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# MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer - A multicenter prospective comparative study 

Sofie Leisby Antonsen ${ }^{\text {a, }}$, Lisa Neerup Jensen ${ }^{\text {b }}$, Annika Loft ${ }^{\mathrm{c}}$, Anne Kiil Berthelsen ${ }^{\mathrm{c}}$, Junia Costa ${ }^{\mathrm{c}}$, Ann Tabor ${ }^{\mathrm{b}, \mathrm{o}}$, Ingelise Qvist ${ }^{\mathrm{d}}$, Mette Rodi Hansen ${ }^{\mathrm{e}}$, Rune Fisker ${ }^{\mathrm{f}}$, Erik Søgaard Andersen ${ }^{\mathrm{g}}$, Lene Sperling ${ }^{\mathrm{h}}$, Anne Lerberg Nielsen ${ }^{\text {i, }}$, Jon Asmussen ${ }^{\mathrm{j}}$, Estrid Høgdall ${ }^{\mathrm{k}}$, Carsten L. Fagö-Olsen ${ }^{\text {a }}$, Ib Jarle Christensen ${ }^{1}$, Lotte Nedergaard ${ }^{\mathrm{m}}$, Kirsten Jochumsen ${ }^{\mathrm{n}}$, Claus Høgdall ${ }^{\circ}$<br>${ }^{\text {a }}$ Gynecologic Clinic, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark<br>${ }^{\text {b }}$ Center of Fetal Medicine and Ultrasound, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark<br>${ }^{\text {c }}$ Department of Clinical Physiology, Nuclear Medicine, E PET, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark<br>${ }^{\text {d }}$ Department of Ultrasound, Aalborg University Hospital, Reberbansgade, Postboks 561, 9100 Aalborg, Denmark<br>${ }^{\text {e }}$ Department of Radiology, Aalborg University Hospital, Reberbansgade, Postboks 561, 9100 Aalborg, Denmark<br>${ }^{f}$ Department of Nuclear medicine, Aalborg University Hospital, Reberbansgade, Postboks 561, 9100 Aalborg, Denmark<br>${ }^{g}$ Department of Gynecology and Obstetrics, Aalborg University Hospital, Reberbansgade, Postboks 561, 9100 Aalborg, Denmark<br>${ }^{\text {h }}$ Department of Fetal medicine, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark<br>${ }^{\text {i }}$ Department of Nuclear medicine, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark<br>${ }^{\text {j }}$ Department of Radiology, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark<br>${ }^{k}$ The Danish CancerBiobank, Department of Pathology, Herlev University Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark<br>${ }^{1}$ The Finsen Laboratory, Rigshospitalet, and Biotech Research and Innovation Centre (BRIC), University of Copenhagen, DK-2200 Copenhagen, Denmark<br>${ }^{\mathrm{m}}$ Department of Pathology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 København Ø, Denmark<br>${ }^{n}$ Department of Gynecology and Obstetrics, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark<br>${ }^{\circ}$ Faculty of Health Sciences, University of Copenhagen, Blegdamsvej 3, 2200 København N, Denmark

## H I G H L I G H T S

- PET/CT and MRI are equal in predicting myometrial invasion, cervical involvement and lymph node metastases in endometrial cancer patients.
- Transvaginal ultrasound has high specificity and accuracy in predicting myometrial invasion and cervical involvement in endometrial cancer patients.
- Imaging cannot replace surgical staging yet. However, the modalities may be valuable in the multidisciplinary treatment planning.


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#### Abstract

Objectives. The aim of this prospective multicenter study was to evaluate and compare the diagnostic performance of PET/CT, MRI and transvaginal two-dimensional ultrasound (2DUS) in the preoperative assessment of endometrial cancer (EC).

Methods. 318 consecutive women with EC were included when referred to three Danish tertiary gynecological centers for surgical treatment. Preoperatively they were PET/CT-, MRI-, and 2DUS scanned. The imaging results were compared to the final pathological findings. This study was approved by the National Committee on Health Research Ethics.

Results. For predicting myometrial invasion, we found sensitivity, specificity, PPV, NPV, and accuracy for PET/CT to be $93 \%, 49 \%, 41 \%, 95 \%$ and $61 \%$, for MRI to be $87 \%, 57 \%, 44 \%, 92 \%$, and $66 \%$ and for 2 DUS to be $71 \%$, $72 \%, 51 \%, 86 \%$ and $72 \%$. For predicting cervical invasion, the values were $43 \%, 94 \%, 69 \%, 85 \%$ and $83 \%$, respectively, for PET/CT, $33 \%, 95 \%, 60 \%, 85 \%$, and $82 \%$, respectively, for MRI, and $29 \%, 92 \%, 48 \%, 82 \%$ and $78 \%$ for 2DUS. Finally, for lymph node metastases, the values were $74 \%, 93 \%, 59 \%, 96 \%$, and $91 \%$ for PET/CT and $59 \%, 93 \%, 40 \%, 97 \%$ and $90 \%$ for MRI. When comparing the diagnostic performance we found PET/CT, MRI and 2DUS to be comparable in predicting myometrial invasion. For cervical invasion and lymph node metastases, however, PET/CT was the best.


[^0]Conclusions. None of the modalities can yet replace surgical staging. However, they all contributed to important knowledge and were, furthermore, able to upstage low-risk patients who would not have been recommended lymph node resection based on histology and grade alone.
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## Introduction

Imaging is important in the multidisciplinary management of uterine malignancy and includes characterization and staging of tumor, treatment planning, and subsequent follow-up. Endometrial cancer (EC) is the most common uterine malignancy. The treatment of EC is primarily surgical, and the extent of surgery relies on the estimated stage and risk of extra-uterine disease. The most important risk factors for extrauterine disease and poor outcome are depth of myometrial invasion (MI), cervical involvement (CI), tumor grade and histological sub-type, and lymph node metastases (LNM). A major obstacle is that these factors cannot be revealed by clinical examination alone. Therefore, the clinical challenge is the optimal selection of patients for more extensive surgical procedures (i.e. lymph node dissection or optimal debulking) in
patients with high risk of advanced disease and relapses, while avoiding overtreatment in low-risk patients, as studies have shown that lymphadenectomy can induce complications and may not increase survival of low-risk EC patients [1,2]. A non-invasive technique that identifies LNM and tumor-extent would be beneficial. However, optimal imaging modality and practice varies among centers and results are not in agreement [3].

Magnetic resonance imaging (MRI) is considered the most accurate imaging technique for preoperative assessment of EC because of its excellent soft-tissue contrast-resolution [4,5]. Unlike ultrasound, MRI is not operator dependent and unlike computed tomography (CT) it has no radiation burden [6].

2-[Fluorine 18] flouro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) is a functional method based on the increased


Fig. 1. Flowchart for the study. RH: Rigshospitalet, Copenhagen University Hospital, OUH: Odense University Hospital, AAL: Aalborg University Hospital.

Table 1
Clinical characteristics of the 318 patients in the ENDOMET study.

| N (\%) |  |
| :--- | ---: |
| Stage |  |
| AEH | $18(5.7)$ |
| IA | $172(54.1)$ |
| IB | $38(11.9)$ |
| II | $36(11.3)$ |
| IIIA | $6(1.9)$ |
| IIIB | $6(1.9)$ |
| IIIC | $24(7.5)$ |
| IVA | $2(0.6)$ |
| IVB | $16(5.0)$ |
|  |  |
| Histological grade |  |
| 1 | $163(51.3)$ |
| 2 | $61(19.2)$ |
| 3 | $24(7.5)$ |
| Not graded | $70(22.0)$ |
| Dominant histological type |  |
| Atypical hyperplasia | $18(5.6)$ |
| Endometrioid adenocarcinoma | $253(79.6)$ |
| Serous adenocarcinoma | $25(7.9)$ |
| Clear cell carcinoma | $4(1.3)$ |
| Carcinosarcoma/sarcoma | $16(5.0)$ |
| Undifferentiated adenocarcinoma | $2(0.6)$ |
|  |  |
| Myometrial invasion |  |
| <50\% | $228(71.7)$ |
| 250\% | $82(25.8)$ |
| Missing | $8(2.5)$ |
| Cervical stromal involvement |  |
| Yes | $63(19.8)$ |
| No | $248(78.0)$ |
| Missing | $7(2.2)$ |
| Lymph node metastases |  |
| Yes | $35(11.2)$ |
| No | $122(38.4)$ |
| Not removed | $161(50.6)$ |
|  |  |

AEH: atypical endometrial hyperplasia.
${ }^{\text {a }}<50 \%$ : superficial + less than $50 \%$ myometrial invasion. $\geq 50 \%$ : equal to or more than $50 \%$ myometrial invasion + invasion of serosa.
glucose-metabolism of malignant tumor cells. The potential value of PET/CT for staging of EC has not yet been established.

In expert hands, transvaginal two-dimensional ultrasound (2DUS) has shown good accuracy in local staging of EC, comparable to that of MRI performed by radiologists specialized in gynecological imaging [7].

The aim of this prospective multicenter study was to evaluate and compare the diagnostic performance of PET/CT, MRI and 2DUS in preoperative staging of EC with special focus on MI, CI and LNM.

## Methods

Patients with a histological diagnosis of EC or atypical endometrial hyperplasia (AEH) were consecutively invited to participate in the Danish endometrial cancer study (ENDOMET). They were referred to the gynecologic clinics at University Hospitals in Copenhagen (Rigshospitalet), Odense, and Aalborg for surgery between September 1, 2009 and January 1, 2012. All participants gave informed oral and written consent. Patients with a preoperative diagnosis of AEH were included because we previously found that up to $59 \%$ of these patients have coexisting EC [8]. The patients were offered PET/CT, MRI and 2DUS examination 1-31 days prior to treatment. Exclusion criteria were: (1) claustrophobia, severe obesity or difficulties in co-operation; (2) severe kidney-disease that contraindicated intravenous contrast-agents; and (3) additional malignant disease, current or former. However, patients with premalignant cancers, cured skin cancer of non-melanoma type and former breast cancer were included. (4) Patients with certain
implanted magnetic objects were excluded from MRI and patients with diabetes mellitus were excluded from PET/CT.

All women were treated according to the national guidelines [9]: the standard care consists of total hysterectomy and bilateral salpingo-oophorectomy (BSO). Additionally, lymphadenectomy is recommended for all patients except low-risk (stage I, $<50 \% \mathrm{MI}$, endometrioid histology, grades $1-2$ ). Stage II patients (CI) are recommended radical hysterectomy, BSO and pelvic lymphadenectomy while stage III/IV patients should have optimal debulking. Furthermore, patients with type 2 histology (serous or clear cell adenocarcinomas) are recommended omentectomy. Patients with stage III and IV disease are recommended adjuvant chemotherapy. Few patients with disseminated disease or poor candidates for surgery are referred to primary chemotherapy. Patients with AEH are treated as low-risk EC patients.

The uterus, fallopian tubes, and ovaries were sent for intraoperative gross evaluation by pathologists with special expertise in gynecological pathology. The surgical specimens were postoperatively evaluated thoroughly and the results were registered in the Danish Gynecological Cancer Database (DGCD) [10]. The International Federation of Gynecology and Obstetrics (FIGO) 2009 criteria [11] were used. The pathological data were used as the reference standard.

## Imaging

Scans were prospectively evaluated by one expert in Nuclear Medicine at each center, one experienced radiologist at each center and one expert in Gynecologic ultrasound. PET/CT scans were reviewed by a nuclear medicine and a radiologist together. Scans were performed according to the same protocol at all centers. The experts had no knowledge about the results of the other scans or the pathological assessment of the specimen. Either the PET/CT or the MRI scan was discussed at a multi-disciplinary meeting at each center to plan further treatment.

## PET/CT

At Rigshospitalet whole-body imaging was performed with a Siemens Biograph 40 or 64, True Point PET/CT-scanner, at Odense University Hospital a GE Discovery VCT or RX was used, and at Aalborg University Hospital a GE Discovery STE or VCT was used. CT and PET covered a region from the meatus of the ear to the proximal thigh. The patient fasted for 6 h prior to PET acquisition. Sixty to ninety minutes after injection of $370-400 \mathrm{MBq}$ FDG in the cubital vein, the CT scan was performed. All patients were asked to void before the scan. Oral and intravenous contrast-agents were given prior to the diagnostic CT scan. Immediately thereafter the static emissions were obtained in $2.5-4$ min per field of view depending on body mass index. The CT data were used for attenuation-correction of the PET data. Images were reconstructed and stored in transaxial, coronal and sagittal slices with a slice thickness of $2.5-3.3 \mathrm{~mm}$. The images were reviewed on a Siemens Leonardo PET/CT or a GE Advantage workstation and findings suspicious of malignancy were recorded.

## MRI

At Rigshospitalet MRI was performed using a Magnetom Espree 1.5 Tesla, in Odense a Philips Achieva 1.5 T system with combined Torso and Cardiac coils was used, and in Aalborg a GE Sigma 1.5 T twinspeed was used. MRI scans were performed using Spin-echo T2, T1 and T2-Singleshot sequences in multiple planes, and T1 and T1-SPIR perpendicular to long axis of uterus before and after administration of gadolinium based contrast agent. Lymph nodes with a short-axis diameter larger than 10 mm were considered pathologic.

## 2DUS

All the ultrasound examinations were performed by using a GE Voluson E8 Expert equipped with a multifrequency endovaginal probe $(5-9 \mathrm{MHz})$ at all centers. The examination was performed in the lithotomic position with an empty bladder. After B-mode evaluation,

Table 2
Performance of PET/CT, MRI and 2DUS in predicting myometrial invasion, cervical invasion and lymph node metastases in endometrial cancer when performed individually.

|  | Histology: myometrial invasion |  |  | Sensitivity <br> (\%) <br> (95\% CI) | Specificity <br> (\%) <br> (95\% CI) | $\begin{aligned} & \text { PPV } \\ & (\%) \end{aligned}$ | NPV <br> (\%) | Accuracy(\%) |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | $\geq 50 \%$ | <50\% | Total |  |  |  |  |  |
| PET/CT |  |  |  |  |  | 40.6 | 94.6 | 60.7 |
| $\geq 50 \%$ | 63 | 92 | 155 | (83.7-97.6) | (38.3-76.5) |  |  |  |
| <50\% | 5 | 87 | 92 |  |  |  |  |  |
| Total | 68 | 179 | 247 |  |  |  |  |  |
| MRI |  |  |  | 87.3 | 57.3 | 44.0 | 92.2 | 65.6 |
| $\geq 50 \%$ | 55 | 70 | 125 | (76.5-94.3) | (49.4-65.0) |  |  |  |
| <50\% | 8 | 94 | 102 |  |  |  |  |  |
| Total | 63 | 164 | 227 |  |  |  |  |  |
| 2DUS |  |  |  | 71.4 | 71.7 | 50.6 | 86.1 | 71.6 |
| $\geq 50 \%$ | 40 | 39 | 79 | (58.8-82.7) | (63.5-79.1) |  |  |  |
| <50\% | 16 | 99 | 115 |  |  |  |  |  |
| Total | 56 | 138 | 194 |  |  |  |  |  |
|  | Histology: cervical invasion |  |  |  |  |  |  |  |
|  | Yes | No | Total | Sensitivity <br> (\%) <br> (95\% CI) | Specificity <br> (\%) <br> (95\% CI) | PPV <br> (\%) | NPV <br> (\%) | Accuracy <br> (\%) |
| PET/CT |  |  |  | 42.9 | 94.3 | 68.6 | 85.0 | 82.7 |
| Yes | 24 | 11 | 35 | (29.7-56.8) | (90.0-97.1) |  |  |  |
| No | 32 | 181 | 213 |  |  |  |  |  |
| Total | 50 | 192 | 248 |  |  |  |  |  |
| MRI |  |  |  | 33.3 | $94.5$ | 60.0 | 85.1 | 82.3 |
| Yes | 15 | 10 | 25 | (20.0-48.9) | (90.1-97.3) |  |  |  |
| No | 30 | 171 | 201 |  |  |  |  |  |
| Total | 45 | 181 | 226 |  |  |  |  |  |
| 2DUS |  |  |  | 28.6 |  | 48.0 | 82.4 | 77.9 |
| Yes | 12 | 13 | 25 | (15.7-44.6) | (85.9-95.4) |  |  |  |
| No | 30 | 140 | 170 |  |  |  |  |  |
| Total | 42 | 153 | 195 |  |  |  |  |  |
|  | Histology: lymph node metastases |  |  |  |  |  |  |  |
|  | Yes | No | Total | Sensitivity <br> (\%) <br> (95\% CI) | Specificity <br> (\%) <br> (95\% CI) | PPV <br> (\%) | NPV <br> (\%) | Accuracy <br> (\%) |
| PET/CT |  |  |  |  | $92.8$ | 59.0 | 96.2 | 90.5 |
| Yes | 23 | 16 | 39 | (53.4-88.2) | (88.4-95.9) |  |  |  |
| No | 8 | 205 | 213 |  |  |  |  |  |
| Total | 31 | 221 | 252 |  |  |  |  |  |
| MRI |  |  |  | 58.8 | 92.8 | 40.0 | 96.5 | 90.2 |
| Yes | 10 | 15 | 25 | (32.9-81.6) | (88.5-95.8) |  |  |  |
| No | 7 | 193 | 200 |  |  |  |  |  |
| Total | 17 | 208 | 225 |  |  |  |  |  |

PPV: positive predictive value, NPV: negative predictive value.
the 2D power-Doppler gate was activated to assess vascularization of the myometrium and endometrium. The depth of MI and Cl was subjectively evaluated.

## Statistics

All continuous data were expressed as median and range. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated. The diagnostic accuracy of PET/CT, MRI and 2DUS was compared using the McNemar test. The probability of deep MI, CI and LNM was modeled using logistic regression analysis with goodness of fit tested using the HosmerLemeshow test. Multivariate analysis included the three imaging modalities, age, grade and histology (dichotomized clear cell/serous versus endometrioid). Age was entered as a continuous covariate. All other covariates are categorical variables. $95 \%$ confidence interval limits were calculated using the exact method. p-Values less than $5 \%$ were considered significant. Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) software version 19.0.

This study was approved by the National Committee on Health Research Ethics (protocol nr: H-A-2009-018) and the Danish Data Protection Agency (j.nr. 2007-58-0015).

## Results

A total of 464 women with EC or AEH were referred in the inclusion period. Twenty-seven patients did not participate and 122 patients had an exclusion criterion leaving 318 patients eligible for the study. A total of 269 patients were PET/CT-scanned, 240 patients had MRI and 209 had 2DUS. 133 patients went through all three imaging modalities (Fig. 1). Median age was 65 years (range 29-94), and 282 (88.7\%) were postmenopausal. Clinical characteristics are listed in Table 1. Hysterectomy was performed in 307 (96.5\%) women of whom 157 (51.1\%) also underwent lymphadenectomy. Eleven patients (3.4\%) were upstaged by the preoperative imaging and biopsies and referred to chemotherapy. Tumor had spread to the lymph nodes (pelvine, paraaotale, inguinale, iliacale) in all patients, to the bones in three, to the bladder or gut in three, to the neck in two, to the lungs in one, and as carcinosis in the lower or upper abdomen in five patients. Final pathology diagnosed 18 patients with AEH. These were excluded from the subsequent

Table 3
Performance of PET/CT, MRI and 2DUS in predicting myometrial invasion, cervical invasion and lymph node metastases in endometrial cancer when performed on the same patients.


PPV: positive predictive value, NPV: negative predictive value.
analyses, as they did not need further staging. However, five patients with AEH had false positive findings on imaging; one patient was diagnosed with MI $\geq 50 \%$ and LNM of 12 mm on MRI, two were diagnosed with $\mathrm{MI} \geq 50 \%$ on MRI, another one on PET/CT and yet another on 2DUS.

The diagnostic performances of PET/CT, MRI and 2DUS in predicting the depth of MI, CI and LNM are shown in Table 2.

When assessing invasion of the serosa, the sensitivities of PET/CT, MRI and 2DUS were $75 \%, 67 \%$ and $67 \%$, respectively, specificities were $90 \%, 90 \%$ and $96 \%$, respectively, and the accuracies were $90 \%, 90 \%$ and $95 \%$, respectively (data not shown).

For comparing the three imaging modalities, calculations were done on the subgroup of women that had undergone the same three scanning modalities ( $\mathrm{n}=133$ ). Results are shown in Table 3. For prediction of MI we found significantly higher sensitivities for PET/CT and MRI compared to 2DUS ( $89 \%$ and $89 \%$ vs. $69 \%$ ), while 2DUS had significantly higher specificity ( $44 \%$ and $57 \%$ vs. $74 \%$ ).

For CI the imaging modalities had similar high specificities ( $93 \%, 94 \%$ and $94 \%$ ) and accuracies ( $81 \%$ (PET/CT), $80 \%$ (MRI) and $79 \%$ (2DUS), respectively). The sensitivities, however, were low but not significantly different. For prediction of LNM there was no difference in accuracy

Table 4
Models for optimizing predictive value of myometrial invasion, cervical invasion and lymph node metastases in endometrial cancer patients.

| Imaging | Sensitivity <br> $(\%)$ | Specificity <br> $(\%)$ | PPV <br> $(\%)$ | NPV <br> $(\%)$ | Accuracy <br> $(\%)$ |
| :--- | :--- | :--- | :--- | :--- | :--- |
| Myometrial invasion |  |  |  |  |  |
| PET/CT + MRI + 2DUS | 100 | 27.8 | 38.7 | 100 | 50.4 |
| PET/CT + MRI | 100 | 35.1 | 37.0 | 100 | 53.0 |
| PET/CT + 2DUS | 95.7 | 35.7 | 41.7 | 94.6 | 55.2 |
| MRI + 2DUS | 95.7 | 45.2 | 43.6 | 95.9 | 60.7 |
|  |  |  |  |  |  |
| Cervical invasion |  |  |  |  |  |
| PET/CT + MRI + 2DUS | 46.2 | 81.3 | 40.0 | 84.8 | 73.8 |
| PET/CT + MRI | 51.3 | 89.8 | 55.6 | 88.1 | 82.1 |
| PET/CT + 2DUS | 45.2 | 86.8 | 48.7 | 85.2 | 77.8 |
| MRI + 2DUS | 40.5 | 87.5 | 47.2 | 84.2 | 77.3 |
| Lymph node metastases |  |  |  |  |  |
| PET/CT + MRI | 85.7 | 88.2 | 37.5 | 98.8 | 88.6 |

[^1]Table 5

| Stage | Lymph nodes | Parametria/ adnexae | Other | Pelvic LN visualized | Paraaortal <br> LN <br> visualized | Other MRI findings | Other PET/CT findings | Stage <br> MRI | Stage <br> PET/CT |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| IIIA |  | AD |  |  |  |  |  | Not scanned | Not scanned |
| IIIA |  | AD |  |  |  |  |  | IB | IB |
| IIIA |  | AD |  |  |  |  |  | IB | II |
| IIIA |  | AD |  |  |  |  | Diaphragm | IB | IVB |
| IIIA |  |  | Fossa douglasii | PET/CT | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | Intestine, parametria, adnexae | Intestine | IVA | IVA |
| IIIA |  | AD |  |  |  |  | Adnexae | Not scanned | IIIA* |
| IIIB |  | PA |  |  |  | Intestinal/rectal involvement |  | IVA | II |
| IIIB |  | PA | Vagina |  |  | Bladder, parametria, adnexae | Intestinal, bladder, vagina | IVA | IIIB* |
| IIIB |  | PA, AD |  |  |  | Peritoneum in pelvis, parametria, vagina, adnexae | Peritoneum in pelvis, parametria, adnexae | IIIB* | IIIB* |
| IIIB |  | PA |  |  |  |  |  | IIIA | IA |
| IIIB |  | PA |  |  |  |  |  |  | IA |
| IIIB |  |  |  | PET/CT |  | Parametria, adnexae | Adnexae | IIIB* | IIIC2 |
| IIIC1 | PE |  |  |  |  |  |  | Not scanned | II |
| IIIC1 | PE |  |  |  |  |  |  | IA | Not scanned |
| IIIC1 | PE | PA |  |  |  |  | Adnexae | Not scanned | IIIA |
| IIIC1 | PE |  |  | PET/CT |  |  |  | Not scanned | IIIC1* |
| IIIC1 | PE |  |  | PET/CT, <br> MRI |  |  |  | IIIC1* | IIIC1* |
| IIIC1 | PE |  |  | MRI |  |  |  | IIIC1* | IB |
| IIIC1 | PE |  |  |  |  |  |  | IB | IB |
| IIIC1 | PE |  |  |  |  |  |  | Not scanned | IIIA |
| IIIC1 | PE |  |  | PET/CT |  |  |  | Not scanned | IIIC1* |
| IIIC1 | PE | PA |  |  |  |  | Adnexae | IB | IIIA |
| IIIC1 | PE |  |  | MRI |  |  |  | IIIC1* | Not scanned |
| IIIC1 | PE |  |  | PET/CT |  |  |  | Not scanned | IIIC1* |
| IIIC1 | PE |  |  | PET/CT |  |  |  | IB | IIIC1* |
| IIIC1 | PE | AD |  |  |  |  |  | Not scanned | IB |
| IIIC1 | PE |  |  | PET/CT, <br> MRI |  |  | Bladder | IIIC1* | IIIC1* |
| IIIC1 | PE |  |  | PET/CT |  |  |  | Not scanned | IIIC1* |
| IIIC2 | PE |  | Other | PET/CT | PET/CT |  | Lymph nodes in mediastinum and lung hili - suspicion of sarcoidosis | IA | IIIC2* |
| IIIC2 | PE, AO |  |  | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ |  |  | IIIC2* | IIIC2* |
| IIIC2 | PE, AO |  |  |  |  |  |  | II | II |
| IIIC2 | AO |  |  | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ |  | Peritoneum in pelvis, parametria, adnexae | IIIC2* | IVB |
| IIIC2 | PE, AO | PA, AD |  |  | PET/CT |  | Colon sigmoideum | Not scanned | IVA |
| IIIC2 | PE, AO |  |  | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ |  |  |  | IIIC1 | IIIC1 |
| IIIC2 | PE, AO |  | Vagina | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | PET/CT | Adnexae |  | IIIC1 | IIIC2* |
| IIIC |  |  |  | MRI | MRI | Bladder, vagina, parametria |  | IVA | Not scanned |
| IVA |  | PA, AD | Omentum |  |  |  |  | Not scanned | Not scanned |
| IVA |  |  | Omental |  |  |  |  | II | IA |
| IVB |  |  | Carcinosis, omentum, diaphragm |  |  | Retrosternal lymph nodes, diaphragm, peritoneum, omentum, adnexae | Thoratical metastases, diaphragm, peritoneum, omentum, appendix, intestines, adnexae | IVB | IVB* |
| IVB |  |  | Lung metastases |  |  |  | Lung metastases | IA | IVB* |
| IVB |  | PA, AD | Omental, spleen, intestinal, paracolic space, ligamentum falciforme, diaphragm | MRI |  | Parametria, adnexae |  | IIIC | Not scanned |


| Stage | Lymph nodes | Parametria/ adnexae | Other | Pelvic LN visualized | Paraaortal <br> LN <br> visualized | Other MRI findings | Other PET/CT findings | Stage <br> MRI | Stage <br> PET/CT |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| IVB |  |  | Lung metastases |  |  |  | Lung metastases | IA | IVB* |
| IVB | PE | PA, AD | Omental | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | MRI | Intestinal, bladder, parametria, vagina, adnexae | Carcinosis, omental, intestinal, bladder, parametria, adnexae | IVB* | IVB* |
| IVB |  | PA | Vagina, bone, bladder, other | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | PET/CT | Left os ilium, bladder, vagina, adnexae | Bone, bladder, vagina, adnexae | IVB* | IVB* |
| IVB |  |  | Lung metastases | MRI |  | Parametria | Lung metastases | IIIC1 | IVB* |
| IVB | PE, AO | PA, AD | Rectum, vagina, omentum, peritoneal carcinosis | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | $\begin{aligned} & \text { PET/CT, } \\ & \text { MRI } \end{aligned}$ | Carcinosis, peritoneum, omentum, parametria, adnexae | Bone, diaphragm, carcinosis, peritoneum, omentum, intestine, adnexae | IVB* | IVB* |
| IVB | AO | PA | Yes | PET/CT | PET/CT |  | Inguinal metastases | Not scanned | IVB* |
| IVB | PE, AO |  | Other |  |  |  |  | Not scanned | Not scanned |
| IVB | PE, AO | PA, AD | Omentum, other | PET/CT | PET/CT |  | Diaphragm, carcinosis, peritoneum, omentum, adnexae | Not scanned | IVB* |
| IVB | PE, AO | PA, AD | Other | PET/CT | PET/CT |  | Adnexae, other | Not scanned | IVB* |
| IVB | PE, AO | AD | Diffuse carcinosis, inguinal lymph nodes | PET/CT | PET/CT |  | Adnexae, peritoneum in pelvis, carcinoses, metastases to Virchow's gland, lymph node in med. sup. ant. and pericardial lipid | Not <br> scanned | IVB* |
| IVB | PE, AO | PA, AD | Vagina, lung/thorax, other | PET/CT | PET/CT |  | Bladder, metastases to cervical column and right os ilium | Not scanned | IVB* |
| IVB | AO |  | Lungs |  | PET/CT |  | Bowel, multiple lung metastases, | Not scanned | IVB* |
| IVB | PE, AO | AD | Other | PET/CT | PET/CT |  | Bone | Not scanned | IVB* |

LN: lymph node, PE: pelvic; AO: paraaortal, PA: parametria, AD: adnexae.
correct stage.
between PET/CT and MRI. PET/CT had, however, a higher sensitivity (86\%) than MRI ( $57 \%$ ), but the difference was not significant ( $p=0.14$ ).

For the sub-group of patients with grades 1-2 endometrioid tumors ( $\mathrm{n}=220$ ) the results for predicting MI were similar to the overall study group: Sensitivity, specificity, PPV, NPV and accuracy for PET/CT were $92 \%, 47 \%, 39 \%, 94 \%$ and $59 \%$. For MRI they were $86 \%, 58 \%, 42 \%, 93 \%$ and $66 \%$, and for 2DUS $73 \%, 76 \%, 57 \%, 86 \%$ and $75 \%$.

The results of the logistic regression analysis regarding prediction of deep MI showed that neither histology $(p=0.96)$, grade ( $p=0.84$ ) nor age ( $p=0.53$ ) was significant, thus these variables were removed from the model. The final regression model for deep MI included all three imaging modalities and the odds ratio (OR) with $95 \%$ confidence interval ( $95 \% \mathrm{CI}$ ) and p -values were: 4.71 (1.39-15.90), $\mathrm{p}=0.013$ (PET/CT); 5.38 (1.61-18.00), $\mathrm{p}=0.006$ (MRI); and 3.91 (1.50-10.16), $\mathrm{p}=0.005$ (2DUS). No interactions between the modalities could be demonstrated. The area under the ROC curve (AUC) for the final MI regression model was 0.840 . For prediction of CI , the results demonstrated that neither histology ( $p=0.35$ ), grade ( $p=0.21$ ) nor age ( $p=0.25$ ) was significant. The final model showed that PET/CT had significant influence on the risk of CI ( $\mathrm{OR}=5.67$ ( $95 \% \mathrm{CI}: 1.73-18.55$ ), $\mathrm{p}=0.004$ ) whereas MRI ( $\mathrm{OR}=3.09$ ( $95 \% \mathrm{Cl}$ : $0.79-12.05$ ), $\mathrm{p}=0.10$ ) and 2DUS ( $\mathrm{OR}=1.57$ ( $95 \% \mathrm{CI}: 0.34-7.33$ ), $\mathrm{p}=0.57$ ) had not. The AUC of the final model for CI was 0.670 . Finally analysis was performed for prediction of LNM. Grade and age were not significantly associated with risk of LNM ( $\mathrm{p}=0.58$ and $\mathrm{p}=0.85$, respectively), but histology was ( $\mathrm{OR}=28.34$ ( $95 \% \mathrm{CI}: 1.50-536.68$ ), $\mathrm{p}=0.026$ ). PET/CT was significant ( $\mathrm{OR}=30.53$ ( $95 \% \mathrm{CI}: 3.88-240.31$ ), $\mathrm{p}=0.001$ ) whereas MRI was not ( $O R=0.76$ ( $95 \% \mathrm{CI}: 0.26-2.20$ ), $\mathrm{p}=0.61$ ). The AUC was 0.945 . Removing histology resulted in similar OR for PET/CT and an AUC of 0.862 for detecting LNM.

As we found that all of the imaging modalities were independently predictive for MI, we combined the imaging results. The combined models reached excellent sensitivities but low specificities (Table 4).

Among the 229 patients with $<50 \%$ MI, 11 ( $4.8 \%$ ) had LNM. The histology of these 11 patients was four endometrioid adenocarcinomas, five serous adenocarcinomas, one clear cell adenocarcinoma and one
carcinosarcoma/sarcoma. Of the 35 patients with LNM, only $19 \%$ had grade 3 tumors and $31 \%$ were type 2 histology. Extra-uterine disease among the 55 patients with stage III-IV tumors and imaging-findings are shown in Table 5. PET/CT staged the patients correctly and found ex-tra-uterine metastases more often than MRI did ( $57 \%$ vs. $32 \%$ ). In three patients lung-metastases were found on PET/CT.

## Discussion

A non-invasive preoperative technique that accurately stages EC patients would be beneficial in improving tailored treatment and minimizing costs. The knowledge of tumor-extension influences the decision whether to perform a more radical hysterectomy with pelvic and/or paraaortic lymphadenectomy.

To our knowledge, this study is the first to compare PET/CT, MRI and 2DUS in the preoperative evaluation of EC patients. We found PET/CT and MRI to be equally good in predicting MI. 2DUS was not as sensitive as the other modalities even though performed by specialists, but had the highest accuracy (73\%). Preoperative prediction of MI is essential as deep MI increases the risk of LNM which worsens the prognosis. For patients with $<50 \%$ MI that could avoid lymphadenectomy, PET/CT evaluated $51 \%$ and MRI $43 \%$ as deep invasion why too many patients would have had lymphadenectomy if assessed by PET/CT or MRI alone. Conversely, if PET/CT or MRI predicted $<50 \%$ MI, this was correct in $94 \%$ and $92 \%$ of the patients. The high NPV of PET/CT and MRI also included the sub-group of grade 1-2 endometrioid tumors that may benefit from less extensive surgery or occasionally avoid surgery altogether (for fertility sparing or the very unfit). Therefore, they could be used in excluding deep MI. These findings are supported by Cade et al. [12].

We only found one small retrospective study assessing MI by PET/CT. They found $83 \%$ sensitivity and $88 \%$ specificity that were similar to that of their MRI scans [13]. Several studies have evaluated the accuracy for MRI and 2DUS in predicting MI. Sensitivities range from 50 to $89 \%$ and specificities from 81 to $100 \%$ [ $7,14-20]$. The differences may reflect the different study populations, study-designs and sample size.

MRI and PET/CT are costly, not always available and require contrast agents. 2DUS, in contrast, is a simple, fast, and low-cost technique for MI assessment. In addition, as technology has evolved, the diagnostic accuracy of 2DUS has become as high as MRI in several studies [7,21-23]. The sensitivities of 2DUS in our study were not as high as those reported in some studies [7,24], but comparable to those in others [25,26]. Most studies are smaller and retrospective. The results of this study showed that the ultrasonographic assessment of MI may not be as reliable as previously suggested. Application of 3D ultrasound and power Doppler angiography has been studied in gynecological oncology and shown promising in experienced hands [27].

In our study, none of the imaging modalities were sensitive in predicting CI. However, they were acceptable in excluding CI with specificities around $95 \%$. Literature findings are diverging. Sensitivities for MRI range from 19 to $100 \%$ and specificities from 87 to $100 \%$ [5,7,16,19,20,28-30]. The low sensitivity reported may be due to inclusion of EC with only endocervical glandular involvement (formerly staged as IIA), which is often undetectable on MRI [30]. Most authors have findings similar to ours. For 2DUS, Akbayir et al. found high diagnostic accuracy for prediction of CI (98\%) [21] and Szantho et al. found accuracy of 70\% [31].

In predicting LNM, Horowitz et al. found only moderate sensitivity (60\%) but high specificity (98\%) [32]. Signorelli et al. found that PET/CT was an accurate method with $78 \%$ sensitivity, $100 \%$ specificity, and $94 \%$ accuracy [33] in agreement with Nakamura et al. [34]. In contrast, Park et al. showed moderate sensitivity and concluded that PET/CT cannot replace surgical staging [35]. The reported sensitivity of MRI for detection of LNM in EC is generally low, ranging from 17 to 80\% [30]. Inubashiri et al. compared FDG-PET with CT and MRI and found no significant differences in their ability of diagnosing LNM. They equally presented low sensitivity and high specificity [36]. Park et al. found, like us, that PET/CT showed higher sensitivity than MRI in detecting LNM ( $46 \%$ vs. $69 \%$ ) but it did not reach significant differences [35].

In our series, four low-risk patients had LNM. These patients would in most centers not have had lymphadenectomy if the metastases were not visualized at preoperative imaging. In low-risk patients the incidence of LNM is $0-10 \%$ [37]. Studies have shown that lymphadenectomy can induce complications and may not increase survival of low-risk EC patients [1,2]. Therefore, it is unethical to stage low-risk patients with systematic lymphadenectomy. Imaging with high NPV can help exclude deep MI and thereby support the decision of avoiding lymphadenectomy in these patients. Furthermore, 11 patients were upgraded to stage IVB solely by imaging and were referred to chemotherapy. This fact supports the need for preoperative imaging. The question of the best preoperative staging modality for determining extent of MI and thereby the risk of extra-uterine disease remains unsolved, although we found PET/CT most reliable in preoperative staging of EC patients.

The strength of our study is that it consists of the largest series of patients in the literature. The distribution of patients reflects the background population. Furthermore, the prospective study-design decreased risk of bias and the results are hereby transferable to other clinics.

There were some limitations too. The fact that only 133 out of 318 patients underwent all imaging modalities decreased the power. Nevertheless, it reflected the challenges in every-day work with EC patients who suffer from various co-morbidities. Another limitation was that not all patients were fully staged which gives us a bias of false negative lymph nodes. Furthermore, we included 11 patients who were not hysterectomized, but were referred to chemotherapy. This fact could prompt false positive stage IV patients. Finally, the surgeons were guided by preoperative imaging findings, and this may have resulted in verification bias.

PET/CT, MRI and 2DUS did not reach high sensitivities in assessing EC preoperatively. None of the modalities can yet replace surgical
staging. However, they all contributed to important knowledge in the preoperative staging, and they can be combined to improve accuracy. With these results in mind gynecological oncology surgeons may use the imaging in assistance to their clinical guidelines. Due to its high NPV in predicting MI and LNM, PET/CT and MRI can be useful in selected patients who are poor candidates for surgical staging. PET/ CT was the most reliable of the three scanning modalities with regard to prediction of MI, CI and LNM.

## Conflict of interest statement

There are no financial disclosures or conflict of interest from any author.

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## References

[1] Benedetti PP, Basile S, Maneschi F, Alberto LA, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst Dec 3 2008;100(23):1707-16.
[2] Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet Jan 10 2009;373(9658):125-36.
[3] Antonsen SL, Ulrich L, Hogdall CK. Need of better preoperative staging of endometrial cancer. Ugeskr Laeger Jan 24 2011;173(4):259-63.
[4] Barwick TD, Rockall AG, Barton DP, Sohaib SA. Imaging of endometrial adenocarcinoma. Clin Radiol Jul 2006;61(7):545-55.
[5] Kinkel K, Kaji Y, Yu KK, Segal MR, Lu Y, Powell CB, et al. Radiologic staging in patients with endometrial cancer: a meta-analysis. Radiology Sep 1999;212(3):711-8.
[6] Loubeyre P, Undurraga M, Bodmer A, Petignat P. Non-invasive modalities for predicting lymph node spread in early stage endometrial cancer? Surg Oncol Jun 2011;20(2):e102-8.
[7] Savelli L, Ceccarini M, Ludovisi M, Fruscella E, De Iaco PA, Salizzoni E, et al. Preoperative local staging of endometrial cancer: transvaginal sonography vs. magnetic resonance imaging. Ultrasound Obstet Gynecol May 2008;31(5):560-6.
[8] Antonsen SL, Ulrich L, Hogdall C. Patients with atypical hyperplasia of the endometrium should be treated in oncological centers. Gynecol Oncol Apr 2012;125(1):124-8.
[9] ULea Mirza M. DGCG Guideline. Retningslinier for visitation, diagnostik, behandling og kontrol af cancer corpus uteri, http://dgc.eu.com/fundanemt/ files/DGC_EC_070409_2udgave.pdf; May 2009. [10.09.09].
[10] Høgdall CK, Nielsen MLS, Taaning L. Annual report 2009/2010. The Danish Gyneacological Cancer DatabaseNationwide clinical database for cancer in the ovaries, uterus and cervix. Copenhagen: Lægeforeningens forla; 2012.
[11] Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet May 2009;105(2):109.
[12] Cade TJ, Quinn MA, McNally OM, Neesham D, Pyman J, Dobrotwir A. Predictive value of magnetic resonance imaging in assessing myometrial invasion in endometrial cancer: is radiological staging sufficient for planning conservative treatment? Int J Gynecol Cancer Oct 2010;20(7):1166-9.
[13] Torizuka T, Nakamura F, Takekuma M, Kanno T, Ogusu T, Yoshikawa E, et al. FDG PET for the assessment of myometrial infiltration in clinical stage I uterine corpus cancer. Nucl Med Commun Jun 2006;27(6):481-7.
[14] Chung HH, Kang SB, Cho JY, Kim JW, Park NH, Song YS, et al. Accuracy of MR imaging for the prediction of myometrial invasion of endometrial carcinoma. Gynecol Oncol Mar 2007;104(3):654-9.
[15] Hwang JH, Lee NW, Lee KW, Lee JK. Magnetic resonance imaging for assessment of deep endometrial invasion for patients with endometrial carcinoma. Aust N Z J Obstet Gynaecol Oct 2009;49(5):537-41.
[16] Ortashi O, Jain S, Emannuel O, Henry R, Wood A, Evans J. Evaluation of the sensitivity, specificity, positive and negative predictive values of preoperative magnetic resonance imaging for staging endometrial cancer. A prospective study of 100 cases at the Dorset Cancer Centre. Eur J Obstet Gynecol Reprod Biol Apr 2008;137(2):232-5.
[17] Sanjuan A, Cobo T, Pahisa J, Escaramis G, Ordi J, Ayuso JR, et al. Preoperative and intraoperative assessment of myometrial invasion and histologic grade in endometrial cancer: role of magnetic resonance imaging and frozen section. Int J Gynecol Cancer Jan 2006;16(1):385-90.
[18] Sanjuan A, Escaramis G, Ayuso JR, Roman SM, Torne A, Ordi J, et al. Role of magnetic resonance imaging and cause of pitfalls in detecting myometrial invasion and cervical involvement in endometrial cancer. Arch Gynecol Obstet Dec 2008;278(6):535-9.
[19] Undurraga M, Petignat P, Pelte MF, Jacob S, Dubuisson JB, Loubeyre P. Magnetic resonance imaging to identify risk of lymph node metastasis in patients with endometrial cancer. Int J Gynaecol Obstet Mar 2009;104(3):233-5.
[20] Vasconcelos C, Felix A, Cunha TM. Preoperative assessment of deep myometrial and cervical invasion in endometrial carcinoma: comparison of magnetic resonance imaging and histopathologic evaluation. J Obstet Gynaecol Jan 2007;27(1):65-70.
[21] Akbayir O, Corbacioglu A, Numanoglu C, Guleroglu FY, Ulker V, Akyol A, et al. Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound. Gynecol Oncol Sep 2011;122(3):600-3.
[22] Ozdemir S, Celik C, Emlik D, Kiresi D, Esen H. Assessment of myometrial invasion in endometrial cancer by transvaginal sonography, Doppler ultrasonography, magnetic resonance imaging and frozen section. Int J Gynecol Cancer Aug 2009;19(6):1085-90.
[23] Yahata T, Aoki Y, Tanaka K. Prediction of myometrial invasion in patients with endometrial carcinoma: comparison of magnetic resonance imaging, transvaginal ultrasonography, and gross visual inspection. Eur J Gynaecol Oncol 2007;28(3):193-5.
[24] Savelli L, Testa AC, Mabrouk M, Zannoni L, Ludovisi M, Seracchioli R, et al. A prospective blinded comparison of the accuracy of transvaginal sonography and frozen section in the assessment of myometrial invasion in endometrial cancer. Gynecol Oncol Mar 2012;124(3):549-52.
[25] Berretta R, Merisio C, Piantelli G, Rolla M, Giordano G, Melpignano M, et al. Preoperative transvaginal ultrasonography and intraoperative gross examination for assessing myometrial invasion by endometrial cancer. J Ultrasound Med Mar 2008;27(3):349-55.
[26] Shin KE, Park BK, Kim CK, Bae DS, Song SY, Kim B. MR staging accuracy for endometrial cancer based on the new FIGO stage. Acta Radiol Sep 1 2011;52(7): 818-24.
[27] Alcazar JL, Galvan R, Albela S, Martinez S, Pahisa J, Jurado M, et al. Assessing myometrial infiltration by endometrial cancer: uterine virtual navigation with three-dimensional US. Radiology Mar 2009;250(3):776-83.
[28] Cicinelli E, Marinaccio M, Barba B, Tinelli R, Colafiglio G, Pedote P, et al. Reliability of diagnostic fluid hysteroscopy in the assessment of cervical invasion by endometrial carcinoma: a comparative study with transvaginal sonography and MRI. Gynecol Oncol Oct 2008;111(1):55-61.
[29] Rockall AG, Meroni R, Sohaib SA, Reynolds K, exander-Sefre F, Shepherd JH, et al. Evaluation of endometrial carcinoma on magnetic resonance imaging. Int J Gynecol Cancer Jan 2007;17(1):188-96.
[30] Haldorsen IS, Salvesen HB. Staging of endometrial carcinomas with MRI using traditional and novel MRI techniques. Clin Radiol Jan 2012;67(1):2-12.
[31] Szantho A, Szabo I, Csapo ZS, Balega J, Demeter A, Papp Z. Assessment of myometrial and cervical invasion of endometrial cancer by transvaginal sonography. Eur J Gynaecol Oncol 2001;22(3):209-12.
[32] Horowitz NS, Dehdashti F, Herzog TJ, Rader JS, Powell MA, Gibb RK, et al. Prospective evaluation of FDG-PET for detecting pelvic and para-aortic lymph node metastasis in uterine corpus cancer. Gynecol Oncol Dec 2004;95(3):546-51.
[33] Signorelli M, Guerra L, Buda A, Picchio M, Mangili G, Dell'Anna T, et al. Role of the integrated FDG PET/CT in the surgical management of patients with high risk clinical early stage endometrial cancer: detection of pelvic nodal metastases. Gynecol Oncol Nov 2009;115(2):231-5.
[34] Nakamura K, Hongo A, Kodama J, Hiramatsu Y. The measurement of SUVmax of the primary tumor is predictive of prognosis for patients with endometrial cancer. Gynecol Oncol Oct 2011;123(1):82-7.
[35] Park JY, Kim EN, Kim DY, Suh DS, Kim JH, Kim YM, et al. Comparison of the validity of magnetic resonance imaging and positron emission tomography/computed tomography in the preoperative evaluation of patients with uterine corpus cancer. Gynecol Oncol Mar 2008;108(3):486-92.
[36] Inubashiri E, Hata K, Kanenishi K, Shiota A, Ohno M, Yamamoto Y, et al. Positron emission tomography with the glucose analog [F]-fluoro-2-deoxy-D-glucose for evaluating pelvic lymph node metastasis in uterine corpus cancer: comparison with CT and MRI findings. J Obstet Gynaecol Res Feb 2009;35(1):26-34.
[37] Chi DS, Barakat RR, Palayekar MJ, Levine DA, Sonoda Y, Alektiar K, et al. The incidence of pelvic lymph node metastasis by FIGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometrioid histology. Int J Gynecol Cancer Mar 2008;18(2):269-73.


[^0]:    * Corresponding author at: Gynecologic Clinic, Section 4074, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 København Ø, Denmark. Fax: + 4535454285. E-mail addresses: Sleisby@dadlnet.dk (S.L. Antonsen), lisa.nerup.jensen@rh.regionh.dk (L.N. Jensen), annika.loft.jakobsen@rh.regionh.dk (A. Loft), anne.kiil.berthelsen@rh.regionh.dk (A.K. Berthelsen), junia.cardoso.corsa@rh.regionh.dk (J. Costa), Ann.tabor@rh.regionh.dk (A. Tabor), iq@rn.dk (I. Qvist), mrh@rn.dk (M.R. Hansen), rvf@rn.dk (R. Fisker), esa@rn.dk (E.S. Andersen), lene.sperling@ouh.regionsydmark.dk (L. Sperling), anne.l.nielsen@ouh.regionsyddanmark.dk (A.L. Nielsen), asmussen@paradis.dk (J. Asmussen), hogdall@dadlnet.dk (E. Høgdall), ib.jarle@finsenlab.dk (I.J. Christensen), lotte.nedergaard@rh.regionh.dk (L. Nedergaard), kirsten.jochumsen@dadlnet.dk (K. Jochumsen).

[^1]:    PPV: positive predictive value, NPV: negative predictive value

