown in Fig. 1. The first research returned 352 hits. 271 studies were excluded by overviewing the title and abstract for being irrelevant. Full texts of remaining 81 studies were evaluated in detail. And only 19 studied (1431 patients in total) were eligible according to inclusion criteria. When some studies had duplicated source of patients, only the study owning larger samples and better design was included.

### Study characteristics and quality assessment

Table 1 summarizes the characteristics of the included 19 studies. Recruitment of patients in nine studies was consecutive. Seven studies were prospective, nine were retrospective, and the remainder three studies did not mention the

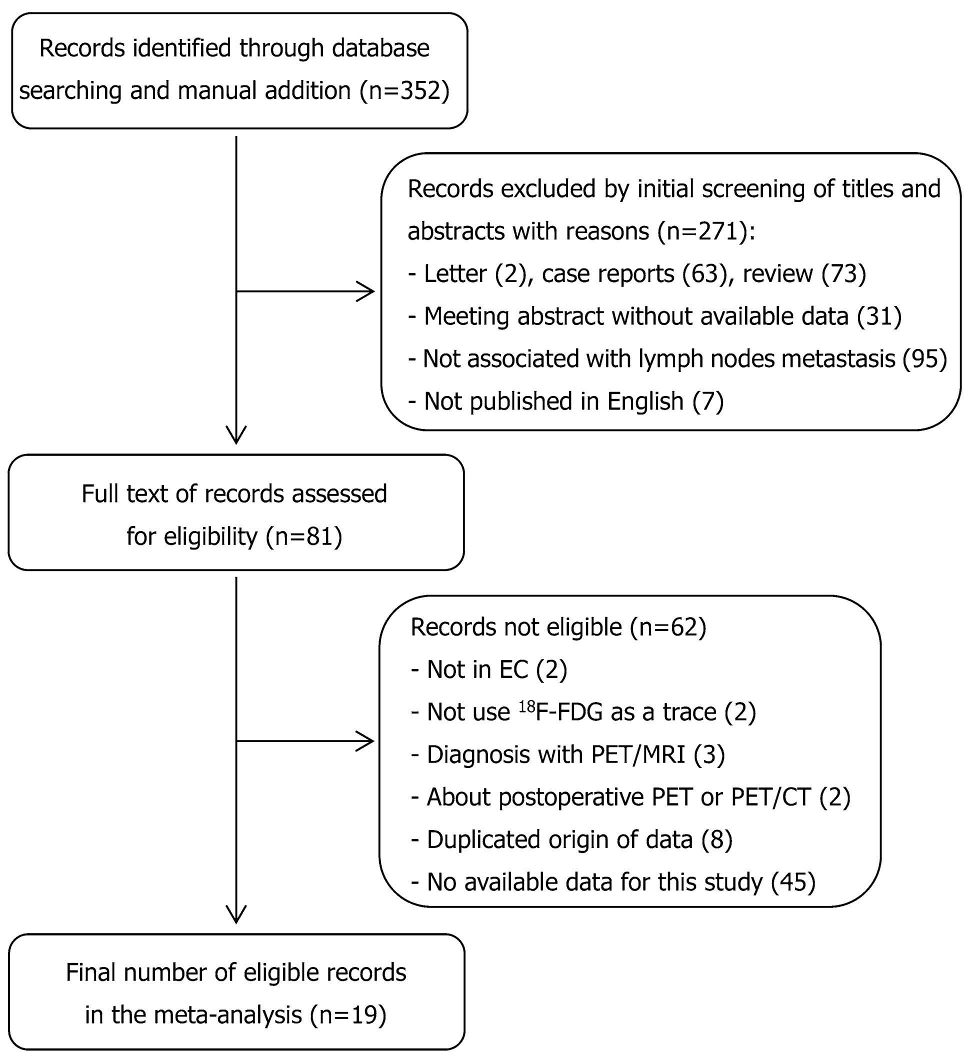


**Fig. 1** PRISMA flowchart of the selection process of eligible records

**Table 1** Characteristics of the included studies

| First author/year | $N$ | Consecutive recruitment | Study type | Mean/median age | Endometrioid cancer (%) | FIGO stage/grade | Patients with nodal metastasis (%) | Imaging method | Average interval time | Blindness |
|---|---|---|---|---|---|---|---|---|---|---|
| Bese 2016 [28] | 95 | N/A | Retro | 58.9 | 95 (100%) | IA: 61; IB: 16; II: 11; IIIA: 1; IIIC1: 4; IVB: 2 | 4 (4.2%) | PET/CT | 16 days | Yes |
| Mayoral 2016 [29] | 13 | YES | Pro | 61.6 ± 9.5 | 8 (61.5%) | N/A | 4 (30.8%) | PET/CT | 4.4 days | Yes |
| Hyun Jeong Kim 2015 [22] | 287 | YES | Retro | 52.3 | 248 (86.4%) | I: 216; II: 12; III: 45; IV: 14 | 51 (17.8%) | PET/CT | 6 days | N/A |
| Husby 2015 [30] | 129 | YES | Pro | 66 | 98 (76.0%) | IA: 73; IB: 22; I: 1; II: 17; III: 12; IV: 4 | 13 (10.1%) | PET/CT | N/A | Yes |
| Nogami 2014 [31] | 53 | N/A | Retro | 58.7 ± 11.4 | 44 (83.0%) | IA: 25; IB: 11; II: 5; IIIA: 4; IIIB: 2; IIIC1: 1; IIIC2: 3; IVA: 0; IVB: 2 | 4 (7.5%) | PET/CT | 37.4 ± 14.9 days | Yes |
| Crivellaro 2013 [27] | 76 | YES | Pro | 62.9 ± 10.9 | 66 (86.9%) | IA: 33; IB: 13; II: 5; IIIA: 5; IIIB: 4; IIIC1: 8; IIIC2: 5; IVB: 3 | 14 (18.4%) | PET/CT | 16 days | Yes |
| Kitajima 2013 [32] | 30 | N/A | Retro | 62.4 | 27 (90%) | Grade1: 10; Grade2: 12; Grade3: 5 | 3 (10%) | PET/CT | within 3 weeks | Yes |
| Antonsen 2012 [33] | 318 | YES | Pro | 65 | 253 (79.6%) | AEH: 18; IA 172; IB: 38; II: 36; IIIA: 6; IIIB: 6; IIIC: 24; IVA: 2; IVB: 16 | 35 (11.2%) | PET/CT | 1–31 days | Yes |
| Nakamura 2011 [34] | 106 | N/A | N/A | 59.32 | 61 (57.6%) | IA: 18; IB: 31; IC: 18; IIA: 3; IIB: 11; IIIA: 9; IIIB: 1; IIIC: 11; IVB: 4 | 12 (11.3%) | PET/CT | N/A | N/A |
| Suga 2011 [35] | 30 | YES | Retro | 56 | 19 (63.3%) | IA:10; IB: 7; II: 2; IIIA: 2; IIIC1: 1; IIIC2: 2; IVB: 6 | 7 (23.3%) | PET | 19 months | No |
| Picchio 2010 [36] | 32 | YES | Retro | 61 | 17 (53.1%) | IA: 1; IB: 4; IC: 4; IIA: 2; IIB: 3; IIIA: 6; IIIC: 5; IVB: 7; all G3 | 7 (21.9%) | PET/CT | 13 days | N/A |
| KLAR 2009 [37] | 13 | N/A | Retro | N/A | 12 (92.3%) | IA: 0; IB: 10; IC: 2; II: 0; III: 1; IV: 0 | 1 (7.7%) | PET | < 30 days | Yes |
| Jeong-Yeol Park 2008 [38] | 53 | N/A | Retro | 52 | 32 (60.4%) | IA: 31; II: 7; III: 8; IV: 7 | 8 (15.1%) | PET/CT | 9 days | N/A |
| Inubashiri 2008 [26] | 46 | YES | Retro | 56 | 29 (63.0%) | IA: 12; IB: 13;IC: 4; II: 2; III: 11; IV: 4 | 11 (23.9%) | PET | 12 days | Yes |
| Nayot 2008 [39] | 12 | N/A | N/A | 62.6 | N/A | I, II, III | 3 (25%) | PET/CT | N/A | Yes |
| Kitajima 2007 [23] | 40 | YES | Pro | 56 | 37 (92.5%) | N/A | 10 (25%) | PET/CT | 12 days | Yes |
| SUZUKI 2007 [40] | 30 | N/A | N/A | 55.4 | 29 (96.7%) | IA: 5; IB: 6; IC: 2; IIA: 2; IIB: 3; IIIA: 5; IIIC: 5; IV: 2 | N/A | PET | 2 weeks | N/A |

**Table 1** (continued)

| First author/year | *N* | Consecutive recruitment | Study type | Mean/median age | Endometrioid cancer (%) | FIGO stage/grade | Patients with nodal metastasis (%) | Imaging method | Average interval time | Blindness |
|---|---|---|---|---|---|---|---|---|---|---|
| Chao 2005 [41] | 49 | N/A | Pro | 55 | 26 (53%) | IA: 9; IB: 6; IC: 3; IIA: 1; IIB: 5; IIIA: 7; IIIB: 1; IIIC: 13; IVB: 3; Unstaged: 1 | N/A | PET | 4.0±9.9 months | N/A |
| Horowitz 2004 [25] | 19 | N/A | Pro | 66 | 15 (78.9%) | IA:3; IB:7, IC:2, II:3, III:2; IV:2 | 3 (15.8%) | PET | 30 days | Yes |

*N/A* not Applicable, *Pro* prospective, *Retro* retrospective, *FIGO* International Federation of Gynecology and Obstetrics, *PLN* pelvic lymph node, *PALN* para-aortic lymph node, *Blind* blindness

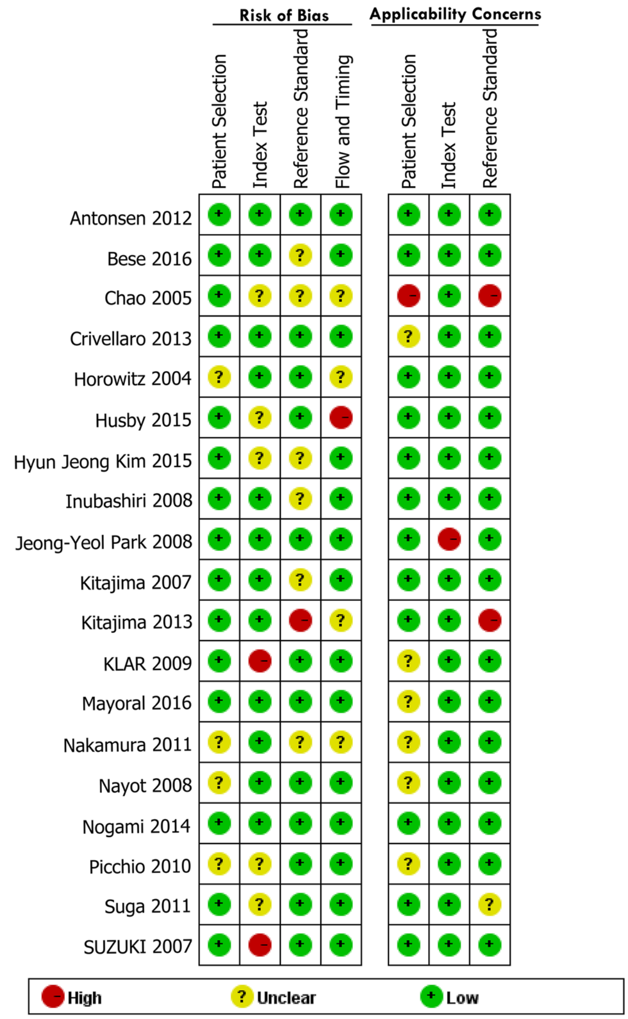


**Fig. 2** Methodological qualities of the included studies according to QUADAS-2. Green circle means low risk; red circle means high risk; yellow circle means unclear risk

study types. Thirteen studies evaluated diagnostic accuracy of preoperative $^{18}$F-FDG PET/CT in detecting PLN and PALN metastasis, while 6 studies evaluated the corresponding diagnostic accuracy of $^{18}$F-FDG PET. The mean prevalence of lymph node metastasis was 17.9% (range from 4.2% to 30.8%). Figure 2 indicates that included studies presented low risk of bias and high applicability concerns as a whole which enhanced the reliability of this article.

## Meta-analysis

### Detection of total lymph node metastasis

In our meta-analysis of total lymph node metastasis, 11 studies were based on lymph nodes. The values of overall pooled sensitivity, specificity, LR +, LR−, DOR for $^{18}$F-FDG PET or PET/CT in detecting total lymph node metastasis were

0.68 (95% CI 0.63–0.73) (Fig. 3a), 0.96 (95% CI 0.96–0.97) (Fig. 3b), 18.50 (95% CI 4–85.51), 0.40 (95% CI 0.30–0.53), and 42.43 (95% CI 13.44–133.96). And the corresponding values on a patient basis (overall 16 studies) were 0.68 (95% CI 0.61–0.75), 0.94 (95% CI 0.92–0.95), 9.26 (95% CI 6.49–13.22), 0.40 (95% CI 0.31–0.52) and 28.81 (95% CI 16.93–49.02), respectively. The SROC curve representing a global summary score for the test performance yielded an AUC of 0.82 and a *Q** value of 0.75 (Fig. 3c) by lymph node, and corresponding values of AUC and *Q** by patient were 0.91 and 0.84, respectively, which indicated a relatively high level of overall accuracy.

Subgroup analysis for instrument methods used (PET vs PET/CT) in the included studies was shown in Table 2. PET/CT presented higher specificity and DOR on a lymph node basis. However, on a patient basis, PET performed better with higher sensitivity, specificity and DOR.

### Detection of PLN metastasis

In the present meta-analysis for PLN metastasis, eight studies were included based on lymph nodes. Pooled diagnostic indices for $^{18}$F-FDG PET or PET/CT in detecting PLN metastasis were as follows: sensitivity 0.61 (95% CI 0.52–0.69) (Fig. 3d), specificity 0.96 (95% CI 0.95–0.97) (Fig. 3e), LR + 12.91 (95% CI 2.27–73.38), LR− 0.48 (95% CI 0.35–0.66), and DOR 29.70 (95% CI 5.75–153.31). Figure 3f showed the SROC curve for $^{18}$F-FDG PET or PET/CT in detecting PLN metastasis. The AUC was 0.79 and the *Q** value was 0.73. And the overall pooled sensitivity, specificity, LR +, LR−, DOR value based on patients (overall three studies) were 0.50 (95% CI 0.23–0.77), 0.94 (95% CI 0.84–0.98), 7.24 (95% CI 1.76–29.76), 0.42 (95% CI 0.06–2.80), and 18.08 (95% CI 0.94–346.05), respectively.

Subgroup analysis based on different imaging modalities used in the included studies (PET vs PET/CT) was performed on a lymph node basis, showing 0.61 (95% CI 0.45–0.76) sensitivity and 0.75 (95% CI 0.67–0.81) specificity for PET group and 0.61 (95% CI 0.50–0.71) and 0.98 (95% CI 0.98–0.99) for PET/CT group (see Table 2). It was clear that PET/CT performed better than PET in detecting PLN metastasis.

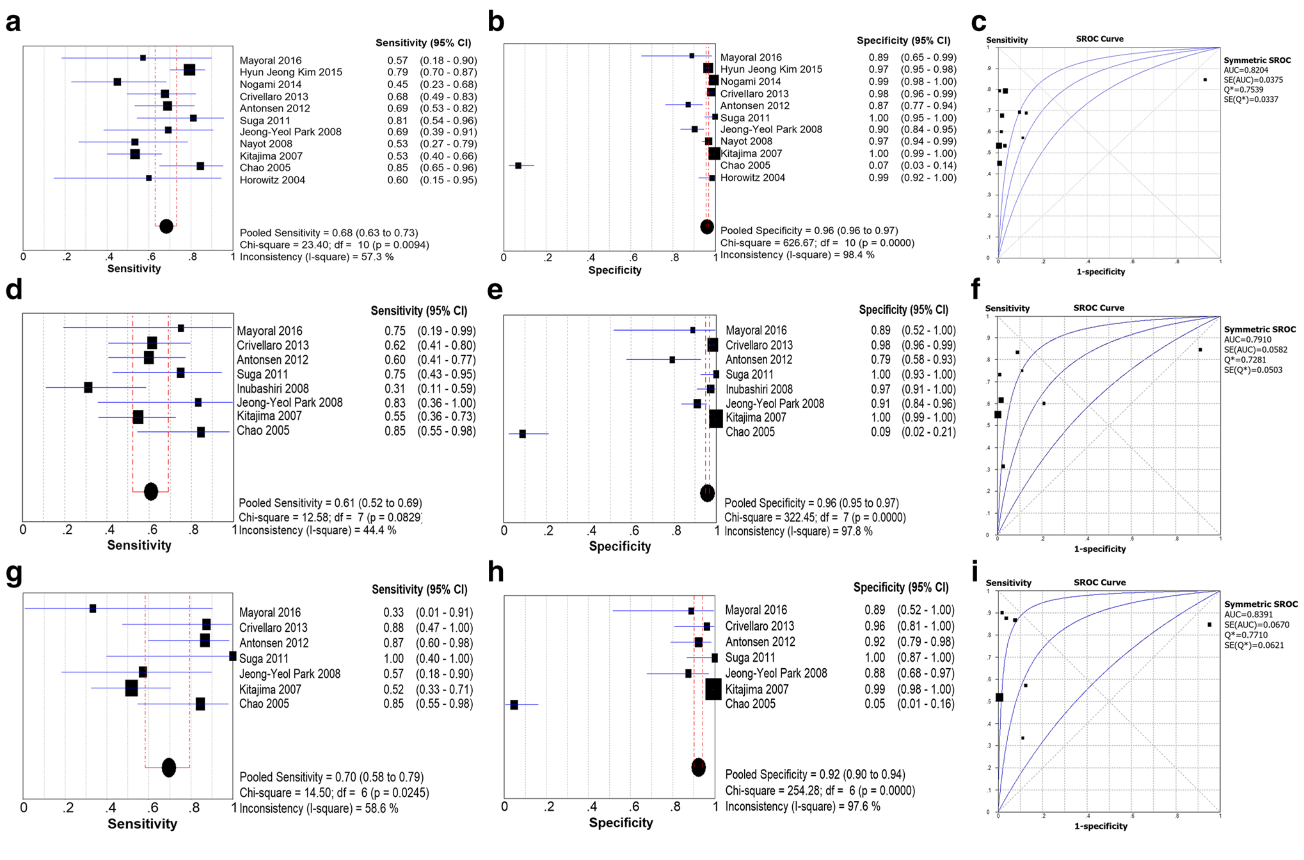


**Fig. 3** Diagnostic value of PET or PET/CT in detecting total lymph node metastasis, including PLN and PALN on a lymph node basis. Total lymph node metastasis: **a** forest plot of sensitivity pooling; **b** forest plots of specificity pooling; **c** SROC curve. PLN metastasis: **d** forest plot of sensitivity pooling; **e** forest plots of specificity pooling; **f** SROC curve. PALN metastasis: **g** forest plot of sensitivity pooling; **h** forest plot of specificity pooling; **i** SROC curve

**Table 2** Subgroup analyses of diagnostic value of preoperative $^{18}$F-FDG PET or PET/CT in detection of total LN, PLN, and PALN metastasis

| | Sensitivity | Specificity | LR + | LR− | DOR |
|---|---|---|---|---|---|
| Total lymph node metastasis | | | | | |
| By lymph node | | | | | |
| PET | 0.81 (0.67–0.91) | 0.64 (0.58–0.71) | 15.33(0.07–3450.19) | 0.55 (0.14–2.17) | 25.22 (0.18–3511.86) |
| PET/CT | 0.66 (0.61–0.72) | 0.98 (0.98–0.99) | 20.98 (9.89–44.54) | 0.39 (0.3–0.5) | 59.58 (26.30–134.97) |
| By patient | | | | | |
| PET | 0.91 (0.59–1.00) | 0.96 (0.87–1.00) | 11.00 (3.34–36.24) | 0.24 (0.07–0.79) | 62.64 (8.31–482.58) |
| PET/CT | 0.67 (0.59–0.74) | 0.93 (0.92–0.95) | 9.05 (6.09–13.43) | 0.41 (0.32–0.53) | 27.10 (15.33–47.91) |
| PLN metastasis | | | | | |
| By lymph node | | | | | |
| PET | 0.61 (0.45–0.76) | 0.75 (0.67–0.81) | 8.31 (0.14–494.39) | 0.61 (0.25–1.47) | 11.23 (0.43–291.51) |
| PET/CT | 0.61 (0.50–0.71) | 0.98 (0.98–0.99) | 17.22 (4.34–68.35) | 0.44 (0.34–0.56) | 53.50 (8.58–333.77) |
| PALN metastasis | | | | | |
| By lymph node | | | | | |
| PET | 0.88 (0.64–0.99) | 0.41 (0.29–0.54) | 5.78 (0.03–1323.60) | 0.63 (0.01–30.02) | 9.40 (0.01–17,648.97) |
| PET/CT | 0.65 (0.51–0.76) | 0.98 (0.97–0.99) | 13.96 (4.07–47.84) | 0.42 (0.24–0.72) | 46.67 (10.60–205.51) |

### Detection of PALN metastasis

The overall pooled estimates of sensitivity and specificity of $^{18}$F-FDG PET or PET/CT in detecting PALN metastasis (total seven studies) based on lymph nodes were 0.70 (95% CI 0.58–0.79) (Fig. 3g) and 0.92 (95% CI 0.9–0.94) (Fig. 3h), respectively. The values of pooled LR + , LR−, DOR were 10.11 (95% CI 1.01–101.56), 0.44 (95% CI 0.24–0.81) and 25.32 (95% CI 3.23–198.65). Figure 3i shows the SROC curve of performance of $^{18}$F-FDG PET or PET/CT. The AUC was 0.84 and overall diagnostic accuracy ($Q^*$ index) was 0.77. And the corresponding indices on a patient basis were not calculated because only one study focused on PALN metastasis by patient.

Subgroup analysis based on different imaging modalities used in the included studies (PET vs PET/CT) showed 0.88 (95% CI 0.64–0.99) sensitivity and 0.41 (95% CI 0.29–0.54) specificity for PET group on a lymph node basis (see Table 2). And the corresponding indices were 0.65 (95% CI 0.51–0.76) and 0.98 (95% CI 0.97–0.99) for PET/CT group, suggesting that PET/CT played more excellent in detecting PALN metastasis.

### Heterogeneity, threshold effect and publication bias evaluation

As shown in Fig. 3, heterogeneity in our study does not seem to be a major issue except for the pooled specificity of lymph node metastasis on a patient basis (*I*-square index for pooled specificity of LN, PLN and PALN metastasis were 98.4%, 97.8% and 97.6%). In other words, variations of diagnostic indices across included studies were acceptable (although not perfectly low) and do not seem to affect the results of our meta-analysis. Threshold analysis showed weak and insignificant statistical correlation between true-positive and false-positive rates (see Table 3). This indicated that a threshold effect was not a major concern in our study and the results were steady in this regard. When considering no threshold effect, univariate regression meta-analysis about possible confounders of sensitivity on a lymph node basis was performed without finding significant cofounders (see Table 4). And Fig. 4 shows no significant publication bias in our study.

**Table 3** Analysis of diagnostic threshold

| | LN metastasis | | PLN metastasis | PALN metastasis |
|---|---|---|---|---|
| | By patient | By lymph node | By lymph node | By lymph node |
| Spearman correlation coefficient | −0.329 | 0.524 | 0.524 | −0.250 |
| *p* value | 0.232 | 0.098 | 0.183 | 0.589 |

**Table 4** Univariate regression met
a-analysis of possible confounders of sensitivity on a lymph node basis

| Possible cofounders | Univariate | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | LN metastasis | | | PLN metastasis | | | PALN metastasis | | |
| | Coefficient | SE | *p* Value | Coefficient | SE | *p* Value | Coefficient | SE | *p* Value |
| Instrument | −0.160 | 0.9110 | 0.8671 | 0.932 | 1.3393 | 0.5584 | −9.235 | 24.6352 | 0.7717 |
| Stage | 0.236 | 0.3628 | 0.5438 | 0.557 | 0.8342 | 0.5729 | −1.930 | 6.7673 | 0.8231 |
| Endometrioid cancer % | 0.885 | 0.5445 | 0.1651 | 2.108 | 2.3056 | 0.4570 | −1.626 | 10.3638 | 0.9010 |
| LN metastasis % | 0.491 | 0.8202 | 0.5752 | 1.375 | 1.9972 | 0.5623 | −8.302 | 26.0350 | 0.8035 |

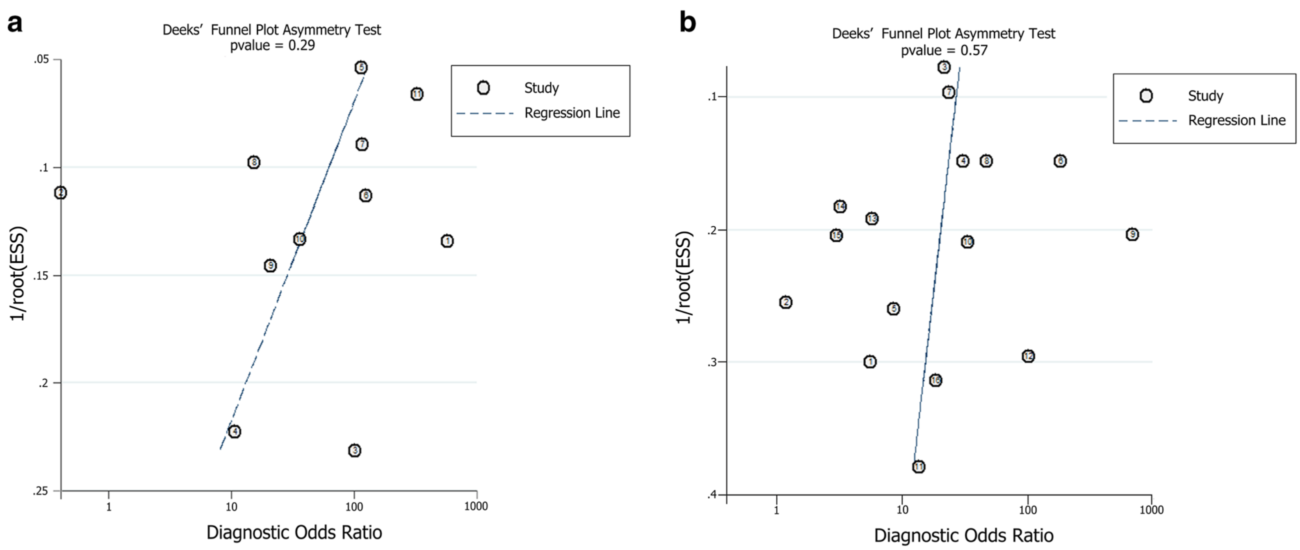


**Fig. 4** Publication bias in our meta-analysis using funnel plot asymmetry of data on a lymph node basis (**a**) and on a patient basis (**b**)

## Discussion

Lymphadenectomy assessing lymph node metastasis historically contributes to stages of EC and influences subsequent strategy of treatment. However, opinions on whether gynecologists should perform lymphadenectomy as routine procedure have not reached an agreement for its few advantages found in patients with early stage but certain survival benefits for patients with high risk of recurrence [19–21]. Herein, noninvasive methods instead of surgical lymph node staging appeared to be more attractive and advantageous. $^{18}$F-FDG PET and PET/CT are such kinds of noninvasive imaging modalities, which have been used for preoperative detection of lymph nodes metastasis of EC in several studies.

### Overall diagnostic accuracy

The pooled sensitivity for preoperative $^{18}$F-FDG PET or PET/CT of detecting total LN metastasis including PLN and PALN in this meta-analysis saw around 60%. This meant as much as about two-fifths of the metastatic lymph nodes were still missed by $^{18}$F-FDG PET and PET/CT. Though pooled sensitivity was moderate, it compares favorably with the reported sensitivity of 34.0% for LN metastasis by conventional MRI [22]. One probable reason for this unsatisfying sensitivity is that the positive expression of $^{18}$F-FDG depends on a sufficient number of malignant cells exhibiting detectable increased glucose metabolism. And the spatial resolution of $^{18}$F-FDG PET and PET/CT is also a main limitation, because it is not good enough to reliably detect LN metastasis smaller than 5 mm [23]. Furthermore, nonmalignant physiological uptake of $^{18}$F-FDG in the normal endometrium, especially in the ovulatory and menstrual phases in the premenopausal women, is more likely to be another cause of suboptimal sensitivity [24]. Moreover, there is no documented threshold for lymph node size allowing $^{18}$F-FDG PET or PET/CT to correctly identify metastatic lymph nodes as positive in EC. Some studies used a five-point ordinal categorical scale and identified scores of 0, 1 and 2 as negative, at the same time scores of 3 and 4 were considered as positive [25]. While others interpreted $^{18}$F-FDG PET abnormalities using a 4-point grading system with scores of 3 and 4 classified as malignant and scores of 1 and 2 as benign [26]. In this regard, combination the expression of $^{18}$F-FDG with standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) can increase the diagnostic sensitivity of $^{18}$F-FDG PET and PET/CT in detecting LN metastasis [27]. Besides, the incidence of LN metastasis in patients with EC is low (mean prevalence was 17.9%, ranged from 4.2 to 30.8% in this study) resulting in the low precision of sensitivity estimation.

High specificity in detecting total lymph nodes metastasis including PLN and PALN (ranged from 92 to 96%) by $^{18}$F-FDG PET or PET/CT was found in this meta-analysis. This specificity is sufficiently high that gives patients chances for not receiving lymphadenectomy at once, especially those diagnosed as type I, early FIGO stage, low grade of EC or in bad condition of health. Patients with negative results of $^{18}$F-FDG PET or PET/CT are expected to have more preoperative examinations to make more appropriate surgical decisions, resulting in reduced operative and postsurgical complications and costs. However, because of the limited spatial resolution of $^{18}$F-FDG PET and PET/CT, it cannot replace the surgical lymph nodes dissection and pathological examination in general. Furthermore, this study presented a high LR +, indicating the positive findings of $^{18}$F-FDG PET or PET/CT on lymph nodes metastasis were reliable in patients with untreated EC. Additionally, a low LR- may assist in ruling out patients without LN metastasis.

The present meta-analysis revealed that, despite of the high specificity, $^{18}$F-FDG PET and PET/CT are moderately sensitive and could not, therefore, replace lymphadenectomy.

### PET/CT outperformed PET

As shown in Table 2, results of subgroup analysis implied that PET/CT, with moderate similar sensitivity and high specificity, performed better than PET in detecting both PLN and PALN metastasis. And DOR (both greater than 20) of PET/CT was also much higher than PET. This was most likely owing to added value of the precise anatomical localization of CT over PET alone. Since $^{18}$F-FDG not only accumulate in malignant tissues but also has normal distribution in the body, physiological uptakes can be misinterpreted as lesions [24]. Therefore, PET/CT can decrease these false-positive results and increase the specificity.

### Limitations

The current analysis has several limitations. First, positive results publication bias is a major concern, because nonsignificant or unfavorable study results tend to be discarded. However, funnel plot asymmetry implied no large bias in our study. Second, regarding the spectrum of the recruited patients, the included studies in our meta-analysis were heterogeneous. Sixteen studies included patients of all preoperative clinical stages. Two studies only contained patients of clinical stage I with high risks and the remainder one consisted of clinical stage III or IV with high risks. Third, not all included studies had prospective study designs. And there were not yet large prospective studies in patients with untreated EC. Fourth, although limiting the publication language in English helped eliminate certain less-qualified studies, this may also miss some valuable data. Fifth, the current meta-analysis lacked of researches on diagnostic accuracy of $^{18}$F-FDG PET or PET/CT in detecting PALN metastasis on a patient basis. Sixth, regardless of the fact that pelvic lymphadenectomy was used in all but three studies consistently, para-aortic lymphadenectomy was done only in selected patients in some studies. And most studies did not describe the exact region of lymphadenectomy and share the same criteria of the operative range. These clouded the results with uncertainty and made inferential assumptions difficult to interpret, as this bias could considerably change the estimated sensitivity and specificity for detection of PALN metastasis without available positive histopathological results. This limitation was, however, hard to circumvent, because it seems unethical to perform biopsies of all PLN and PALN in patients due to risk of unexpected complications. Finally, the present study did not compare $^{18}$F-FDG PET and PET/CT with other imaging modalities such as MRI and diagnostic CT scan simultaneously.

## Conclusion

Overall, $^{18}$F-FDG PET and PET/CT presented high diagnostic accuracy in identifying LN metastasis including PLN and PALN metastasis preoperatively. And $^{18}$F-FDG PET/CT was preferable to PET alone for detecting PLN and PALN metastasis. By high overall diagnostic accuracy, both $^{18}$F-FDG PET and PET/CT may be proved beneficial to surgeons when making better-tailored surgical decision for patients who are predicted to have lymph node metastasis. But due to the shortage of them, they cannot replace lymphadenectomy completely now. And larger prospective studies are needed to validate the high diagnostic performance of $^{18}$F-FDG PET and PET/CT in EC and further help surgeons select patients with particular clinical benefit from applying these advanced imaging modalities.

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## Compliance with ethical standards

**Conflict of interest** The authors have no conflicts of interest to declare.

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