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

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HIGHLIGHTS

- 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 2DUS 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.

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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.

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 extra-uterine 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

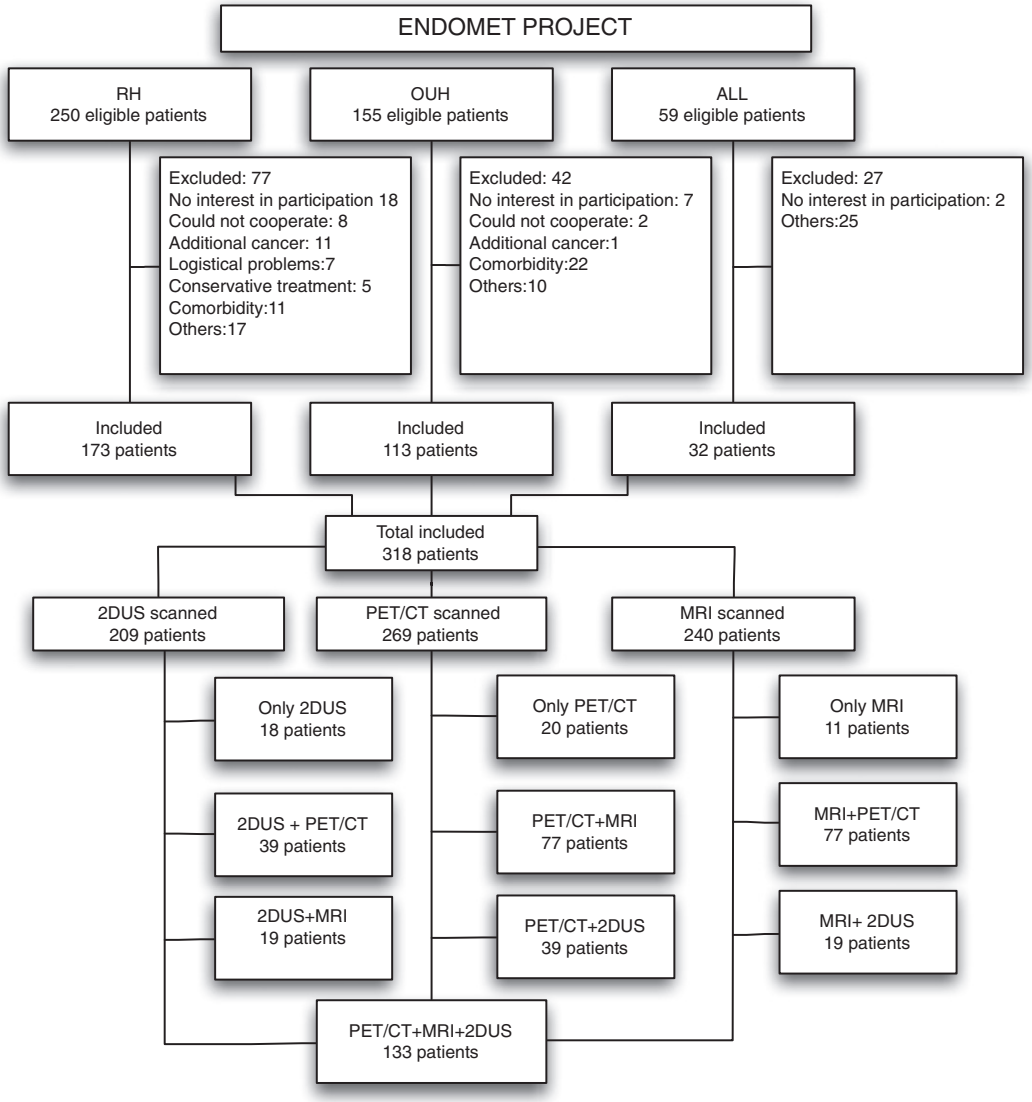

Fig. 1. Flowchart for the study. RH: Rigshospitalet, Copenhagen University Hospital, OUH: Odense University Hospital, AAL: Aalborg University Hospital.

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[a]	
<50%	228 (71.7)
≥50%	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.
[a] <50%: superficial + less than 50% myometrial invasion. ≥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%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 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 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 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							
	≥50%	<50%	Total	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT				92.6	48.6	40.6	94.6	60.7
≥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
≥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
≥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 (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
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	91.5	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 (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT				74.2	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 CI 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 Hosmer–Lemeshow 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.

	Histology: myometrial invasion							
	≥50%	<50%	Total	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT				88.9	43.5	44.4	92.0	63.9
≥50%	32	40	72	(73.9–96.9)	(42.4–64.3)			
<50%	4	46	50					
Total	36	86	122					
MRI				88.9	57.0	46.4	92.6	66.7
≥50%	32	37	69	(73.9–96.9)	(45.9–67.6)			
<50%	4	50	54					
Total	36	87	123					
2DUS				69.4	74.4	53.2	85.5	73.2
≥50%	25	22	47	(71.9–83.6)	(63.9–83.2)			
<50%	11	65	76					
Total	36	87	123					
	Histology: cervical invasion							
	Yes	No	Total	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT				38.5	92.8	62.5	84.1	81.3
Yes	10	6	16	(20.2–59.4)	(85.7–97.1)			
No	17	90	107					
Total	27	96	123					
MRI				26.9	93.8	58.3	82.7	80.3
Yes	7	5	12	(11.6–47.8)	(87.0–97.7)			
No	19	80	99					
Total	26	85	111					
2DUS				19.2	93.8	54.5	81.3	78.9
Yes	6	5	11	(7.6–39.3)	(87.0–97.7)			
No	21	91	112					
Total	27	96	123					
	Histology: lymph node metastases							
	Yes	No	Total	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
PET/CT				85.7	91.7	44.4	98.2	90.8
Yes	12	15	27	(67.2–98.2)	(86.6–95.3)			
No	3	166	169					
Total	15	181	196					
MRI				57.1	93.3	38.1	96.6	90.3
Yes	8	13	21	(28.9–83.3)	(88.6–96.5)			
No	6	168	174					
Total	14	1681	195					

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 ≥50% and LNM of 12 mm on MRI, two were diagnosed with MI ≥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 (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 (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
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

PPV: positive predictive value, NPV: negative predictive value.

Table 5

Stage	Lymph nodes	Parametria/ adnexae	Other	Pelvic LN visualized	Paraaortal LN visualized	Other MRI findings	Other PET/CT findings	Stage MRI	Stage 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	PET/CT, MRI	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	IA
IIIB		PA, AD		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, 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, 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			PET/CT, MRI	PET/CT, MRI			IIIC2*	IIIC2*
IIIC2	PE, AO							II	II
IIIC2	AO			PET/CT, MRI	PET/CT, MRI		Peritoneum in pelvis, parametria, adnexae	IIIC2*	IVB
IIIC2	PE, AO	PA, AD			PET/CT		Colon sigmoideum	Not scanned	IVA
IIIC2	PE, AO			PET/CT, MRI				IIIC1	IIIC1
IIIC2	PE, AO		Vagina	PET/CT, MRI	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

(continued on next page)

Table 5 (*continued*)

Stage	Lymph nodes	Parametria/ adnexae	Other	Pelvic LN visualized	Paraaortal LN visualized	Other MRI findings	Other PET/CT findings	Stage MRI	Stage PET/CT
IVB			Lung metastases				Lung metastases	IA	IVB*
IVB	PE	PA, AD	Omental	PET/CT, MRI	MRI	Intestinal, bladder, parametria, vagina, adnexae	Carcinosis, omental, intestinal, bladder, parametria, adnexae	IVB*	IVB*
IVB		PA	Vagina, bone, bladder, other	PET/CT, MRI	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	PET/CT, MRI	PET/CT, MRI	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 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 ($n = 220$) 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% CI) and p-values were: 4.71 (1.39–15.90), $p = 0.013$ (PET/CT); 5.38 (1.61–18.00), $p = 0.006$ (MRI); and 3.91 (1.50–10.16), $p = 0.005$ (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 (OR = 5.67 (95% CI: 1.73–18.55), $p = 0.004$) whereas MRI (OR = 3.09 (95% CI: 0.79–12.05), $p = 0.10$) and 2DUS (OR = 1.57 (95% CI: 0.34–7.33), $p = 0.57$) 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 ($p = 0.58$ and $p = 0.85$, respectively), but histology was (OR = 28.34 (95% CI: 1.50–536.68), $p = 0.026$). PET/CT was significant (OR = 30.53 (95% CI: 3.88–240.31), $p = 0.001$) whereas MRI was not (OR = 0.76 (95% CI: 0.26–2.20), $p = 0.61$). 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 extra-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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