High diagnostic value of FDG-PET/CT in endometrial cancer:

Systematic review and meta-analysis of the literature.

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Running title: FDG-PET/CT in endometrial cancer.

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Conflict of Interest Statement

The author’s state that the research presented in this manuscript is free of conflicts of interest.
Aim: To evaluate the diagnostic performance of fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) for the preoperative assessment of lymph node metastases (LNM) in endometrial cancer patients and for the assessment of endometrial cancer recurrence (ECR) after primary surgical treatment.

Methods: A comprehensive search was performed on Pubmed/MEDLINE databases for studies reporting the diagnostic performance of FDG-PET/CT for assessment of LNM and ECR published up to August 15th 2015. Twenty one studies (13 for LNM and 8 for ECR) were included in the systematic review and meta-analysis. Pooled estimates of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) of the FDG-PET/CT were calculated along with 95% confidence intervals (CI). A summary receiver operating characteristics curve (SROC) was constructed and the area under the SROC curve (AUC) was determined along with Q* index.

Results: The overall pooled sensitivity, specificity, PLR, NLR, DOR and AUC (with 95% CI) of FDG-PET/CT for detection of LNM were 0.72 (0.63-0.80), 0.94 (0.93-0.96), 10.9 (7.9-15.1), 0.36 (0.27-0.48), 39.7 (21.4-73.6) and 0.94 (0.85-0.99), respectively; whereas the corresponding numbers for detection of ECR were 0.95 (0.91-0.98), 0.91 (0.86-0.94), 8.8 (6.0-12.7), 0.08 (0.05-0.15), 171.7 (67.9-434.3) and 0.97 (0.95-0.98), respectively. The overall diagnostic accuracy (Q* index) in LNM and ECR were 0.88 and 0.93, respectively.

Conclusions: FDG-PET/CT has an excellent diagnostic performance for detecting LNM preoperatively and disease recurrence postoperatively in endometrial cancer patients.

Keywords: Endometrial cancer, FDG, PET and CT.
Endometrial cancer is the most common gynaecological malignancy in the developed countries (1). The prognosis is traditionally determined by clinical and histopathologic factors i.e. age, histologic type, grade, stage of disease including assessment of cervical invasion, depth of myometrial invasion, lymph node spread and distant metastases (2–4). The 5-year overall survival rate is generally favourable, around 80%. However, pelvic LNM represents the most common site for extra uterine disease at primary treatment and the 5 year survival rate is around 50% for this patient subgroup (5).

Currently, the final staging of endometrial cancer is based on histopathologic findings at primary surgery, which includes abdominal exploration, peritoneal cytology washing from the pelvis, hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy in selected patients presumed to have high risk of disease spread (6–8). Routine systemic pelvic lymphadenectomy for early stage endometrial cancer disease, although not well defined as surgical technique, improves detection of LNM, but the procedure showed no survival benefit in two randomized clinical trials (9,10). Valid preoperative identification of patients with LNM who may benefit from lymphadenectomy is thus essential if futile surgical staging and unnecessary postoperative staging related complications are to be minimized. If a non-invasive imaging technique could accurately preclude lymph node metastases preoperatively, lymphadenectomy procedures, currently with unproven clinical benefit for survival, could be safely circumvented. Hence, the development of non-invasive imaging methods enabling more accurate preoperative staging of endometrial cancer may facilitate better tailored surgical decision making based on selection of appropriate risk groups for LNM.

Conventional diagnostic imaging by transvaginal ultrasound (TVU), magnetic resonance imaging (MRI) and computed tomography (CT) provide detailed anatomical information, while functional
or metabolic tumor characteristics may remain undetected. However, vigorous debate has challenged the use of anatomic assessments solely relying on tumor morphological information, not taking into account functional tumor characteristics that may prove highly relevant for the clinical phenotype (11–13). In this regard, to better understand the tumor microenvironment, metabolic positron emission tomography (PET) tracers such as fluorodeoxyglucose (FDG), in combination with CT can overcome the limitations of morphological imaging alone, since functional changes possible to detect by FDG-PET/CT often precede morphological changes detectable by conventional MRI or CT (14,15).

FDG-PET/CT has long been used successfully for evaluation of several malignancies including endometrial cancer (15,16) (Fig.1). Based on a systematic review, we here report diagnostic indices of FDG-PET/CT for preoperative prediction of lymph node metastases and for detection of disease recurrence after surgery with curative intent in endometrial cancer patients.

MATERIALS AND METHODS

Search Strategy

Because the study was not conducted on patients, no informed consent or ethical committee approval was needed. To identify all relevant publications we performed systematic searches in the bibliographic databases PUBMED.com from inception to August 17, 2015. Search terms included controlled terms from Mesh in PUBMED.com using the following search terms ‘FDG PET’ in combination with ‘Endometrial neoplasms’. The references of the identified articles were also searched for relevant publications.

Selection Process
One physician (VRB) and one statistician (OBB) reviewed each published article independently to determine the eligibility for inclusion in the meta-analysis, and to extract information regarding clinical patient data and PET/CT characteristics. From the studies selected, data on first author, year of publication, number of patients included, study design (prospective or retrospective), patient age (mean/median), results from surgical International Federation of Gynecology and Obstetrics (FIGO) staging, percentage with nodal metastases, percentage with endometrioid subtype, FDG-PET/CT technical characteristics and numbers for diagnostic performance of FDG-PET/CT (i.e. true negatives, false negatives, true positives, false positives, positive predictive value and negative predictive value) were extracted and recorded. Any differences were resolved by consensus.

PET/CT studies that met the following criteria were included. First, studies which reported the diagnostic performance of FDG-PET/CT in detecting lymph node metastases preoperatively and/or disease recurrence in endometrial cancer patients after primary surgery. Secondly, clinical studies which included at least 10 patients. Third, studies which applied FDG as a tracer on dedicated device and published after peer review. Studies on animals or in vitro studies, studies not available in full text or not written in English and non-original articles (e.g. reviews, editorials, letters, legal cases, interviews, case reports) were not evaluated systematically in this review.

**Statistical Analysis**

We performed standard methods recommended for meta-analysis of diagnostic test evaluations (17). Statistical analyses were carried out using Meta-Disc 1.4 software (18). We computed pooled measures for the following test indices of each study: sensitivity, specificity, positive
likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR). Further the summary receiver operating characteristics curve (SROC) was constructed and the area under the SROC curve (AUC) was determined.

A random effects model was used for statistical pooling of the data. Pooled data were presented with 95% confidence intervals (CI). The CI for diagnostic indices are exact, i.e they are based on the binomial distribution and hence are asymmetric. The I-square index was used to test for heterogeneity between studies. The AUC was calculated to measure the overall diagnostic performance of FDG-PET/CT in detecting the LNM and endometrial cancer recurrence. The sensitivity and specificity for the single test threshold identified for each study were used to plot the SROC curve along with Q* index representing an overall measure of the test’s discriminatory power.

RESULTS

Literature Search Results

The literature search yielded a total of 58 references in PUBMED.com. In addition, three relevant recent articles on LNM in endometrial cancer and one in ECR that we were aware of, were included in our database. The flow chart of the search and selection process is presented in Fig 2. Out of a total of 62 articles, only 21 were eligible according to the criteria. Tables 1 and 2 summarize details for the included endometrial cancer studies of LNM and ECR by FDG-PET/CT imaging, respectively.

Preoperative Detection of Lymph Node Metastases
In our meta-analysis of LNM, 13 studies were included, comprising a total of 861 endometrial cancer patients. The overall pooled diagnostic indices of preoperative FDG-PET/CT for detecting LNM are calculated on the patient basis. The pooled sensitivity and specificity values are 0.72 (95% CI: 0.63 to 0.80) (Fig. 3A) and 0.94 (95% CI: 0.93 to 0.96) (Fig. 3B), respectively. The pooled PLR is 10.9 (95% CI: 7.9 to 15.1), the pooled NLR is 0.36 (95% CI: 0.27 to 0.48), and the DOR is 39.7 (95% CI: 21.4 to 73.6).

The SROC representing a global summary score for the test performance yielded an AUC of 0.94 and a Q* value of 0.88 (Fig. 3C), indicating a relatively high level of overall accuracy.

Detection of Endometrial Cancer Recurrence

In the present meta-analysis for ECR, 8 studies comprising 378 patients have been included. The pooled sensitivity is 0.95 (95% CI: 0.91 to 0.98) (Fig. 4A), while the pooled specificity is 0.91 (95% CI: 0.86 to 0.94) (Fig. 4B). The pooled PLR is 8.8 (95% CI: 6.0 to 12.7), NLR 0.08 (95% CI: 0.05 to 0.15) and the DOR 171.7 (95% CI: 67.9 to 434.3). The SROC curve for the FDG-PET/CT in the detection of endometrial cancer recurrence yields an AUC and Q* values of 0.97 and 0.93 (Fig. 4C), respectively, suggesting that the level of overall accuracy is high.

DISCUSSION

Lymphadenectomy is currently commonly applied for lymph node staging in endometrial carcinoma as part of the surgical FIGO staging systems. However, non-invasive accurate lymph node staging in endometrial cancer by preoperative imaging seems advantageous compared to the more invasive nature of surgical lymph node staging, also with an unproven survival benefit from the procedure (9,10). Similar to other tumors, endometrial cancer has an increased tumor glucose metabolism and glycolysis rate which makes it suitable for FDG-PET/CT imaging (19–21). The
present meta-analysis yields very high diagnostic performances of FDG-PET/CT for diagnosing LNM preoperatively- High diagnostic accuracy was also demonstrated for the procedure detecting endometrial cancer recurrence after primary surgical treatment. This clearly supports a role of FDG-PET/CT to enable more accurately tailored primary surgical endometrial cancer treatment and subsequent patient care.

The pooled sensitivity for preoperative detection of lymph node metastases by FDG-PET/CT in this meta-analysis was 72%, highlighting that as much as about 1/4 of the metastatic lymph nodes are still missed by FDG-PET/CT. One possible explanation for this finding is that FDG avidity relies on the presence of sufficient number of malignant cells exhibiting increased glucose metabolism. Furthermore, the spatial resolution of PET/CT is not good enough to reliably detect small tumors or micro metastatic disease. There is no documented threshold for lymph node size allowing PET/CT to correctly identify metastatic lymph nodes in endometrial cancer, although one study, reported node based sensitivities of 17% (4/24) for nodes ≤4 mm, 67% (14/24) for nodes measuring 5-9 mm, and 93% (14/15) for nodes ≥10 mm (22). Similar figures with node-based sensitivities of 13%, 67% and 100% in metastatic lymph nodes of ≤4 mm, 5-9 mm and ≥10 mm, respectively, in endometrial cancer was reported in another study (23). It should, however, be kept in mind, that although this meta-analysis found the overall sensitivity of FDG-PET/CT to be moderate for the detection of LNM in endometrial cancer, it compares favourably with the reported sensitivities for LNM detection by conventional MRI and CT (24).

A very high pooled specificity of 0.94 for metastatic lymph node detection by FDG-PET/CT was found in this study, and it may be argued that this specificity is sufficiently high to safely omit a major surgical procedure in patients with low risk based on results from preoperative endometrial biopsy and preoperative imaging, reducing operative and post-surgical complications and costs
Furthermore, the present meta-analysis, showed that FDG-PET/CT has a very high PLR (10.9), pinpointing that FDG-PET/CT findings suggesting metastatic lymph nodes are very likely to be confirmed at surgical staging. The high diagnostic performance of FDG-PET/CT for detecting endometrial cancer lymph node metastases is also justified by high AUC of 0.94 in this meta-analysis. Interestingly, Kang et al. (26), reported almost identical figures for the diagnostic performance of FDG-PET/CT for detecting LNM in cervical cancer, with reported sensitivity of 0.73 (95% CI 0.53 to 0.87) and specificity of 0.93 (95% CI 0.86 to 0.97). Thus, FDG-PET/CT seems to be equally feasible in endometrial and cervical cancer for lymph node staging, and FDG-PET/CT may be particularly justified in endometrial- and cervical cancer patients with high risk for disease spread, in order to identify metastatic lymph nodes preoperatively.

Several recent studies in endometrial cancer have demonstrated that preoperative primary tumor metabolic parameters have been associated with the presence of LNM. In a prospective study, Antonsen et al. (27) found significantly higher SUVmax values in patients with LNM compared to those with no LNM (P=0.04). Additionally, they found that SUVmax was significantly higher in patients with high FIGO stage, myometrial invasion and cervical invasion. Furthermore, Crivellaro et al. (28) found strong association between the presence of LNM and metabolic tumor volume in endometrial cancer. Recently, we demonstrated that the preoperative metabolic tumor volume cut-off value of 30 ml yielded sensitivity and specificity of 85% and 76% for LNM, respectively, suggesting that the metabolic tumor volume is a promising marker for LNM (25). In this regard, preoperative FDG-PET/CT imaging of primary endometrial carcinomas may provide an adequate tool for prognostication and LNM detection that facilitate personalized patient care. However, additional prospective studies are required to define optimal cut-off values for predicting LNM based on FDG-PET/CT metabolic parameters. Earlier studies describe measures
for SUV values from a single region of interest, which does not represent the overall tumor profile. Therefore, advanced techniques like the whole tumor voxel-by-voxel analysis may be a preferable approach to reduce operator dependence and capture more relevant and comprehensive measures for tumor microenvironment and heterogeneity.

The pooled sensitivity and specificity of FDG-PET/CT for the detection ECR were 0.95 and 0.91, respectively with AUC in ROC analysis of 0.97 (95% CI: 0.95 to 0.99), all supporting high level of overall diagnostic accuracy. Again, similar FDG-PET/CT diagnostic performance indices were reported for detecting recurrent uterine cervical carcinomas with reported pooled sensitivity, specificity and AUC of 0.92 (95% CI 0.91 to 0.94), 0.84 (95% CI 0.74 to 0.91) and 0.95, respectively (29). Thus, FDG-PET/CT seem to perform equally well in the diagnosis of endometrial and cervical cancer recurrences, supporting a promising role of FDG-PET/CT as diagnostic tool for patients with suspected recurrence.

The findings in this study regarding FDG-PET/CT and ECR must, however, be interpreted with care, considering that the studies report lack of histological confirmation of all putative metastases based on FDG-PET/CT, and they report variable follow-up of the cases considered non-metastatic based on FDG-PET/CT. Thus, some of the cases classified as correctly staged for ECR by FDG-PET/CT, may have been erroneously classified. This limitation shared by most published studies including the studies on cervical cancer recurrence, is however hard to circumvent, as it seems unethical to perform biopsies of all suspected metastatic lesions in patients due to risk of complications. Furthermore, frequent FDG PET/CT follow-up scans is both very expensive and implies unwanted radiation exposure for the patients.
As both LNM and endometrial cancer recurrence studies exhibit inter study heterogeneity, the SROC curve should be asymmetric (Supplementary Fig. 1 for both symmetric and asymmetric SROCs). Since all possible curves with the same true odds ratio and different degrees of heterogeneity would pass through the same point on the anti-diagonal, the heterogeneity does not affect the \( Q^* \) estimate, but rather the shape of the curve and its standard errors. Walter et al. (30) notes that the AUC standard errors calculated under the homogeneity assumption provide a good approximation for heterogeneous studies. The approximation may be poor for extremely high DOR values (higher than 20), as is the case in both meta-analyses presented here (37.5 and 171.7 for LNM and recurrence, respectively). However, the bias in the homogeneity-based standard errors is mostly positive, and hence conservative, i.e. can be overestimated, but rarely underestimated. The supplementary Fig. 1 illustrates that the confidence intervals of the asymmetric SROC are much narrower compared to those of the symmetric SROC, while the difference between the AUC estimates is negligible.

This meta-analysis has several limitations. First, positive result publication bias is a major concern, since non-significant or unfavourable study results tend to be discarded. However, we evaluated publication bias in our meta-analysis using funnel plot asymmetry, finding the funnel plots to be symmetric for both sensitivity and specificity pooling, implying no large bias in our study. Second, the current meta-analysis did not include region by region or node by node evaluation since this was not reported in most studies; however, this could have provided additional information. Third, not all included studies had a prospective study design. Fourth, the gold standard for confirmation of LNM or ECR, being histopathological examination from biopsies, was not obtained from all the lesions reported in the studies. However, clinical follow-up data and results from renewed diagnostic imaging were recorded and clinically putative lymph
nodes metastases or endometrial cancer recurrence was used as gold standard when histologic confirmation was missing.

CONCLUSION

Overall FDG-PET/CT demonstrated high diagnostic performance in identifying lymph node metastases preoperatively and in detecting recurrence after endometrial carcinoma surgery with curative intent. Larger prospective studies are needed to validate this high diagnostic performance of FDG-PET/CT in endometrial cancer and further assess patient subgroups with particular clinical benefit from applying this advanced imaging procedure.

ACKNOWLEDGMENTS

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REFERENCES


Cancer Inst. 2008;100(23):1707-1716.


Figure 1: 87 year old patient with FIGO stage III C1 and Endometrioid grade 2.

A) Contrast enhanced CT depicting a non-enlarged lymph node (arrow) close to the right internal iliac vessels.

B) PET scan depicting FDG-uptake (red cross hair lines) in the region of the same pelvic lymph-node.

C) Co-registered FDG-PET/CT scan depicting increased FDG-PET uptake (red cross hair lines) corresponding to the histologically confirmed metastatic internal iliac lymph node.
Figure 2: Flow chart of selection process of eligible studies

- Records identified through database searching and manual addition ($n = 62 \ (58 + 4^*)$)
- Records screened ($n = 62$)
  - Records excluded ($n = 19$)
    - Review papers ($n = 12$)
    - Not in English ($n = 4$)
    - No abstract availability ($n = 3$)
  - Records not eligible ($n = 22$)
    - Not in EC ($n = 8$)
    - Other than FDG ($n = 3$)
    - No numbers reported for diagnostic performance ($n = 11$)
- Full-text articles assessed for eligibility ($n = 43$)
- Articles included ($n = 21$)

Meta analysis objectives:
- $^{18}$F-FDG PET/CT diagnostic performance in determining LNM pre-operatively ($n = 13$)
- $^{18}$F-FDG PET/CT diagnostic performance in determining ECR after primary surgical treatment ($n = 8$)
Figure 3: LNM: (3A) Forest plot of sensitivity pooling; (3B) Forest plot of specificity pooling; (3C) SROC curve.

Individual study estimates of sensitivity and specificity of FDG-PET/CT for identifying LNM in endometrial cancer. In the detection of LNM the FDG-PET/CT have a moderate sensitivity of 0.72, high specificity of 0.94 and AUC of 0.94 demonstrating good diagnostic performance.
Figure 4: ECR: (4A) Forest plot of sensitivity pooling; (4B) Forest plot of specificity pooling; (4C) SROC curve.

Individual study estimates of sensitivity and specificity of FDG-PET/CT for identifying disease recurrence in endometrial cancer. In the detection of ECR the FDG-PET/CT have a high sensitivity of 0.95, high specificity of 0.91 and AUC of 0.97 demonstrating excellent diagnostic performance.
Table 1: Summary of clinical studies on LNM in endometrial cancer

<table>
<thead>
<tr>
<th>Study type (reference)</th>
<th>No. of Patients</th>
<th>Patient age (median)</th>
<th>FIGO stage</th>
<th>Endo-metrioid (%)</th>
<th>Purpose</th>
<th>Results</th>
<th>Conclusion(s)</th>
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<tr>
<td>P (27)</td>
<td>236</td>
<td>65</td>
<td>IA-IVB</td>
<td>79%</td>
<td>Evaluate the value of FDG-PET/CT SUVmax as a tool in the preoperative work-up of EC patients particularly focus on MI, CI, FIGO stage, risk stratification and LNM.</td>
<td>Patient based sensitivity (75%), specificity (93%), PPV (60%), NPV (96%) and accuracy (90%) for LNM. High risk EC patients (high FIGO, MI&gt;50%, CI compared to no CI, LNM compared to no LNM, showed significantly higher SUVmax values compared with low risk tumors.</td>
<td>FDG-PET/CT SUVmax is a promising biomarker to distinguish between high and low risk EC, indirectly determine the tumor aggressiveness.</td>
</tr>
<tr>
<td>P (25)</td>
<td>129</td>
<td>67</td>
<td>IA-IVB</td>
<td>76%</td>
<td>Determine the diagnostic value of preoperative FDG-PET/CT for staging of EC and to relate FDG-PET/CT parameters to clinicopathological tumor characteristics.</td>
<td>Sensitivity (85%), specificity (92%), PPV (65%), NPV (98%) and accuracy (91%) in detecting LNM. FDG-PET parameters (SUVmax, MTV and TLG) were significantly related to deep MI, LNM and high histological grade.</td>
<td>Preoperative FDG-PET/CT is a valuable tool in detecting LNM in EC. FDG-PET parameters are also associated with tumor aggressiveness and aid preoperative identification of high risk patients.</td>
</tr>
<tr>
<td>(31)</td>
<td>106</td>
<td>61</td>
<td>IA-IVB</td>
<td>88%</td>
<td>Determine the clinical value of FDG-PET/CT in determining the pelvic LNM in EC.</td>
<td>Patient based sensitivity (97%), specificity (69%), PPV (75%), NPV (96%), and accuracy (93%), respectively for LNM.</td>
<td>Preoperative FDG-PET/CT is a valuable tool in detecting LNM in EC.</td>
</tr>
<tr>
<td>P (28)</td>
<td>76</td>
<td>63</td>
<td>IA-IVB</td>
<td>87%</td>
<td>Evaluate the role of FDG-PET/CT parameter as a predictor of LNM in EC</td>
<td>Positive correlation between LNM and SUVmax (P=0.003), MTV (P=0.007), and TLG (P=0.003) of the primary tumor. Patient based sensitivity (79%); specificity (98%), accuracy (95%), PPV (92%) and NPV (95%) for LNM</td>
<td>FDG-PET/CT parameters have a potential to predict LNM in EC patients</td>
</tr>
<tr>
<td>R (32)</td>
<td>53</td>
<td>58</td>
<td>IA-IVB</td>
<td>83%</td>
<td>Determine the accuracy of FDG-PET/CT for LNM in EC.</td>
<td>Patient based sensitivity (50%), specificity (94%), PPV (40%) and NPV (96%), respectively for LNM.</td>
<td>High specificity and NPV may be useful in selecting patients who may benefit from lymphadenectomy, minimizing surgical complications.</td>
</tr>
<tr>
<td>P (33)</td>
<td>46</td>
<td>56</td>
<td>I-IV</td>
<td>63%</td>
<td>The clinical value of FDG-PET/CT in determining the pelvic LNM in EC.</td>
<td>The sensitivity (50%) and specificity (92%) of FDG-PET for detecting pelvic LNM.</td>
<td>FDG-PET might increase the accuracy for detecting LNM and reduce the false positive results in preoperative EC patients.</td>
</tr>
<tr>
<td>Patient</td>
<td>Age</td>
<td>Stage</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Accuracy</td>
<td>Methodology</td>
<td>Results</td>
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<tr>
<td>P (22)</td>
<td>40</td>
<td>IA-IIIC</td>
<td>92%</td>
<td></td>
<td></td>
<td>Evaluating FDG-PET/CT to detect LNM in EC</td>
<td>Patient based sensitivity (50%), specificity (86%) and accuracy (77%) of LNM. FDG-PET/CT is a valuable tool to detect LNM prior to treatment.</td>
</tr>
<tr>
<td>P (34)</td>
<td>37</td>
<td>IA-IVB</td>
<td>83%</td>
<td></td>
<td></td>
<td>Determining FDG-PET/CT to detect LNM in high risk EC</td>
<td>Patient based sensitivity (78%), specificity (100%), PPV (100%), NPV (93%), and accuracy (94%) for LNM. FDG-PET/CT is an accurate procedure for preoperative evaluation of pelvic LNM.</td>
</tr>
<tr>
<td>R (35)</td>
<td>33</td>
<td>N/A</td>
<td>94%</td>
<td></td>
<td></td>
<td>Evaluating the diagnostic sensitivity of FDG-PET/CT compared to MRI alone in EC patients and also to evaluate the correlation between FDG-PET/CT SUVmax and clinicopathological tumor characteristics.</td>
<td>Patient based sensitivity (80%), specificity (96%) and accuracy (94%) for LNM. The diagnostic sensitivity of FDG-PET/CT is superior to CT or MRI alone in detecting both primary tumor and LN.</td>
</tr>
<tr>
<td>R (36)</td>
<td>30</td>
<td>IA-IIIC</td>
<td>90%</td>
<td></td>
<td></td>
<td>Evaluating the accuracy of FDG-PET/CT and PET/MR in assessment of LNM in EC.</td>
<td>Patient based sensitivity (100%), specificity (96%) and accuracy (97%) for detecting LNM for both PET/MR and PET/CT. However, accuracy of PET/MR is superior to PET/CT in tumor staging (80% vs 60%, P&lt;0.04). Integrated FDG-PET/MR is superior to PET or MRI alone. It is a valuable tool in detecting primary tumor and nodal staging in EC patients.</td>
</tr>
<tr>
<td>R (37)</td>
<td>30</td>
<td>IA-IVB</td>
<td>63%</td>
<td></td>
<td></td>
<td>Evaluating the clinical usefulness of FDG-PET/CT for preoperative evaluation in EC.</td>
<td>Patient based sensitivity (100%) and specificity (100%) for detecting LNM. FDG-PET/CT demonstrated high diagnostic performance in EC patients preoperatively.</td>
</tr>
<tr>
<td>R (38)</td>
<td>26</td>
<td>IA-IVB</td>
<td>53%</td>
<td></td>
<td></td>
<td>Determining the clinical value of FDG-PET/CT in the primary staging of high risk EC patients.</td>
<td>Patient based sensitivity (57%), specificity (100%), PPV (100%), NPV (86%) and accuracy (88%), respectively for revealing lymph node involvement. Whereas for detecting distant metastases sensitivity (100%), specificity (96%), PPV (87%), NPV (100%) and accuracy (97%) respectively. FDG-PET/CT is a valuable tool to detect distant metastases in the abdomen and extra-abdominal regions with high diagnostic performance.</td>
</tr>
<tr>
<td>P (39)</td>
<td>19</td>
<td>IA-IVB</td>
<td>75%</td>
<td></td>
<td></td>
<td>Determining the sensitivity and specificity of preoperative FDG-PET in detecting LNM in EC.</td>
<td>Patient based sensitivity (67%) and specificity (94%), respectively for predicting LNM disease preoperatively in endometrial cancer. Preoperative FDG-PET may be helpful with safe omission of lymphadenectomy in selected patients.</td>
</tr>
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</table>
Abbreviations:
CI: Cervical invasion; EC: Endometrial cancer; FIGO: International federation of gynecology and obstetrics; FDG: Fluorodeoxyglucose; LNM: Lymph node metastases; MRI: Magnetic resonance imaging; MTV: Metabolic tumor volume; MI: Myometrial invasion; NED: No evidence of disease; NPV: Negative predictive value; P: prospective; PPV: Positive predictive value; PET/CT: Positron emission tomography/Computed tomography; R: retrospective; SUVmax: Maximum standardized uptake value; TLG: Tumor lesion glycolysis.
Table 2: Summary of clinical studies on endometrial cancer recurrence in endometrial cancer

<table>
<thead>
<tr>
<th>Study Type (reference)</th>
<th>No. of Patients</th>
<th>Patients age (Median)</th>
<th>FIGO stage</th>
<th>Endometrioid (%)</th>
<th>Purpose</th>
<th>Results</th>
<th>Conclusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R (40)</td>
<td>127</td>
<td>52</td>
<td>IA-IVB</td>
<td>86%</td>
<td>Feasibility of FDG-PET/CT for post therapy surveillance in EC patients who showed NED.</td>
<td>The sensitivity (100%), specificity (88%), PPV (59%) and NPV (100%) of FDG-PET for detecting the recurrence in EC showing NED.</td>
<td>FDG-PET could effectively detect early recurrences in patients with EC showing NED after primary treatment.</td>
</tr>
<tr>
<td>R (41)</td>
<td>101</td>
<td>56</td>
<td>IA-IVB</td>
<td>n/a</td>
<td>Evaluate the accuracy of FDG-PET/CT for the identification of suspected EC recurrence.</td>
<td>Sensitivity (89%), specificity (93%), PPV (94%), NPV (88%), and accuracy (91%) of FDG-PET/CT respectively.</td>
<td>FDG-PET/CT has a high diagnostic yield in detecting recurrent EC.</td>
</tr>
<tr>
<td>R (42)</td>
<td>31</td>
<td>61</td>
<td>IA-IVB</td>
<td>n/a</td>
<td>Determine the value of post-treatment FDG-PET/CT compared to conventional imaging and CA-125 in the EC patients.</td>
<td>The overall sensitivity (100%), specificity (96%) and accuracy (97%) for PET/CT imaging. Whereas for conventional imaging the corresponding values were 46%, 87% and 74% respectively.</td>
<td>Post-treatment FDG-PET/CT is a more clinically useful modality than conventional imaging in the evaluation of suspected EC recurrence.</td>
</tr>
<tr>
<td>R (43)</td>
<td>31</td>
<td>53</td>
<td>IA-IVB</td>
<td>88.5%</td>
<td>Evaluate accuracy of PET/CT for the identification of suspected EC recurrence after treatment.</td>
<td>The overall patient based sensitivity (100%); specificity (84%), PPV (100%), NPV (97%) and accuracy (92%). A significantly better PFS was observed in patients with negative PET/CT result than those with positive PET/CT scan (P&lt;0.015).</td>
<td>FDG-PET/CT demonstrated high diagnostic indices in detecting ECR.</td>
</tr>
<tr>
<td>R (44)</td>
<td>30</td>
<td>59</td>
<td>IA-IVB</td>
<td>90%</td>
<td>Evaluate the diagnostic accuracy of FDG-PET/CT compared to PET alone, in the diagnosis of suspected EC recurrence.</td>
<td>Overall patient based sensitivity (93%), specificity (93%) and accuracy (93%) for PET/CT in detecting EC recurrence. Whereas with PET alone the corresponding values were 80%, 80% and 80% respectively.</td>
<td>Diagnostic accuracy of FDG-PET/CT is superior to PET alone in detecting localization of sites of recurrence during follow-up.</td>
</tr>
<tr>
<td>Study</td>
<td>Cases</td>
<td>PET/CT Sensitivity (%)</td>
<td>PET/CT Specificity (%)</td>
<td>PET/CT PPV (%)</td>
<td>PET/CT NPV (%)</td>
<td>PET/CT Accuracy (%)</td>
<td>PET/CT Diagnosis</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>R (45)</td>
<td>24</td>
<td>81%</td>
<td>94%</td>
<td>96%</td>
<td>95%</td>
<td>100%</td>
<td>False positive</td>
</tr>
<tr>
<td>R (46)</td>
<td>21</td>
<td>67%</td>
<td>88%</td>
<td>84%</td>
<td>85%</td>
<td>93%</td>
<td>False positive</td>
</tr>
<tr>
<td>P (47)</td>
<td>13</td>
<td>n/a</td>
<td>100%</td>
<td>100%</td>
<td>92%</td>
<td>90%</td>
<td>True positive</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI: Cervix invasion; DFS: Disease free survival; EC: Endometrial cancer; FIGO: International federation of gynecology and obstetrics; FDG: Fluorodeoxyglucose; LNM: Lymph node metastases; MRI: Magnetic resonance imaging; NED: No evidence of disease; NPV: Negative predictive value; P: prospective; PPV: Positive predictive value; PET/CT: Positron emission tomography/Computed tomography; R: retrospective; SUVmax: Maximum standardized uptake value.
High diagnostic value of FDG-PET/CT in endometrial cancer: Systematic review and meta-analysis of the literature.

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