Functional imaging to promote individualized and targeted therapy in endometrial cancer

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Scientific environment

This project is a derived from Bergen Abdominal Imaging Research Group (headed by main supervisor Prof. Haldorsen) and Bergen Gynecologic Cancer Research Group (headed by co-supervisor professor Salvesen and the imaging node is headed by professor Haldorsen). The latter is embedded in the Centre for Cancer Biomarkers (CCBIO) at the University of Bergen, which, in 2013, was awarded the prestigious title "Norwegian Centre of Excellence". CCBIO is focused on translational research, primarily biomarkers and personalized cancer treatment. Bergen Gynecologic Cancer Research Group, which includes an imaging node, consists of 11 PhD students and 6 post-docs/senior researchers and the group has contributed to a range of high impact scientific journals as primary investigators, including Lancet Oncology and PNAS. In particular, the large clinically annotated tissue bank (currently containing more than 3000 samples) facilitates a link between clinical practice and experimental studies, and serves as a tool to develop translational platforms for multidisciplinary projects in which clinical, paraclinical and basic scientists contribute. It also serves as the foundation for international studies called Molecular Markers in the treatment of Endometrial Cancer (MOMaTEC 1-2).

The imaging studies have been conducted in collaboration with scientists/clinicians/PhD students at the Department of Radiology and Centre for NM/PET at Haukeland University Hospital in Bergen (MD Sigmund Ytre-Hauge, MD Bernt Reitan, MD Inger J Magnussen, MD Martin Biermann, MD PhD Jarle Rørvik, MD PhD Ingfrid Haldorsen). Haldorsen is a board member in the MedViz Consortium, in which many existing collaborators are active partners; this network has also been utilized for cross-disciplinary collaboration.

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your telephone calls brighten my days, thank you for your constant care and support, and for getting on a plane whenever I need you.

Last, but not least, my deepest gratitude to the patients voluntary participating in the conducted and on-going studies. Your effort is highly valued, without you, none of these studies would have been possible.

Bergen, 3rd of September 2015

Jenny Hild Aase Husby

Katten

Katten sit
i tunet
når du kjem.
Snakk litt med katten.
Det er han som er varast i garden.

Olav H. Hauge

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by

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Abstract

Background: Endometrial carcinoma is the most common pelvic malignancy in the Western world and the incidence is increasing. Endometrial carcinomas are surgically staged according to FIGO 2009 criteria, and the lack of robust preoperative staging methods results in overtreatment of this patient population, mostly by unnecessary invasive surgery and lymphadenectomy in patients with localized disease. New imaging methods are highly warranted to aid more accurate preoperative staging and thus potentially reduce unwanted post-operative side effects, decrease the amount of unnecessary resource-demanding surgery and to provide better individualized therapy for this patient group.

Aims: Promote individualized treatment, reduce morbidity and facilitate implementation of targeted therapy among endometrial carcinoma patients by investigating functional and structural imaging biomarkers in pre-operatively acquired MRI and FDG-PET/CT.

Methods: All patients with histologically confirmed endometrial carcinoma at Haukeland University Hospital were consecutively referred to pre-operative MRI and/or FDG-PET/CT for a period of four years. Images were individually read by two to four radiologists and nuclear medicine physicians conducting staging and image quantifications in a standard imaging report. Results were compared to the results of surgical staging regarding the tumors depth of myometrial invasion, cervical stromal involvement and the presence of lymph node metastases, these three criteria being well-established parameters predicting aggressiveness of disease and survival in endometrial cancer.

Main Results: The evaluation of the staging criteria depth of myometrial invasion, cervical stromal involvement and the presence of lymph node metastases on pre-operative 1.5T MRI are prone to considerable inter-observer variability (κ=0.4, 0.5 and 0.6, respectively), and the staging accuracy is variable with a sensitivity (specificity) of 80%, 63% and 38% respectively (53%, 94% and 100%, respectively). For image quantifications, the inter-observer agreement is good (ICC=0.56-0.98) and the measured parameters show significant correlations to established staging criteria. Tumor apparent diffusion coefficient (ADC) value on diffusion-weighted imaging (DWI) is significantly lower in tumors with deep myometrial invasion (ADC = 0.75×10^{-3}mm^2/s) compared with tumors with superficial or no myometrial invasion (ADC = 0.85×10^{-3}mm^2/s; $p < 0.001$), and the ADC value is negatively correlated to tumor size (p=0.007). Large tumor size measured on preoperative MRI is associated with reduced progression/recurrence free survival ($p \leq 0.005$ for all size parameters), and

CC diameter has an independent impact on survival (adjusted hazards ratio, 1.04; p = 0.009). FDG-PET/CT is excellent in ruling out lymph node metastases (NPV=97%) and SUVmax, SUVmean, MTV and TLG are significantly related to deep myometrial invasion, presence of lymph node metastases and high histological grade (p<0.015 for all). Calculated optimal cut-off values for MTV in predicting deep myometrial invasion (20 ml) and presence of lymph node metastases (30 ml), yield ORs of 7.8 (p<0.001) and 16.5 (p=0.001), respectively, outperforming the current pre-operative ground for decision-making based on pathology findings in endometrial biopsies.

Conclusion: Functional and structural imaging biomarkers from MRI and FDG-PET/CT are promising for preoperative identification of high-risk patients in endometrial carcinoma.

List of publications

1. Haldorsen IS, **Husby J**, Werner H, Magnussen IJ, Rørvik J, Helland H, Trovik J, Salvesen ØO, Espeland A, Salvesen HB: Standard 1.5-T MRI of endometrial carcinomas: modest agreement between radiologists. *European Radiology* 2012, 22:1601-1611.

2. **Husby JA**, Salvesen ØO, Magnussen IJ, Trovik J, Bjørge L, Salvesen HB, Haldorsen IS: Tumour apparent diffusion coefficient is associated with depth of myometrial invasion and is negatively correlated to tumour volume in endometrial carcinomas. *Clinical Radiology* 2015, 70(5):487-94.

3. Ytre-Hauge S, **Husby JA**, Magnussen IJ, Werner HM, Salvesen ØO, Bjørge L, Trovik J, Stefansson IM, Salvesen HB, Haldorsen IS: Preoperative tumor size at MRI predicts deep myometrial invasion, lymph node metastases, and patient outcome in endometrial carcinomas. *International Journal of Gynecologic Cancer* 2015, 25(3):459-66.

4. **Husby JA**, Reitan BC, Biermann M, Trovik J, Bjørge L, Magnussen IJ, Salvesen ØO, Salvesen HB, Haldorsen IS: Metabolic Tumor Volume on 18F-FDG PET/CT Improves Preoperative Identification of High-Risk Endometrial Carcinoma Patients. *Journal of Nuclear Medicine* 2015, 56(8):1191-8.

Contents

APPENDIX

1. Abbreviations

1.5T	1.5 Tesla
18F-FDG-PET	18F-flouorodeoxyglucose positron emission tomography
3.0T	3.0 Tesla
ADC	Apparent diffusion coefficient
AKT	Protein kinase B
AP	Anteroposterior
AUC	Area under the curve
b1000	Measure for degree of diffusion weighting in DWI
BMI	Body mass index
BOLD-MRI	Blood oxygenation level dependent magnetic resonance imaging
CA-125	Cancer antigen 125
CC	Craniocaudal
CE	Contrast-enhanced
CI	Confidence interval
cm	Centimeters
CT	Computed tomography
DCE	Dynamic contrast enhanced
DNA	Deoxyribonucleid acid
DWI	Diffusion weighted imaging
EBRT	External beam radiation therapy
ESGO	European Society for Gynecologic Oncology
FDG	Fluoro-deoxyglucose
FGFR2	Fibroblast growth factor receptor 2
Fig	Figure
FIGO	Federation of Gynecology and Obstetrics
GATA3	Transcription factor characterized by its ability to bind to the DNA sequence "GATA"
GDF 15	Growth differentiation factor 15

HER-2/neu	Human epidermal growth factor receptor 2
IARC	International Agency for Research on Cancer
ICC	Intraclass correlation coefficient
K-ras	v-Ki-ras2 kirsten rat sarcoma viral oncogene homolog
MDC	Minimal detectable change
min	Minutes
Min	Minutes
ml	Milliliter
mm	Millimeter
MoMaTEC	Molecular markers in treatment of endometrial cancer
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
mTOR	Mechanistic target of rapamycin
MTV	Metabolic tumor volume
NORDCAN	Association of the Nordic Cancer Registries
NPV	Negative predictive value
OR	Odds ratio
p16	Cyclin-dependent kinase inhibitor 2A
p53	Phosphoprotein 53
PCOS	Polycystic ovary syndrome
PET	Positron emission tomography
PI3	Phosphoinositide 3-kinase
PTEN	Phosphatase and tensin homolog
PVE	Partial volume effect
ROC	Receiver operating characteristic
ROI	Region of interest
RR	Relative risk
s	Seconds
SEER	Surveillance, epidemiology and end results program
SUV	Standardized uptake value

T1	The relaxation time in one of the basic MRI sequences
T2	The relaxation time in one of the basic MRI sequences
TLG	Total lesion glycolysis
TV	Transverse
TVUS	Transvaginal ultrasonography
VB	Vaginal brachytherapy
VOI	Volume of interest
K	Kappa

2. Introduction

2.1 EPIDEMIOLOGY

Cancer of the endometrium (the inner lining of the uterus) is the most common pelvic gynecologic malignancy in industrialized countries and the seventh most common malignancy amongst women worldwide (1, 2). The incidence differs between continents, and is presently ten times higher in Europe and North-America, than in less developed regions of the world. Increasing incidence is registered, supporting the notion that environmental factors like obesity and physical inactivity contribute to the development of the disease, in addition to increased life-expectancy. In developing countries, endometrial cancer is the second most common gynecologic malignancy (cervical cancer being by far the most common), but the specific mortality rate is higher (1) . According to the Cancer Registry of Norway, 656 new patients were diagnosed with uterine cancers in Norway in 2012, and 92 women died from the disease in 2011. The life-time risk of developing the disease is 2.0% (3), with comparable figures for the rest of the Western world (1, 2). The five-year survival rate is high, reaching 84.3% in the latest figures from the Cancer Registry of Norway (3). In international studies, the 5-year survival for all stages taken together, is reportedly around 80% (1).

In Europe around 9000 women are estimated to die from endometrial cancer every year, and no considerable decrease in this number can be expected within the nearest future, as neither early detection nor different treatment approaches have significantly influenced mortality (1). On a worldwide basis, the annual figures for disease-specific deaths are 42,000.

The median age at diagnosis in Norway is 66 years, and the highest incidence is found in the group aged between 70-74 years. Endometrial cancer is relatively rare among premenopausal women, and is rarely diagnosed in patients below the age of 35 years; still the need for fertility-preserving therapy is relevant for women in childbearing age. At the time of diagnosis, 74.4% of patients have tumors confined to the uterus (NORDCAN 2007-11).

2.2 ETIOLOGY, PATHOGENESIS AND RISK FACTORS

80-90% of endometrial cancers are adenocarcinomas arising from endometrial cells, of which the endometrioid carcinoma is the most common subtype (1). Endometrioid tumors typically present at an early stage with abnormal uterine bleeding, and tend to have a favorable prognosis (2). Non-endometrioid subtypes (e.g. serous, clear cell, undifferentiated, carcinosarcoma) are classified as high-risk, and associated with considerably poorer prognosis (1). Overall, up to 20% of endometrial carcinomas follow an aggressive course (2).

The most prevalent and considered main risk factor for developing endometrial carcinoma is excess endogenous or exogenous estrogen stimulation, not counterbalanced by progesterone. This factor is linked to endometrioid endometrial carcinoma in particular, also classified as type 1 tumors (except for grade 3 endometrioid endometrial carcinoma, which is classified as type 2) (1). Excess estrogen relative to progesterone stimulates endometrial cell proliferation, inhibits apoptosis and promotes angiogenesis, all processes favoring carcinogenesis. Other risk factors for type 1 tumors include obesity, null parity, diabetes mellitus and hypertension. Reported relative risk of endometrial cancer related to presence of different risk factors are given in Table 1.

The main source of exogenous estrogen stimulation is postmenopausal estrogen therapy without opposing progesterone, resulting in a markedly increased risk of endometrial hyperplasia and carcinoma, with reported relative risk ranging from 1.1 to 15 (4-6).   Also, Tamoxifen treatment is reported to increase risk in postmenopausal women whereas no increased risk in premenopausal women has been established (7).

Common causes of endogenous estrogen stimulation are excessive conversion of adrenal precursors to estrogen and estradiol by adipose cells in obese women (8) and chronic anovulation where sex steroid hormones, including estrogen unopposed by adequate progesterone production, are produced continuously and induce uninterrupted proliferation of the endometrium (9). For the most common disease associated with anovulation, polycystic ovary syndrome (PCOS), a recent study indicates that the increased risk of endometrial cancer may be overestimated (10). In a meta-analysis of 19 prospective studies including over three million women, an

increase in body mass index (BMI) of 5 kg/m^2 incurred a significantly increased risk of developing endometrial carcinoma with reported relative risk (RR) of 1.59 (confidence interval (CI) of 1.50-1.68) (11).

Early menarche and late menopause are reported risk factors in some studies (12), but not in all studies (13). The tentative explanation for increased risk under these circumstances is prolonged estrogen stimulation during a life span.

Lynch syndrome (hereditary nonpolyposis colorectal cancer) leads to a life time risk of endometrial carcinoma of 40-60% and accounts for 2-5% of all endometrial carcinomas. Women with Lynch syndrome tend to develop endometrial carcinoma at an earlier age (46-54 years), but the disease usually presents at an early stage and has a course similar to sporadic endometrial carcinomas (14).

Having a first degree relative with endometrial carcinoma has been suggested as a risk factor, and a meta-analysis of 16 comparative studies concluded on a RR of 1.82 (95% CI 1.65-1.98); however, only three of these studies excluded patients with Lynch syndrome (15). The cumulative risk of endometrial cancer up to 70 years in women with a first-degree relative with endometrial cancer was estimated to be 3.1% compared with <2.0% in the general population.

Non-endometrioid tumors are not clearly associated with estrogen stimulation. They account for 10-20% of endometrial carcinomas, are classified as high-grade and have a poor prognosis. Unlike endometrioid tumors, non-endometrioid tumors are commonly associated with p53 mutations, aneuploid karyotype and human epidermal growth factor receptor 2 (HER-2)/neu overexpression (1). Serous carcinoma is believed to develop by transformation of the endometrial surface epithelium in an atrophic endometrial environment (16). In this group, 70% of the patients present with advanced stage (stage 3 or 4) with tumor extension beyond the uterus. The corresponding number for clear cell carcinomas is 50% (17, 18). No clear epidemiologic risk factors have been identified for non-endometrioid tumors, but one study of more than one million Norwegian women followed for an average of 25 years, found that obesity was associated with increased risk also in the non-endometrioid subtype, although less pronounced than for the endometrioid subtype (19).

Table 1 Risk factors for endometrial cancer

Risk factor	Relative Risk (RR)*
Unopposed estrogen therapy	2-10
Tamoxifen therapy	2
Late menopause (after age 55)	2
Null parity	2
Polycystic ovary syndrome	3
Obesity	2-4
Diabetes mellitus	2
Lynch syndrome (hereditary nonpolyposis colorectal cancer)	22-50% lifetime risk
Cowden syndrome (multiple hamartoma disease)	13-19% lifetime risk

*other statistics are noted when used

Adapted from data in Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society Guidelines for Early Endometrial Cancer Detection: Update 2001.

2.3 HISTOPATHOLOGY

Endometrial cancers are often classified as type I or type II endometrial tumors, type I being the low-grade endometrioid cancers, including cases with squamous cell differentiation, and type II comprising high-grade endometrioid tumors and non-endometrioid tumors as serous, clear-cell, mucinous and mixed carcinoma, and the more rare subtypes squamous-cell, transitional-cell, small-cell and undifferentiated carcinoma and currently also carcinosarcomas (1).

The endometrioid subtype is commonly well-differentiated adenocarcinomas with a gland-forming growth pattern, easily recognizable in the microscope (1). Histologic grading is decided by assessing gland formation and nuclear atypia.

Serous and clear cell carcinomas are more invasive and aggressive. Serous carcinomas have a complex papillary architecture, resembling the serous carcinoma of the ovary. The papillae are often covered with highly pleomorphic tumor cells with frequent mitosis and necrosis (1). Nearly all serous carcinomas are characterized by distinct p53 antigen-staining on immunohistochemistry. Clear cell carcinomas are characterized by tubulocystic, papillary and solid patterns. These lesions often involve the surface of a benign, endometrial polyp, the cytoplasm is clear and cell walls are distinct (1). Gene expression profile shows a specific pattern in clear cell carcinomas, but in contrast to serous carcinomas, they are negative to p53 mutations. The cytoplasm of the tumor cells contains glycogen, thus the clear appearance.

In cases where endometrioid carcinomas are difficult to distinguish from the serous/mixed type, genetic profiling can aid by showing microsatellite instability (MSI) and specific mutations (PTEN, K-ras, beta-catenin) in the endometrioid subtype, contrasting the p53 mutations that characterize the non-endometrioid subtype.

Some rare histologic subtypes classified as non-endometrioid endometrial carcinomas are squamous cell (an invasive tumor forming well differentiated squamous pearls), transitional cell (a neoplasm forming papillae lined by low grade stratified transitional type epithelium), mucinous (with tumor cells often containing voluminous intracytoplasmic mucin), and small cell (tumor composed of small cells with high nuclear to cytoplasmic ratio), constituting <2% of all endometrial carcinomas (20).

2.4 CLINICAL FEATURES

2.4.1 Biopsy, cytology and curettage

Abnormal uterine bleeding is the most typical early symptom in endometrial cancer, most commonly found among postmenopausal women and with increasing age in premenopausal women. Suspicion of endometrial neoplasia (hyperplasia or carcinoma) will depend on the severity of symptoms, age and the presence of risk-

factors. Abnormal bleeding pattern is found in 75-90% of women with endometrial cancer (21-23), whereas a small percentage of patients present with no abnormal uterine bleeding, but with atypical findings on cervix cytology.

The first step in the initial work-up of patients suspected of having endometrial neoplasia is endometrial sampling, usually performed by curettage producing an endometrial biopsy. If the material is sparse or unfitted for histopathological evaluation, a dilatation and curettage (fractionated curettage) is performed, collecting specimens from the endometrial lining and the cervix separately. Cancers can be distinguished from benign samples by endometrial cytology only, but supplementary samples of the endometrial mucosa are needed for preoperative histologic subtyping and grading. The histopathological diagnosis lays the basis for the planning of all further treatment. Patients are categorized into low- and high risk disease based on subtyping and grading. Non-endometrioid subtypes and high-grade endometrioid subtypes are regarded as high risk phenotypes, more likely to represent aggressive disease with increased risk of extra-uterine spread and poor prognosis (24, 25).

2.4.2 Sonography

Transvaginal ultrasonography (TVUS) is routinely used by gynecologists as a diagnostic tool in the evaluation of postmenopausal bleeding. It has the benefit of low cost and immediate availability in every gynecologist's practice. The method is well suited to depict the thin endometrial lining in postmenopausal women and the reported sensitivity and specificity for detection of endometrial carcinoma is 96% and 61%, respectively, when applying a threshold of 5mm for normal endometrial thickness (26). The evaluation of premenopausal women is more challenging due to the cyclical changes in thickness of the endometrium.

A recent meta-analysis reported a sensitivity of 68-100% and a specificity of 71-90% for the subjective assessment of deep myometrial invasion by TVUS, while the reported sensitivity and specificity for assessment of cervical stromal invasion are ranging from 19-100% and 82-99%, respectively (27).

There are insufficient data on the performance of TVUS in the detection of lymph node metastases (28), but the limited field of view is a challenge and will also rule out the possibility of finding lymph node metastases outside the pelvis.

2.4.3 Radiological diagnostics

Computed tomography (CT) of the thorax, abdomen and pelvis is widely applied preoperatively for the detection of lymph node metastases and distant spread. For local status in the pelvic area, magnetic resonance imaging (MRI) is considered superior (29-31), and serves as part of the standard preoperative work-up for endometrial carcinoma patients at many centers. Neither CT nor MRI, however, is considered sufficiently accurate for the prediction of lymph node metastases or deep myometrial invasion (1, 29, 31). 18F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography (18F-FDG-PET/CT) is costly, and although it is considered promising, especially for detection of metastases, its role in the preoperative staging of endometrial cancer is not yet established (1, 32-35).

2.4.4 Serological analyses and tumor biomarkers

No serological analyses are routinely applied for diagnostics of endometrial carcinoma. Several studies support CA-125 in the preoperative work-up (36-39), and a future role of CA-125 in a preoperative risk assessment algorithm and as a marker of disease progression seems likely (40-42). Also serum calprotectin and growth differentiation factor (GDF) 15 have been linked to aggressive phenotype in clinical studies (2).

Several molecular biomarkers of the primary tumors have also been identified in endometrial carcinomas. Presence of estrogen and progesterone receptors, transcription factor GATA3, Stathmin overexpression, DNA ploidy and p53/p16 staining are linked to prognosis in retrospective and prospective studies (43-45), but for implementation in risk stratification models, further studies are needed (2). Drugs targeting the PI3/PTEN/AKT/mTOR pathway and FGFR2 have been identified and seem promising in molecular studies (46); ongoing phase 1 and 2 trials will further evaluate the benefit of this therapeutic approach.

2.5 IMAGING CHARACTERISTICS

2.5.1 Sonography

TVUS is often the first-line imaging method applied to evaluate possible etiologies of abnormal vaginal bleeding. In postmenopausal women without risk factors, an endometrial thickness of $\leq$ 4-5 mm assessed by TVUS is associated with low cancer risk (47-49). When the endometrium reaches a thickness of 20 mm, cancer becomes more frequent relative to benign disease (48). TVUS may also be useful to identify non-malignant structural lesions of the uterus (e.g. polyps, myomas) as possible differential diagnosis for abnormal bleeding episodes. In premenopausal women, the use of TVUS to exclude endometrial disease is not established (50, 51), as there is no defined threshold for endometrial thickness to validly differentiate between benign and malignant endometrial thickening in this younger patient group.

2.5.2 Magnetic resonance imaging

For preoperative evaluation of endometrial carcinoma patients, conventional MRI including two T2-weighted sequences in sagittal, axial oblique or coronal oblique orientation (short and long axis of the uterus) and contract-enhanced, T1-weighted sequences including post-contrast images acquired 2 min $\pm$ 30 s after contrast medium injection is recommended in recent guidelines (52), in addition to a section orientated perpendicular on the axis of the endocervical channel, to evaluate cervical invasion.

On T2-weighted images, the majority of endometrial carcinomas have a heterogeneous and mainly hyperintense appearance compared to the normal myometrium (28, 53) (Fig 1 A, B) but some tumors may be iso- or hypointense (**F**ig 2 A,B). Endometrial irregularities, lobulation or local thickening may also point towards the diagnosis (53).
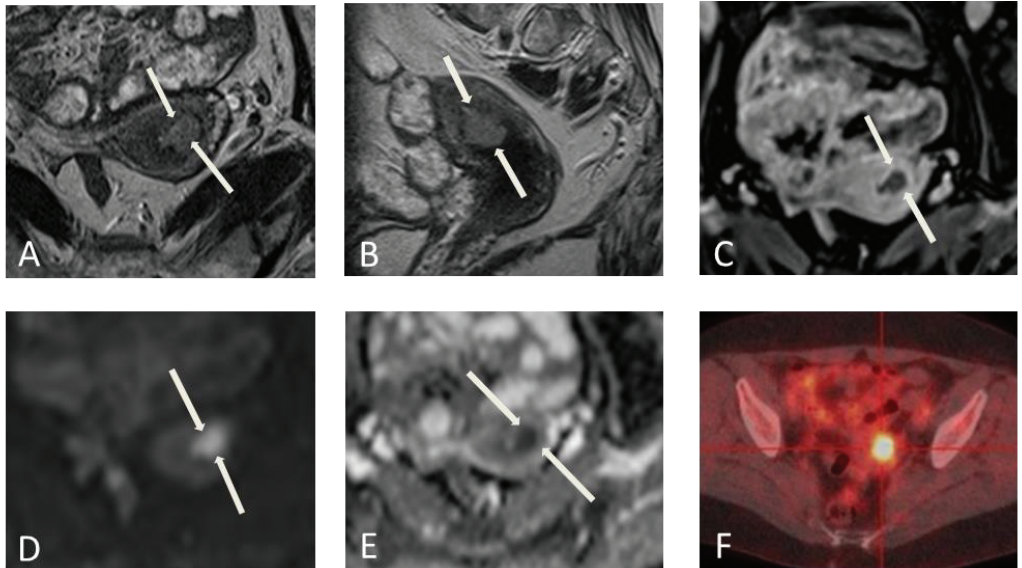
Fig.1 Stage 1A endometrial carcinoma invading < 50% of the endometrium (endometrioid, grade 1) in a 68-year-old woman. **A** Axial and **B** sagittal T2-weighted images show a hyperintense (relative to the myometrium) endometrial lesion and **C** contrast-enhanced T1-weighted images show a hypointense (relative to the myometrium) endometrial lesion in the uterine cavity. **D** Axial b1000 diffusion weighted image (DWI) show a hyperintense lesion, with corresponding hypointensity on the Apparent Diffusion Coefficient (ADC) map indicating restricted diffusion. **F** F18-FDG-PET/CT depicts the same tumor brightly FDG-avid.

Unenhanced T1-weighted images depict endometrial carcinomas isointense to the adjacent myometrium (53), while contrast-enhanced T1-series typically exhibit endometrial carcinomas as less enhancing than the highly vascularized myometrium (30, 54-56) (Fig 1 C and 2 C).

The preoperative evaluation of pelvic MRI in endometrial carcinoma patients aims to assess the depth of myometrial tumor invasion (≥/< 50%), and identify presence of cervical stromal invasion and lymphatic spread. The diagnostic performance of contrast-enhanced MRI is well documented for myometrial and cervical tumor invasion, and considered superior to that of ultrasonography, CT and unenhanced MRI (28, 31, 53). For lymphatic spread, the performance is however rather low, with reported sensitivities of 17-80% in recent literature(56). A recent meta-analysis including 52 studies examining MRI in the assessment of high-risk features of endometrial carcinoma found pooled sensitivity (specificity) of 80.7% (88.5%) for ≥50% myometrial invasion, 57% (94.8%) for cervical stromal invasion

and 43.5% (95.9%) for lymph node spread, respectively (57). Given the rather low results on sensitivity, the authors conclude that patients with negative findings on MRI should not forgo surgical staging.

Nevertheless, MRI has long been the preferred imaging tool in the preoperative staging for treatment planning in endometrial carcinoma patients, and in particular in the evaluation of disease spread within the pelvic region (1, 31, 58). The considerable variation in reported accuracy of MRI in the detection of important staging parameters (56, 59-61) may be due to different MRI protocols applied, as well as interobserver variability in the interpretation of the images. When introducing MRI as a diagnostic tool in preoperative staging, the validity and reproducibility of the method must be thoroughly explored in order to render a successful and safe clinical implementation.
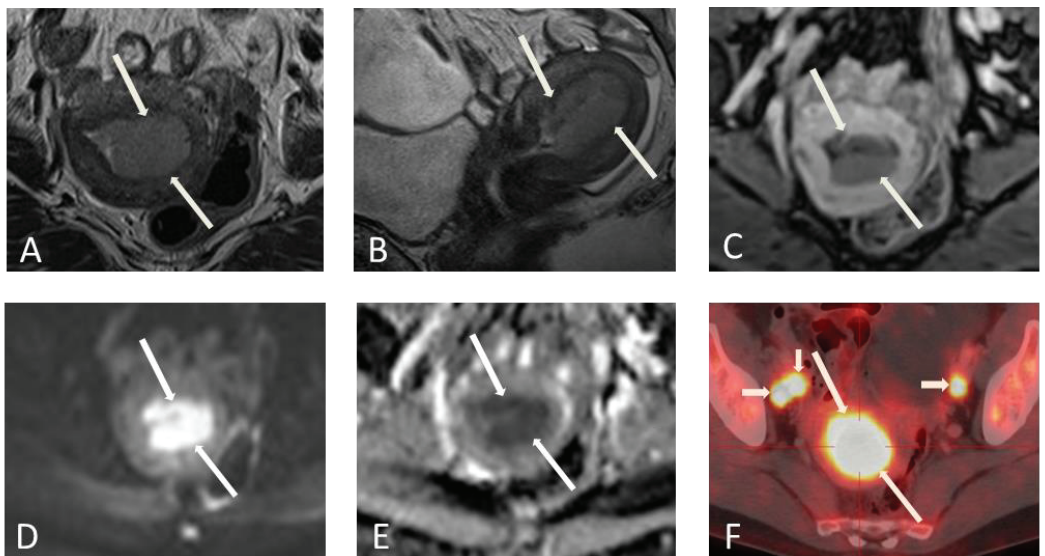
Fig.2 Stage IIIC2 endometrial carcinoma invading < 50% of the endometrium (endometrioid, grade 3) in a 63-year-old woman. **A** Axial and **B** sagittal T2-weighted images show an isointense (relative to the myometrium) endometrial lesion in the uterine cavity , **C** contrast-enhanced T1-weighted images show a hypointense endometrial lesion, **D** Axial b1000 diffusionweighted image (DWI) show a hyperintense lesion, with corresponding corresponding hypointensity on the Apparent Diffusion Coefficient (ADC) map. **F** F18-FDG-PET/CT depicts the same tumor brightly FDG-avid (long arrows), together with three metastatic lymph nodes (short arrows).

Diffusion-weighted imaging (DWI) is a functional imaging technique routinely in use at many centers as an adjunct to conventional MRI for preoperative staging of endometrial carcinomas (56, 62, 63), and it may aid in the differentiation between benign and malignant lesions (56). Endometrial carcinomas typically exhibit restricted diffusion with decreased apparent diffusion coefficient (ADC) values compared to the surrounding normal myometrial tissue (56), appearing as brightly hyperintense on the DWI series (Figs. 1D, 2D) and hypointense on the corresponding ADC map (Figs. 1E, 2E). Reported mean ADC values range from 0.84-0.98x 10^{-3} mm^2/s in endometrial carcinomas, 1.21-1.76x10^{-3} mm^2/s in benign lesions, 1.45-1.71x10^{-3} mm^2/s in normal endometrium, and 1.53-1.65x10^{-3} mm^2/s in normal myometrium (63-67).

Other novel MRI methods like MR perfusion, spectroscopy, and BOLD-MRI may represent additional MR tools for preoperative staging and tumor characterization in endometrial carcinomas in the future, but these techniques are not yet fully explored for endometrial cancer (56).

2.5.3 18-Fluoro-Deoxy-Glucose (FDG)-Positron Emission Tomography (PET) / computed tomography (CT)

This non-invasive, functional diagnostic imaging method uses a radio-labelled glucose analogue (2-deoxy-2-(^{18}F) fluoro-D-glucose) as tracer, and takes advantage of the increased glucose metabolism in malignant cells to identify cancer in human tissue. CT images for attenuation correction and anatomic correlation are acquired successively in the same gantry system, allowing co-registration, reconstruction and combination into a single, superposed imaging series.

FDG-PET/CT is currently not routinely in use for the preoperative evaluation of endometrial cancer in most centers. It is, however, the preferred imaging method for staging of many cancer types (68), and the diagnostic value in endometrial carcinomas is currently the subject of recent and ongoing research (32-35, 69-74).

The primary endometrial tumor is normally highly FDG-avid (Figs 1F and 2F) if the size of the tumor is >5 mm with reported mean preoperative maximum standardized uptake value (SUVmax) of 14.3 (range 3.9-33.8) in a recent study of 101 patients (75), and 11.2 (SD of 5.9) in a review from 2010 (76). When FDG-uptake is

seen also in the cervix, this may suggest cervical stromal invasion. Down to the size of 5 mm, lymph node metastases are usually detectable by increased FDG-uptake, and for endometrial carcinoma patients, the whole-body scanning is advantageous for detecting para aortic lymph node metastases that may be present in addition to, or in the absence of pelvic lymph node metastases. The sensitivity, specificity and accuracy of PET/CT in detecting lymph node metastases are reportedly 53-86%, 92-99% and 91-98%, respectively (33, 77). Antonsen et al. (33) reported sensitivity, specificity and accuracy also for deep (≥50%) myometrial invasion and cervical invasion to be 88.9%, 43.5%, 63.9% and 38.5%, 92.8%, 81.3%, respectively.

Additionally, recent literature reports that preoperative SUVmax of endometrial tumors is an independent prognostic marker of recurrence and death (70), and an important indicator of tumor aggressiveness and high-risk disease (34, 69, 75). Other FDG-PET-specific quantitative measurements like SUVmean, metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have also recently been explored as prognostic markers. MTV and TLG have appeared as significant predictors of several clinical pathological characteristics and these parameters are superior to SUVmax in differentiating high-risk from low-risk patients in a recent study of 56 endometrial carcinoma patients (69). In addition, MTV is suggested in the literature as a promising marker for lymph node metastases and poor outcome (71, 78). SUVmean has been less studied, but similar to SUVmax, it has been associated with International Federation of Gynecology and Obstetrics (FIGO) stage, histologic grade and maximum tumor size in endometrial cancer (72).

2.6 STAGING

Endometrial carcinoma is surgically staged according to the 2009 FIGO classification system (79) (Table 2). In the prior surgical staging system (FIGO 1988 staging system), stage I had three substages, but stage IC had a poorer survival than stage IIA, and stage IIIC did not differentiate between patients with pelvic and para aortic lymph nodes, although the prognosis between these groups is significantly different. The current system better reflects treatment relevant prognostic groups after eliminating these contradictions by merging former stage IA and IB (currently IA), eliminating the

former stage IIA, and stratifying stage IIIC into IIIC1 (pelvic lymph node metastases) and IIIC2 (para aortic lymph node metastases) (80).

For the complete surgical staging procedure, a total hysterectomy with bilateral salpingo-oophorectomy with pelvic and para aortic lymph node dissection is recommended. Pelvic and para aortic lymph node sampling or removals are performed selectively, but as a minimum, these nodes are palpated during surgery and suspicious or enlarged lymph nodes are removed if possible. The extent of uterine disease is evaluated during surgery by gross examination of the surgical specimen, and provides some guidance to the extent of staging needed for each individual (for instance if lymphadenectomy is required). Surgical treatment is also guided by the assessment of tumor subtype and grade provided by the pathologists from the preoperative endometrial biopsies and preoperative imaging findings.

Results from the surgical staging procedure further guide the clinician in deciding which patients should be recommended adjuvant treatment. This decision is also based on the histopathologic subtype detected in the initial and final histopathological report, dividing the patients into low-risk and high-risk groups.

Table 2: FIGO 2009 classification of endometrial carcinoma (79)

Stage	Criteria
IA	Tumour confined to the uterus, < 50% myometrial invasion
IB	Tumour confined to the uterus, ≥ 50% myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
IIIA	Tumour invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvement
IVA	Tumour invasion bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

2.7 TREATMENT

2.7.1 Surgery including lymphadenectomy

Surgery is the cornerstone in primary endometrial cancer treatment, and usually curative for women with low-risk disease confined to uterus (1). The standard procedure comprises total hysterectomy with bilateral salpingo-oophorectomy. If the tumor invades the cervix (stage II), an extended, radical hysterectomy procedure is recommended, including excision of paracervical and parametrial structures. Most surgeons also perform peritoneal washing for cytological diagnostics, but results will not guide further treatment as an integrated part of the FIGO staging after the revision in 2009. In case of evident intraperitoneal metastases, debulking is recommended, in line with the experience from debulking surgery in ovarian cancer surgical treatment, although the survival benefit is uncertain (81). If histology has confirmed clear cell or serous carcinoma, omentectomy is frequently performed as these subgroups have a high frequency of intra-abdominal spread and may clinically often resemble ovarian carcinomas (82).

Lymphadenectomy is recommended as part of a complete surgical staging procedure according to the FIGO (79, 83). A total staging lymphadenectomy normally includes the left and right common, external and internal iliac and obturator chains, in addition to left and right para aortic nodes. Tumor infiltration of more than 50% of the myometrial wall is an established marker for significantly increased risk of lymph node metastases (1, 83), and represents one of the main factors in the preoperative decision-making regarding the extent of lymphadenectomy performed during primary surgery (84, 85). The approach to lymph node assessment is, however, controversial, particularly in women preoperatively classified as low-risk patients (86). The extent to which lymphadenectomy is actually performed varies considerably between centers. A survey among tertiary cancer centers in USA reported that 45% routinely performed the procedure (87), while 24% of European centers reported lymphadenectomy as routine procedure in endometrial cancer surgery (88).

The Norwegian guidelines (Salvesen et al. Endometriecancer, Kvalitetsutvalget Norsk Gynekologisk Forening, 2009) were revised in 2009 to recommend considering pelvic lymph node sampling for medium-risk patients and pelvic and para

aortic lymphadenectomy for high-risk patients, according to risk stratification based on preoperative assessment of subtype and grade and the extent of myometrial invasion.

Although it is established that the presence of metastatic lymph nodes is a strong predictor of poor prognosis, with a 5-year survival of 57% compared to 74-91% for stages with no lymph node spread, the survival benefit from lymph node sampling is not well documented, and no survival benefit has been found in randomized trials, and for low-risk groups in particular (89). Also, the risk of complications (lymph edema, lymph cyst formation and surgically related systemic complications) in lymph node sampled patients is significantly increased (86), and the subject remains an issue of controversy.

Surgery is performed by open laparotomy, laparoscopy or robot-assisted laparoscopy. In selected cases with medical comorbidities or severe obesity vaginal hysterectomy may be performed, but is generally not recommended (90, 91) .

2.7.2 Adjuvant therapy

Radio- and chemotherapy

Radiotherapy can be offered vaginally as brachytherapy (VB), as external radiation to the pelvis (EBRT) or to an extended region comprising the para aortic area or the whole abdomen. Radiotherapy is widely used and reduces pelvic relapse from about 20% to 5%, but the effect on survival for patients with stage I tumors have not been documented (92) and radiation is no longer recommended routinely in low-risk patients with FIGO stage I endometrioid grade 1 or 2 disease with <50% invasion of the myometrium (93). Brachytherapy is locally effective and associated with a significant reduction in long-term side effects (the most common being bowel obstruction and chronic diarrhea) (92), but for high-risk cases (including higher tumor stages and tumors with non-endometrioid histology), external radiation therapy is still the treatment of choice (94), also reflected in the revised Norwegian National guidelines (95).

Chemotherapy is increasingly recommended for patients with high-risk endometrial carcinomas, although the optimal regimen is yet to be better defined. It can be administrated as a single-agent therapy or in combinations; the most commonly

used drug combination in Norway is currently carboplatin and paclitaxel, although other combination therapies including cisplatin, paclitaxel, ifosfamide or doxorubicin are options, all producing response rates of 20-37% (96). Undesired side effects of combination therapies tend to exceed those of single-agent therapy, and include leukopenia and cardiotoxicity. From 1996 to 2001, the reported portion of patients with endometrial carcinoma receiving adjuvant chemotherapy has increased, in line with current recommendations (83).

Anti-hormonal therapy
Endometrial cancer patients are no longer subjected to anti-hormonal therapy as adjuvant treatment due to lack of support for efficacy. A large Cochrane review of six randomized controlled trials with both adjuvant and recurrent settings could not find sufficient evidence for any survival benefit of anti-hormonal treatment (97). Not all included trials had, however, incorporated the tumor hormone-receptor status. It may thus be argued that trials including hormonal status in order to stratify patients for anti-hormonal treatment are needed to evaluate the true potential of anti-hormonal therapy in selected patient groups, also in line with current practice for breast cancer therapy (98).

2.8 PROGNOSTIC FACTORS AND OUTCOME
For the majority of endometrial carcinoma patients the prognosis is excellent (80-90% 5-year survival), due to early detection of uterine confined disease of most commonly the endometrioid subtype. The strongest prognostic factor in endometrial carcinoma patients is FIGO stage (Table 2), where survival is significantly lower in the higher stages. The reported 5-year survival is 90% for stage IA, 78% for IB, 74% for stage II, 36-57% for stage III depending on the site of extra-uterine tumor manifestation and 21/22% for stage IVA /IVB, respectively (80). Moreover, a study of 27 000 endometrial carcinoma patients identified myometrial invasion of >50% as an independent risk factor for advanced, high-stage disease with metastatic spread and poor survival (99). The same study, a large trial from the American Surveillance, Epidemiology, and End Results Program (SEER) registry, also found that the presence

of pelvic or para aortic lymph node metastases was associated with significantly lower survival even when adjusted for uterine risk factors such as cervical stromal invasion, deep myometrial invasion and high histological grade, and thus represents an independent prognostic marker for poor outcome (99).

Other strong predictors of outcome are histological subtype and grade. The non-endometrioid subtypes have significantly worse outcome than tumors with endometrioid histology; the reported 5-year survival for non-endometrioid tumors within stage I is 78-85%, contrasting 90-93% for patients with endometrioid histology, and undifferentiated high-graded tumors, also within the endometrioid group, have significantly lower survival than the well differentiated low-grade tumors (83).

Lymphovascular space invasion is a histological tumor feature often linked to poor outcome (100), and the importance of the pathologists reporting this information has become increasingly advocated.

3. Specific background and aims of the study

Specific background

Endometrial carcinoma is the most common gynecological malignancy in industrialized countries, and the incidence is increasing attributed to epidemic obesity (1). Treatment and prognosis is influenced by surgical International Federation of Gynecology and Obstetrics (FIGO) stage i.e. depth of myometrial invasion, cervical extension, and lymph node, pelvic or distant metastases (1, 2). Also, histologic subtype and tumor grade have prognostic impact (1). Depending on tumor stage, the 5-year survival for endometrial carcinoma patients range from 20% to 91%, with generally an 80% survival rate reflecting that 75% of cases are diagnosed at early stage (83). There are few treatment options for women with recurrent, metastatic or inoperable disease. Response rates to hormones are modest in the range of 9-25% and prognosis is poor. The most active chemotherapy regimen has a response rate of up to 60%; however, overall survival is short and is associated with significant toxicity in a largely elderly population. Knowledge of tumor dissemination prior to surgery is critical in determining the treatment strategy for each individual patient. The prognostic unfavorable impact of deep myometrial invasion is well established (101), and accurate preoperative identification of deep myometrial infiltration and cervical stromal involvement is important to tailor surgical treatment to also include lymphadenectomy and radical hysterectomy, respectively (2). It is established that low-risk patients do not necessarily benefit from lymphadenectomy as this procedure is associated with more complications (86).

The present project focuses on preoperative characterization of endometrial carcinomas by structural and functional MRI and FDG- PET/CT in combination with histological and molecular classification of endometrial biopsies. The overall aim of the project is to **promote individualized treatment, reduce morbidity, and facilitate implementation of targeted therapy** amongst these patients. Non-invasive imaging methods may potentially aid the preoperative identification of high-risk patients before primary surgery. This can provide a better basis for individualized treatment, planning of the surgical procedure, and referral to specialized units. Furthermore, it may

potentially reduce the morbidity from extensive lymphadenectomy in the low-risk groups.

Aims of the study

1. To evaluate the diagnostic performance of pelvic MRI as well as interobserver agreement for the detection of deep myometrial invasion, cervical stroma invasion and lymph node metastases in endometrial carcinoma patients in relation to surgical staging (**Paper I**).

2. To explore the utility of ADC value measurement on DWI in the preoperative evaluation of endometrial carcinomas and to investigate the potential of tumor ADC value as a biomarker reflecting clinical and histological tumor characteristics. A further aim was to assess the interobserver agreement for measurement of ADC values and for preoperative evaluation of staging parameters based on standard pelvic MRI including DWI (**Paper II**).

3. To explore the relationship between different preoperative tumor size measurements using MRI and the surgical pathological staging parameters deep myometrial invasion, cervical stromal invasion and metastatic lymph nodes. Secondarily to assess the interobserver variability for the different tumor measurements and to explore the value of these preoperative tumor size measurements to identify patients with poor outcome (**Paper III**).

4. To prospectively explore the diagnostic value of preoperative FDG-PET/CT for staging purposes in endometrial carcinomas, and to investigate to what extent FDG-PET-specific quantitative tumor parameters reflect clinical and histological tumor characteristics. To further explore clinical applicability we also aimed to assess interobserver agreements for FDG-PET/CT staging- and quantitative tumor parameters and to review the prevalence and significance of incidental findings in the context of prospective and consecutive FDG-PET/CT investigations of a population based endometrial carcinoma cohort (**Paper IV**).

4. Materials and methods

4.1 PATIENTS AND DATA COLLECTION

Since April 2009, all patients with histologically confirmed endometrial carcinoma at Haukeland University Hospital have been consecutively referred to preoperative pelvic 1.5-T MRI in a prospective setting. The diagnosis is verified in hysterectomy specimens and final stage is established based on surgical staging. From October 2010, the same patient group was also prospectively included in a study of preoperative FDG-PET/CT, to further evaluate the usefulness of advanced imaging methods for staging and assessment of potential imaging biomarkers for aggressive disease and poor outcome. The patients signed informed consent for collection of data and specimens for biomarker studies under institutional review board-approved protocols. All participants were diagnosed and treated at Haukeland University Hospital; a European Society for Gynecologic Oncology (ESGO) accredited training center for gynecologic oncology, serving a population of ~1 million inhabitants.

Paper I included 67 patients with suspected endometrial carcinoma prospectively referred to preoperative MRI. Ten of the patients were excluded, due to change in the final diagnosis (endometrial hyperplasia in six patients, an endometrial polyp in one patient and one patient was diagnosed with cervical cancer), lack of surgery/histologic diagnosis (n=1) or incomplete MRI (n=1), leaving 57 patients with confirmed endometrial carcinoma eligible for further analyses.

Paper II included 105 consecutive patients referred to preoperative MRI up to December 2011, partially overlapping the cohort of **Paper I**. Also in **Paper III** the cohort is partially overlapping the preceding, but it includes patients consecutively referred up to December 2013, yielding a patient sample of 212.

In the FDG-PET/CT based study (**Paper IV**), 129 consecutive patients were included, inclusion ending in September 2013. The images were acquired prospectively and the results reported to the responsible clinician together with all relevant preoperative imaging performed. In this cohort, the medical records for all patients with significant incidental findings (defined as imaging findings without link to endometrial cancer, but with a possible therapeutic consequence) were examined

retrospectively ~ one year after the PET/CT scan to register how the clinical team had dealt with the follow-up of the incidental findings.

Image reading for staging parameters, reproducibility assessments and quantifications were all conducted retrospectively. The follow-up data regarding recurrence, progression and survival, have been collected from patient records and from correspondence with the responsible primary physicians or gynecologists. The FIGO 2009 criteria (79, 80) were used for staging of all patients, and this was used as the reference standard throughout the studies. Surgical specimens were sectioned along the longitudinal plane of the uterus, and depth of myometrial invasion and presence of cervical stromal invasion were estimated macroscopically and confirmed microscopically according to standard procedures (102). Routine histopathology reports were generated in a tumor board setting and the reporting pathologists were blinded to the result of preoperative imaging. The responsible surgeon decided the extent of lymph node sampling based on knowledge of histologic risk profile in the endometrial biopsy, results of preoperative imaging and the patient's general health condition. The operating gynecologist then labelled all lymph nodes according to anatomical localization (common, internal and external iliac, internal obturator and lumboaortic node groups) and the pathologists documented number and size of the metastatic lymph nodes.

4.2 IMAGE READING
4.2.1 MRI reading
All images were deidentified and read independently by four (**Paper I**) or three (**Paper II and III**) observers blinded for clinical data, tumor stage, histological diagnosis and patient outcome. The observers' experience in pelvic imaging ranged from 2 to >10 years, and the pool included both residents and consultants. All observers reported the imaging findings in a standardized form (appendix).

For **Paper I** they recorded primary location, number, size (AP, width and height), minimum distance from tumor to serosa, maximum depth of myometrial invasion and margins (sharp, moderately sharp or diffuse) of the endometrial tumors. Contrast-enhanced (CE) T1-weighted images were used to measure tumor size (except

sagittal diameter as sagittal CE T1-weighted images were not acquired), distance from tumor to serosa and depth of myometrial invasion (assessed at the deepest point in which the tumor extends into the myometrium). Tumor signal intensity relative to normal myometrium (lower, similar or higher) was recorded on T1-weighted and T2-weighted unenhanced series and CE T1-weighted series. Cervical stromal invasion (defined as disruption of the low-signal intensity cervical stroma on T2-weighted images), tumor growth in serosa, adenexa, vagina, bladder or rectum, intraperitoneal fluid, enlarged para aortic or para iliac lymph nodes (largest short-axis diameter > 10mm), distant metastases and concomitant findings such as uterine adenomyosis and myomas were recorded. Before analysis, the recorded presence (yes / no) of the three following findings was noted:

1. Deep myometrial invasion (tumor invading ≥50% of the myometrium)
2. Cervical stromal invasion
3. Enlarged pelvic or para aortic lymph nodes

For **Paper II**, the staging parameters and the measurements of tumor diameters were assessed on T2-weighted and CE T1-weighted images, using DWI only as a supplementary sequence guiding the measurements performed on the conventional series. The overall quality of the DWI was considered, and images with major artefacts (e.g. due to hip implants blurring the anatomy) were excluded from the DWI analyses (five of 105 cases). A region of interest (ROI) was manually drawn in the ADC map depicting the largest part of the tumor in each patient. The ROI aimed to comprise a representative part of the tumor tissue in closest proximity to normal myometrial tissue (in order not to falsely include normal tissue), and also leaving out necrotic or hemorrhagic areas if present (Fig. 3). Median volume of the drawn ROIs in tumor tissue was 0.88 ml (mean 1.85 ml; range 0.12-16.9 ml) for observer 1, 0.35 ml (mean 0.40 ml; range 0.12-2.2 ml) for observer 2 and 0.35 ml (mean 0.48 ml; range 0.12-3.4 ml) for observer 3. Imaging findings suggestive of deep myometrial invasion, cervical stromal invasion, and/or pelvic or para aortic lymph node metastases were recorded after the same criteria as in Paper I. Tumor volume was estimated based on the standard anatomical images with measurements of maximum tumor diameter in

three orthogonal planes (x, y, and z) using the following equation (assuming a spherical tumor shape): Tumor volume = x × y × z / 2.
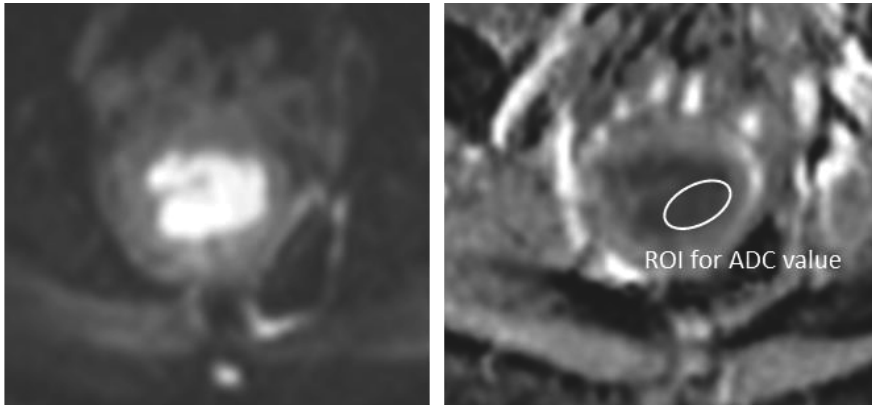

Fig 3 Axial b1000 diffusion-weighted image (DWI) (left) and the corresponding Apparent Diffusion Coefficient (ADC) map (right). The regions of interest (ROIs) for measuring the ADC values were drawn on the ADC map (right).

For **Paper III**, the maximum tumor diameters were measured in 3 orthogonal planes: anteroposterior (AP) and transverse (TV) diameters on axial CE T1-weighted oblique images (perpendicular to the long axis of the uterus) as well as craniocaudal (CC) diameters on sagittal T2-weighted images (Fig. 4). Tumor volume was then estimated based on these measurements of maximum tumor diameter in 3 orthogonal planes using the following equation: tumor volume = AP diameter × TV diameter × CC diameter/2. The staging parameters deep myometrial invasion, cervical stromal invasion and the presence of lymph node metastases were also recorded using the same criteria as described for Paper I and II.

For Paper **I, II and III**, a majority rating for the registered parameters was established by using the value given by the majority of the observers for categorical variables and the median value for continuous variables. For **Paper I**, in which there were four observers, an expert majority rating was established by applying the same method on the ratings of the three consultants.
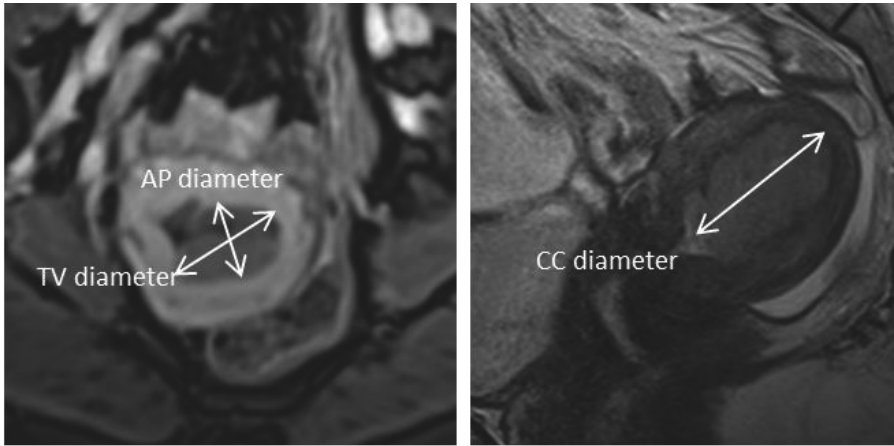
Fig 4 Axial oblique CE T1-weighted image (left) and sagittal T2-weighted image (right) for measurements of maximum tumor diameters in three orthogonal planes. AP and maximum TV diameters were measured on the axial oblique image (left), whereas CC diameters were measured on the sagittal image (right).

A new dataset consisting of the majority ratings was computed for each paper, and this rating was used to explore the different parameters in relation to clinical and histological tumor characteristics.

The MRI readings were always preceded by a pilot study of five cases independently read by the participating observers, and recorded in the standardized form. Eventual disagreements could then be discussed to achieve a common understanding of the image reading criteria applied. The five pilot cases were always excluded from the final analyses.

4.2.2 FDG-PET/CT reading

A standard imaging report was generated by the responsible nuclear physician and radiologist and reported to the clinical team as part of the routine clinical diagnostic work-up. This imaging report was read and approved by a specialist in nuclear medicine and a radiologist subspecialized in the field of pelvic imaging as part of the standard reading set-up at our institution.

After use for routine diagnosis, all images were deidentified, processed and reviewed retrospectively and independently by two physicians experienced in both nuclear medicine and radiology, on a Segami Oasis workstation (v. 1.9.4.2; Segami Corporation Columbia, MD, USA). Both readers had ~ four years' experience with PET-CT prior to the study. They were blinded to clinical data and results of surgical staging, and reported imaging findings in a standardized form. This registration form (see appendix) included information on tumor avidity and uptake intensity as well as metabolic tumor volume. Information on presence of increased FDG uptake of the cervix (interpreted as cervical stroma invasion), in lymph nodes (interpreted as lymph node metastases) and at distant sites (interpreted as likely metastases), was also recorded. The depth of myometrial invasion based on FDG uptake was not registered, due to the low resolution of PET signals, perceived to preclude myometrial invasion assessment.

The PET images were fused with both the diagnostic and the low-dose CT images on the Oasis workstation. All measurements were performed using the low-dose fusion, whereas the diagnostic fusion was used for staging. For the measurements of metabolic tumor volume (MTV) and average standardized uptake value (SUVmean), voxels with SUV >2.5 were included in the volume of interest (VOI) (Fig.5). Total lesion glycolysis (TLG) in the tumor was also estimated using the following equation: TLG = SUVmean * MTV (103). For the statistical analyses of continuous variables, the mean of the two observers' measurements was applied. To achieve a common understanding of the image reading criteria for assessing tumor avidity and uptake intensity as well as metabolic tumor volume, the two observers independently recorded five selected pilot cases in the registration form. Disagreements and different interpretations were discussed to reach a common understanding of the criteria applied. These five cases were then excluded from the cohort.

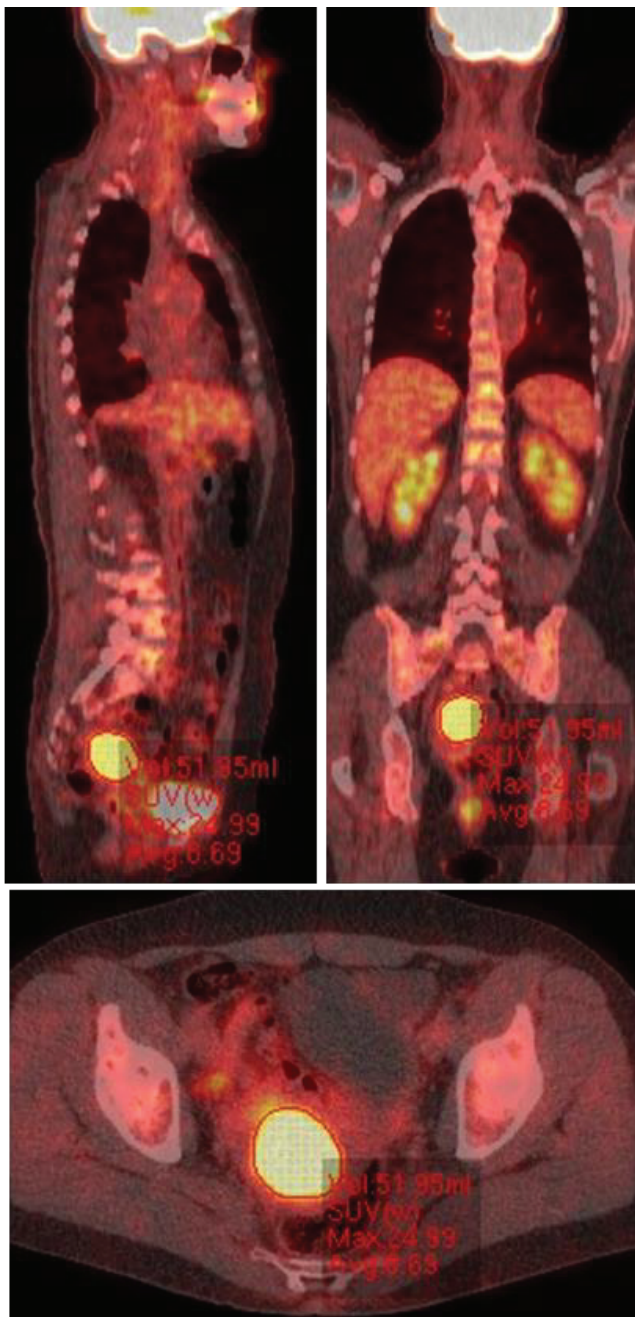**Fig 5** Sagittal (upper left), frontal (upper right) and axial (lower) F18-FDG-PET/CT images for measurement of metabolic tumor volume (MTV) on a Segami Oasis workstation. The volume of interest (VOI) comprises all tumor voxels with SUVmax > 2.5.

4.3 STATISTICAL METHODS

Interobserver agreements were measured using exact Fleiss kappa (κ). Agreement beyond chance was interpreted as poor (κ ≤ 0.20), fair (κ = 00.21–0.40), moderate (κ = 00.41–0.60), good (κ = 00.61–0.80) or very good (κ = 00.81–1.00). Intraclass correlation coefficient (ICC) was used to assess the consistency and reproducibility of ADC value measurements (**Paper II**), tumor size measurements (**Paper III**) and the quantitative PET/CT parameters (**Paper IV**), and minimal detectable change (MDC; 1.96 × standard error of the mean × square root of 2) for the measured ADC values (**Paper II**) and the measured tumor diameters (**Paper III**) were also calculated. For the imaging findings of deep myometrial invasion, cervical stromal invasion and suspected lymph node metastases, the following analyses were performed:

1. Sensitivity, specificity, accuracy, positive and negative predictive values (with binominal 95% CIs in **Paper I**), and number of false positive/negative findings were calculated for each observer, for the majority rating (**Paper II and III**), the expert majority (**Paper I**) and for the clinical report (**Paper IV**).
2. Differences in sensitivity, specificity and accuracy between observers and the expert majority were collectively analyzed with Cochran's exact Q test; if significant, McNemar's test was used for pairwise analysis of the same, and the prevalence of imaging findings and surgical staging was compared using Cochran's exact Q test (**Paper I**).

Odds ratios for the presence of deep myometrial invasion, cervical stromal invasion and lymph node metastases at surgical staging were calculated using Fisher's exact test for dichotomous variables and univariate logistic regression for continuous and categorical variables.

For the examinations of relationships between clinical histological tumor characteristics and imaging quantifications, univariate linear regression models (**Paper II**), Mann-Whitney U test, Jonckheere-Terpsta trend test (**Paper III and IV**), Kruskal-Wallis H test, X^2 test and binary logistic regression analysis (**Paper III**) and multivariate logistic regression analyses (**Paper IV**) were used.

Receiver operating characteristic (ROC) analyses were utilized to evaluate the diagnostic value of the different tumor quantifications in identifying important staging parameters. ROC analyses were also applied to determine the best cut-off values for ADC (**Paper II**), tumor size (**Paper III**) and MTV (**Paper IV**), by aiming for values achieving the best separation between groups by the Youden index.

Differences in time to recurrence or progression (**Paper III**) were assessed by the Mantel-Cox (log-rank) linear trend test. The Cox proportional hazards model was used to study effects on survival and univariate analyses using Kaplan-Meier was applied to explore the prognostic value of different tumor size categories.

In **Paper III** sample size was estimated by X^2 test using software East4 2005 (Cytel Software Corp). For all other analyses, SPSS 20.0-22.0 (Chicago, IL, USA) and STATA 12.1 (College Station, TX) were used. All reported *P* values were two-sided and considered significant when < 0.05.

5. Main results

In **Paper I**, we evaluate the interobserver agreement among radiologists evaluating a cohort of 57 consecutive patients with histologically confirmed endometrial carcinoma, all prospectively included in a study of preoperative 1.5-T MRI. We report overall and pairwise agreement among four readers blinded to clinical information and results of surgical staging in the evaluation of three key features for risk assessment in endometrial carcinoma: deep myometrial invasion (tumor invading ≥ 50% of the myometrium), cervical stromal invasion and the presence of lymph node metastases. Overall agreement among all observers was moderate for cervical stroma invasion (κ=0.50 [95% CI 0.27–0.73]) and lymph node metastases (κ=0.56 [0.09–0.80]) and fair for deep myometrial invasion (κ=0.39 [0.26–0.55]). Sensitivity (specificity) values for the four observers were 72–92% (44–63%) for deep myometrial invasion, 38–63% (82–94%) for cervical stroma invasion and 25–38% (90–100%) for lymph node metastases.

In **Paper II**, we explore possible correlations between tumor apparent diffusion coefficient (ADC), morphological tumor volume, and clinical and histological characteristics in 105 consecutive endometrial carcinoma patients and evaluate interobserver agreement for preoperative staging by MRI and for ADC measurements. Analyses of ADC values in relation to histomorphological characteristics and tumor volume showed that the mean tumor ADC was significantly lower in tumors with deep myometrial invasion (ADC = 0.75×10^{-3} mm2/s) compared with tumors with superficial or no myometrial invasion (ADC = 0.85×10^{-3} mm2/s; $p < 0.001$). ADC was negatively correlated to tumor size ($p = 0.007$). The interobserver agreement was fair ($\kappa = 0.32$) for depth of myometrial invasion, good for cervical stromal invasion ($\kappa = 0.66$), and moderate for lymph node metastases ($\kappa = 0.54$), and the interobserver variability for ADC value measurements was low (ICC = 0.60).

In **Paper III**, we investigate the relation between preoperative tumor size based on MRI and the surgical pathological staging parameters (deep myometrial invasion, cervical stromal invasion and metastatic lymph nodes) in a cohort of 212 consecutive

patients with histologically confirmed endometrial carcinoma. The overall aim is to assess the prognostic impact of tumor size in endometrial carcinomas, and we find that anteroposterior tumor diameter independently predicts deep myometrial invasion (P = 0.001), whereas CC tumor diameter tends to independently predict lymph node metastases (P = 0.06). Based on ROC curves, the following tumor size cut-off values are identified: anteroposterior diameter greater than 2 cm predict deep myometrial invasion (unadjusted odds ratio [OR], 12.4; P < 0.001; adjusted OR, 6.7; P < 0.001) and CC diameter greater than 4 cm predict lymph node metastases (unadjusted OR, 6.2; P < 0.001; adjusted OR, 4.9; P = 0.009). Large tumor size is associated with reduced progression/recurrence-free survival (P ≤ 0.005 for all size parameters), and CC diameter has an independent impact on survival (adjusted hazards ratio, 1.04; P = 0.009). The interobserver variability for the different size measurements was also calculated, and proved very low (ICC 0.78-0.85).

In **Paper IV**, we prospectively examine the diagnostic value of 18F-FDG-PET/CT for preoperative staging in endometrial carcinomas and possible correlations between 18F-FDG-PET/CT specific imaging quantifications and clinical and histological characteristics in 129 consecutive endometrial carcinoma patients. Sensitivity (specificity) and accuracy of FDG-PET/CT for the detection of lymph node metastases are 77-85% (91-96%) and 89-93%, respectively. SUVmax, SUVmean, MTV and TLG are significantly related to deep myometrial invasion, presence of lymph node metastases and high histological grade (p<0.015 for all), and independently predict deep myometrial invasion (p<0.015) and lymph node metastases (p<0.025) after adjusting for preoperative histological risk (based on subtype and grade) in endometrial biopsies. Optimal cut-off values for MTV in predicting deep myometrial invasion (20 ml) and presence of lymph node metastases (30 ml), yield ORs of 7.8 (p<0.001) and 16.5 (p=0.001), respectively.

6. Discussion

6.1 METHODOLOGICAL CONSIDERATIONS

The patient cohort included in this thesis is population-based, as all patients have been consecutively recruited since the beginning in 2010. Exclusion criteria have been lack of suitability or adequacy of the patient, such as severe claustrophobia or dementia which have been the case in very few patients. Retrospectively, also patients with unconfirmed diagnosis and cases where the diagnosis was changed after surgery have been excluded. Finally, we excluded patients in whom the imaging performed was not interpretable due to artifacts or technical errors.

Even if Haukeland University Hospital serves a population of about one million inhabitants, the single institution design of these studies is a study limitation, and further studies including multiple centers is warranted to confirm that the current findings can be reproduced independent of institution size and location. In **Paper I**, the sample size is relatively small, in **Paper II**, **III** and **IV**; however, the sample sizes are larger. In all studies, however, the sample size seems satisfactory for the line of conclusions drawn.

In both **Paper I** and **Paper III**, the imaging protocols were based on the guidelines of the European Society of Urogenital Imaging and thus expected to be quite similar to those applied in most centers treating endometrial cancer patients. In **Paper I**, the choice of imaging protocols may have affected the staging accuracy and the interobserver agreement, and one may speculate that application of newer MRI techniques such as DWI and DCE imaging could improve these parameters, although this would call for an interobserver evaluation of these methods as well.

In addition to the interobserver variability which is crucial to examine in order to validate the clinical application of radiological examinations, intraobserver variability is another significant feature of radiological image reading. This has not been assessed in any of our studies, but is expected to be lower than the interobserver variability, thus probably on an acceptable level in our material.

For the DWI in **Paper II**, we acknowledge that an optimization of the protocol could have been favorable. We could have used at least two orthogonal planes instead of one and with more than two b-values in the ADC map. Our protocol is, however,

similar to that reported in comparable studies at the time (62, 104). Also, the method for calculation of tumor volume in this study may be a limitation as it assumes a spherical tumor shape. Alternatively, we could have drawn a manual ROI on every single slice resulting in a perhaps more precise tumor volume. Assuming a spherical tumor shape seemed however more feasible in clinical practice, as the alternative would have been much more time consuming.

For the size and location of the tumor ROIs measuring the ADC value in **Paper II**, there was no absolute standardization, giving rise to some variation between readers. Due to variable tumor size and shape, however, exact criteria for ROI size and placement were difficult to define. Still, we do not believe that varying ROI sizes and shapes have largely affected the results, as two of the readers measured very similar ROIs, and linear regression analysis showed that ROI size was not correlated to ADC value for any of the readers (p>0.05).

Finally, there is a certain limitation in the fact that the ROC analyses are conducted *a posteriori* in **Paper II, III and IV**. It may have been conceivable to prespecify a cut-off value by implementing a learning dataset including a smaller number of patients from the same patient population and achieve *a priori* cut-offs for utter validation (105). However, our patient cohort is presently considerably extended, and we plan to validate the proposed cut-off values in this larger, consecutive patient group.

6.2 DISCUSSION OF RESULTS

6.2.1 Inter-rater agreement

Inter-rater variability is a crucial feature in evaluating the accuracy of a diagnostic test. In order to secure reproducibility, inherent subjectivity must be low, and concordance between measures high (106). In our studies we have observed various degrees of agreement between readers, both for image interpretations and quantifications. Diagnostic imaging suffer from a certain degree of variability since most images are read and interpreted by humans (in contrast to computer read imaging); yet many imaging techniques and diagnostic tests are implemented in the clinic before measures of intra- and interobserver variability has been thoroughly assessed (107).

In in **Paper I** we found modest agreement among four readers on preoperative staging of endometrial carcinomas by MRI, varying from fair (κ=0.39) for the presence of deep myometrial invasion to moderate (κ=0.50/0.56) for cervical stromal invasion and lymph node metastases, respectively. This study comprising 57 endometrial carcinoma patients is to the best of our knowledge the largest and most comprehensive report on interobserver variability for pelvic MRI after implementing the revised FIGO 2009 system. Similar results for interobserver agreement were found in **Paper II,** comprising a larger patient cohort (n=105) and with readers having access to the b1000 DWI series and the corresponding ADC maps during the image interpretation**. In Paper II** the agreement between the three readers was fair (κ=0.32) for deep myometrial invasion, good (κ=0.66) for cervical stromal invasion and moderate (κ=0.54) for the presence of lymph node metastases. Interestingly, the agreement for these clinically relevant staging parameters was apparently not affected by the readers' access to the b1000 DWI series and the corresponding ADC maps during the image interpretation, series that were not accessible during the reading of the images in **Paper I**.

Previous studies of preoperative MRI staging of endometrial carcinomas include only two readers (108-110), and report good interobserver agreement on T2-weighted imaging for deep myometrial invasion (κ=0.66/0.67 at 3.0 and 1.5 T, respectively), cervical stromal invasion (κ=0.77/0.76) and lymph node metastases (κ=0.64/0.74) (108), good to excellent agreement on 3.0 T T2-weighted imaging (κ=0.63), DCE T1-weighted imaging (κ=0.84) and fused DWI (κ=0.79) (109), and good to excellent agreement on 1.5 T T2-weighted imaging (κ=0.91) and DWI (κ=0.74) and moderate agreement on DCE T1-weighted imaging (κ=0.45) (110). Compared with these reported numbers, our figures for interobserver agreement seem to be in the lower range. There is no obvious explanation for this apparent lower agreement in our studies. We find that agreement is relatively similar among both experienced and less experienced readers, indicating that the duration of training in pelvic MRI (in this case non-standardized) does not have significant impact on the degree of interobserver variability. It is conceivable that a more standardized and dedicated training program could reduce the interobserver variability, but this remains

unexplored so far. There are some differences between our protocol and those applied by in comparable studies; ours did not include dynamic contrast-enhanced series as used in two of the previous studies (109, 110), but this is not likely to have a large impact on the agreement as the equilibrium phase (with 2 min delay; used in our protocol) is regarded as the optimal phase for assessing deep myometrial invasion (54, 111).

For the quantitative imaging parameters (ADC value in **Paper II**, diameters/volume in **Paper III** and SUVmax/mean, MTV and TLG in **Paper IV**), the interobserver variability was lower than for the staging parameters. ADC measurements have previously shown a high degree of interobserver reproducibility when applied in normal pancreatic tissue (112). Similarly, our interobserver agreement for these measurements was good with an ICC of 0.60. This result suggests that for the evaluation of the depth of myometrial invasion, tumor ADC measurements are less prone to subjective influence than the assessment based on conventional MRI, where the agreement was fair (κ=0.32). In **Paper III**, the interobserver variability for different tumor size measurements at MRI was assessed, to our knowledge as the first study in the literature. Interobserver variability turned out to be very low, and interestingly, there was no striking difference related to the readers' previous experience. Tumor size measurements thus seem to represent robust potential biomarkers for inclusion in future risk stratification models in endometrial cancer. For the quantitative parameters studied in **Paper IV**, the interobserver agreement was moderate for MTV (0.56) and TLG (0.57) and very good for SUVmax (0.98) and SUVmean (0.87). This difference is probably due to the subjective steps involved in the MTV measurement, where the size of the VOI is determined manually in three planes. The SUV measurements are more robust, as SUVmax only depends on the one single voxel with the highest value being included in the VOI. No previous studies of endometrial cancer have assessed the interobserver agreement for PET parameters, but other types of cancer have been examined, reporting ICC of 0.60-1.00 and 0.85-0.97 for SUVmax and SUVmean, respectively (113-115), seemingly in line with our results. One study of interobserver variability in whole-body MTV measurements in small-cell lung cancer (116) found concordance correlation coefficients of 0.90

(good); however, this is a study assessing the whole-body tumor burden, and thus not directly comparable to our study measuring the primary metabolic tumor volume only. Our observations and the literature taken together, it seems that the volume dependent parameters are less robust than the SUV measurements. However, the very similar ROC curves (117) for the different observers in our study, suggest that MTV may still represent a robust imaging biomarker for the prediction of deep myometrial invasion and the presence of lymph node metastases.

6.2.2 Diagnostic performance of loco-regional staging

Improved preoperative imaging tools to enable tailoring of surgical and adjuvant therapies for endometrial carcinoma patients have long been highly warranted, especially to reduce the need for staging lymphadenectomy, which is currently frequently performed despite lack of documented survival benefit (2). MRI is presently the preferred imaging method for preoperative evaluation of endometrial carcinoma patients (1, 31, 56), but the method has some limitations (56, 118). In the present **Paper I**, the staging performance of MRI for deep myometrial invasion for all four observers was mostly within the lower range of what has been previously reported (sensitivity of 72-92% among the four readers), and with a lower specificity (44-63%). Recent literature reports 51-89% and 72-100%, respectively, for these staging criteria (54, 56, 59-61, 108, 118-125). One explanation for our lower specificity may be the tendency to overestimate the prevalence of deep myometrial invasion, a tendency also reported by others (110, 126). The study setting may also have contributed to over-reading of abnormal findings, as opposed to the reading situation in an every-day clinical setting.

In **Paper II**, where the patient cohort was larger, and the three readers had access to the DWI series and the ADC map in addition to the conventional MRI, the sensitivity for prediction of deep myometrial invasion was lower, (68-74%), but the specificity somewhat higher (56-93%) than in **Paper I**. One may speculate if the readers have changed their staging strategy after learning that they had a tendency to overstage deep myometrial invasion in **Paper I**. The staging performance may

potentially also have been improved by adding at least two orthogonal planes in the DWI protocol and fused DW and T2/T1 CE imaging for the staging purposes.

For the important staging criterion of lymph node spread, the staging performance in **Paper I** was low with a sensitivity of 25-38%. Still, these numbers are comparable to what have been reported by others (17-80%) (54, 59, 60, 108, 120, 127). In **Paper II,** the sensitivity had increased (38-46%), but must still be characterized as modest. We never aimed to perform a detailed comparison node by node of imaging findings and histopathological lymph node findings. All suspicious nodes (based on the size criterion of ≥ 10mm short-axis diameter (128) were, however, known to the surgeons preoperatively by the routine imaging report, and attempted removed and sent to histopathological evaluation. The use of additional malignancy criteria for lymph nodes (irregular contour, central necrosis, and increased short axis to long axis ratio) (128) may potentially have increased sensitivity in both studies, but would also have introduced an additional element of subjectivity in the evaluation, possibly decreasing the reproducibility and thus, the validity of the method.

In **Paper IV,** FDG-avidity was used to evaluate potential metastatic lymph nodes, and size was not taken into consideration, except for the understanding of FDG-PET's limited value in characterizing structures < 7mm (129). The sensitivity for detection of metastatic lymph nodes by FDG-PET/CT in **Paper IV** was 77-85% for the two readers and the clinical report. This is within the higher range compared to most previous studies reporting sensitivities of 60-83% (32, 33, 35, 71, 130). An interestingly high negative predictive value (NPV) of 97-98% confirms two previous reports finding NPV of 95% (71) and 96% (33), and indicates that FDG-PET/CT presently is the most promising method for ruling out the presence of lymph node metastases and need for a staging lymphadenectomy. This could be implemented in the decision-making and planning of surgery in order to avoid potentially harmful short and long- term side effects from unnecessary staging procedures.

For the staging criterion of cervical stromal invasion, none of our studies yielded high detection rates, **Paper I** reporting a sensitivity of 38-63%, **Paper II;** 44-56% and **Paper IV**; 25-33%. A recent review of 12 studies reporting on the reliability of contemporary MRI in the assessment of high-risk features in endometrial

carcinoma, including 1153 patients, (57) reported a pooled sensitivity of 57% for the detection of cervical stromal invasion, seemingly comparable to our results in **Paper I** and **II**. Comparable reports for the detection of cervical stromal invasion for FDG-PET/CT seem to be lacking in the literature, thus we do not know if our sensitivity in **Paper IV** is lower than expected. Anyhow, it seems fair to conclude that FDG-PET/CT is less accurate in the detection of cervical involvement from endometrial cancer than MRI. On the other hand, for stage II disease evidence from randomized trials for any survival benefit from radical hysterectomy compared to simple hysterectomy is missing, leaving no strong evidence that this distinction is critical for surgical therapy. The prognostic information will be obtained when assessing the hysterectomy specimen, allowing tailored adjuvant therapy for stage II disease nevertheless.

6.2.3 Imaging quantifications

Several risk models based on surgicopathological tumor features have been proposed in endometrial cancer (83, 131, 132), based on histologic grade, subtype and tumor extent, including gross tumor size. The limitation of these models is obviously the fact that the surgicopathological staging results are only available postoperatively, and cannot be used in a preoperative risk stratification aiming to tailor the extent of surgery. Advanced preoperative imaging grants the possibility to establish several tumor measurements for implementation in risk stratification models in order to individualize not only adjuvant treatment, but also primary surgery.

In **Paper II**, the tumor ADC value in DWI was explored as a potential biomarker for tumor aggressiveness in endometrial carcinoma. We found that the tumor ADC value was significantly lower in tumors with deep myometrial invasion, and that tumor volume was negatively correlated to tumor ADC value. Low tumor ADC value reflects restricted diffusion of water molecules. Carcinomas are expected to have increased cellularity due to the abnormal growth pattern of malignant cells, leaving less extracellular space for water molecule diffusion. Two previous studies including cohorts of 48 (109) and 70 (133) patients contrast our finding of lower ADC value in tumors with deep myometrial invasion, however, the negative correlation

between tumor ADC value and volume is supported by some previous studies (109, 134), though not all (133). Tumor volume is an established indicator for aggressive disease in many cancer types (135), and a lower ADC value in large tumors may reflect an increased cellular density in a presumably faster growing tumor. As deep myometrial invasion is an established marker for aggressive disease in endometrial carcinomas (101), low tumor ADC values in both large and deeply infiltrating tumors go well with the current literature in the field.

  Paper III reported a significant predictive value of preoperative tumor size measurements based on MRI to identify deep myometrial invasion and lymph node metastases. We also found that survival was significantly influenced by tumor size, also after adjusting for preoperative risk profile based on the results of endometrial biopsy. All the measured tumor size parameters (all three orthogonal planes) predicted deep myometrial invasion, in accordance with the findings of Todo et al (136) who reported high volume indexes (defined as the product of maximum AP, TV and CC tumor diameters in MRI) to be associated with deep myometrial invasion. Unlike Todo et al, our study also explored the impact of the different size measurements when evaluated independently in a multivariate model including preoperative risk status based on endometrial biopsy. The AP diameter then proved to be the only size variable independently predicting deep myometrial invasion. The proposed cut-off of 2 cm for the AP diameter was achieved using ROC curves, and interestingly, this cut-off turned out to have comparable accuracy (sensitivity, specificity) to conventional MRI reading for the identification of deep myometrial invasion: 79% (66%, 86%) and 74% (70%, 77%), respectively. AP measurement is a relatively simple approach compared to conventional MRI reading, and possibly easier attained, also for inexperienced readers. A macroscopic tumor diameter greater than 2 cm in hysterectomy specimens has been reported to independently predict lymph node metastases and survival (137), but this finding is not consistently confirmed in the literature (131, 138). Another report based on macroscopic gross inspection of the cut-up of the uterus, found that a maximum tumor dimension greater than 3.75 cm independently predicted deep myometrial invasion, distant recurrence and death (139). In our study, the CC diameter was almost unexceptionally the largest tumor diameter, so our cut-off of 4 cm seems to be in line

with Chattopadhyay et al (139), even if tumor measurements on macroscopic fresh tissue is not directly comparable to tumor measurements on MRI, due to the potentially different planes of measurement and the differences in stretching and compression of tumor tissue ex vivo compared to in vivo. However, large tumor size as a predictor of increased metastatic potential and unfavorable prognosis in endometrial carcinomas seems to be broadly supported in the present literature (131, 136-141).

The significant impact of tumor size (specifically AP diameter>2 cm and CC diameter>4 cm both independently and combined) on progression/recurrence free survival lacks comparable data in current literature, but we suggest further exploration of these tumor size parameters in relation to other preoperative biomarkers such as p53, hormone receptor and DNA ploidy status in preoperative biopsies and functional imaging parameters from MRI or PET/CT, which also provide preoperative prognostic information (134, 142-145).

Paper IV suggests MTV in FDG-PET/CT as a potential useful tool in preoperative risk stratification in endometrial carcinoma. The proposed cut-offs of 20 ml for deep myometrial invasion and 30 ml for lymph node metastases interestingly improve sensitivity (specificity) of detection; 79% (68%) and 85% (76%) respectively; compared to the clinically established method based on assessment of histologic subtype and grade in preoperative biopsies, which in this cohort yielded sensitivity (specificity) of 47% (72%) for deep myometrial invasion and 85% (66%) for lymph node metastases. In line with this, MTV independently predicted deep myometrial invasion and lymph node metastases, after adjusting for the preoperative biopsy risk assessment in logistic regression analyses. These results support one recent study of 56 endometrial carcinoma patients (69), that reports MTV and TLG as significant predictors of several clinicopathological characteristics and superior to SUVmax for stratification into high- and low-risk. Two other recent studies, both including cohorts of 76 endometrial carcinoma patients (71, 78), propose MTV as a promising predictor of lymph node metastases and poor outcome.

An MTV cut-off value of 9.4 ml has been suggested in one prior study of 56 patients (69), aiming to differentiate between high-risk and low-risk tumors (based on

surgicopathological assessment). This dissimilar result may be explained by unlike definitions between high- and low-risk groups and the higher proportion of patients with advanced FIGO stage in this smaller cohort of 56 patients. To our knowledge, **Paper IV** is the first study proposing cut-offs for MTV based on ROC curves predicting deep myometrial invasion and presence of lymph node metastases.

All four parameters measured in the FDG-PET images (SUVmax, SUVmean, MTV and TLG) were independent predictors of deep myometrial invasion and lymph node metastases after adjusting for high-risk based on histological subtype and grade in preoperative uterine biopsies. Previous studies have also assessed the prognostic value of SUVmax in cohorts of 101, 268 and 56, respectively (34, 69, 75), but none of these adjusted for the routinely applied methods for preoperative risk assessment. A recent review including 10 studies and 771 patients (70) concluded that SUVmax may aid in prediction of outcome, but that the value in preoperative risk stratification is limited, even if a statistically significant difference in SUVmax of high- and low-risk groups was present. SUVmean is less studied in the literature, but was associated with FIGO stage, histologic grade, lymphovascular space invasion and maximum tumor size (similar to SUVmax) in a study of FDG-PET/CT in 60 endometrial carcinoma patients (72). Our findings that MTV and TLG are associated with the depth of myometrial invasion and tumor invasion of the cervical stroma, are in line with three previous, smaller studies including cohorts of 76, 84 and 56 patients (69, 71, 146).

When performing quantifications in PET tumor imaging, it is crucial to be aware of the partial volume effect (PVE) when tracer uptake in small tumors is measured, and when imaging quantification methods are used in clinical practice and research. PVE is the result of two distinct phenomena; the first is a three-dimensional image blurring introduced by the limited spatial resolution in PET images. This phenomenon causes a so-called "spill-over" between regions, and can make tracer uptake in a small structure look larger, but dimmer (147). The second phenomenon is the tissue fraction effect, referring to the fact that each voxel in the image usually consists of more than one type of tissue, and the uptake measured in the voxel is the mean of different signal intensities. This effect is especially present on the edges of tracer-positive structures, as the voxels here often consist of both avid tissue and

background tissue, and is often referred to as "spill-out" (a well-known phenomenon also in CT and MR imaging). To counteract these effects in our FDG-PET/CT study, all imaging was obtained at the same PET/CT scanner with standardized acquisition, processing and analyses of imaging data.

6.2.4 Incidental findings

When introducing a new imaging modality in a cancer patient group, the cost-effectiveness of the method is an issue of consideration. FDG-PET/CT is highly sensitive for detecting increased cellular metabolism, but the cause of increased metabolism is not always obvious and additional imaging work-up, blood tests, biopsies and clinical follow-up may be required.

In the population based patient cohort in **Paper IV**, four synchronous cancers were detected (one lung cancer, one breast cancer, one thyroid cancer and one B-cell lymphoma) all with potentially poorer prognosis than the primary endometrial cancer. Incidental findings have not been published for a cohort of endometrial carcinoma patients before, but the finding of synchronous cancers in FDG/PET-CT imaging is previously reported for other primary cancer types (148, 149), and the prevalence seems to be comparable. A systematic and thorough cost-benefit analysis of FDG/PET-CT has not been aimed for in this study, and would probably be difficult to attain in this mixed, casuistic group, but we may speculate that the four patients with synchronous cancers detected and treated with curative intent particularly benefitted from the scanning. Whether this benefit could be considered cost-effective, needs to be elucidated in more comprehensive studies. In 13 patients with incidental findings, however, no significant pathology was confirmed during additional work-up, illustrating that follow-up examinations often yield negative results also known from the literature (148, 149).

7. Conclusions

Interobserver agreement and diagnostic accuracy are modest for standard MRI in the evaluation of depth of myometrial invasion, the presence of cervical stromal invasion and lymph node metastases in endometrial carcinomas. In a population-based cohort, standard MRI alone is suboptimal for preoperative staging purposes, and improved imaging methods, possibly combined with histological and molecular classifications of endometrial biopsies (43-45) are warranted for improved preoperative risk stratification and promotion of individualized surgery (**Paper I**).

Low tumor ADC value is associated with the presence of deep myometrial invasion, and the ADC value is negatively correlated to tumor volume in endometrial carcinomas. The interobserver agreement for ADC measurements is higher than that of preoperative staging by standard MRI with DWI. Measurement of tumor ADC values in endometrial carcinomas may contribute to the preoperative identification of high-risk patients with deep myometrial invasion (**Paper II**).

Preoperatively assessed tumor size by MRI predicts the presence of deep myometrial invasion, cervical stromal invasion and lymph node metastases and is a considerable prognostic factor in endometrial carcinomas. We propose cut-off values of 2 cm for AP diameter and 4 cm for CC diameter to be clinically useful by alarming the clinician of a potentially high-risk endometrial cancer. The two tumor size measures, both individually and in combination, should be tested further in a prospective biomarker implementation study of preoperative risk stratification models in endometrial carcinomas (**Paper III**).

FDG-PET/CT is a valuable imaging tool for the detection of lymph node metastases in endometrial carcinoma patients, and particularly precise in identifying patients with low likelihood of lymph node spread. PET specific image quantification parameters all correlate positively with the presence of deep myometrial invasion and lymph node metastases. The proposed cut-off for MTV outperforms histologic subtyping and grading from endometrial biopsies which is currently used in clinical practice to

preoperatively stratify patients into high- and low-risk groups (**Paper IV**). Thus, MTV is a promising biomarker for preoperative risk stratification in endometrial cancer.

8. Future perspectives

Some future perspectives have already been highlighted, such as the need for cost-effectiveness studies of the implementation of new imaging tools like FDG-PET/CT (Incidental findings paragraph, 7.2.4). Analyses must, in addition to the cost/benefit of incidental findings, also consider the costs of imaging compared to the costs related to unnecessary and potentially harmful treatments and/or staging procedures. In the process of introducing new diagnostic tools, an evaluation of the existing diagnostic algorithm must be performed; including considerations regarding potential exclusion of currently employed diagnostic tests in the preoperative work-up.

The novel imaging biomarkers proposed in this thesis need to be consolidated in large, prospective study settings, where cut-offs are applied *a priori* for the cohort. Such validation will be crucial in order to safely apply the results in an algorithm for individualized treatment. Furthermore, there is need for clinical implementation studies yielding long term outcome data, where risk stratification models are standardly applied. Another aspect worth considering regarding clinical implementation is the importance of robustness of the parameters. A future development of methods for automatic assessments of imaging parameters could potentially increase robustness by ruling out the subjective element of image interpretation, an issue of constant concern in all imaging based diagnostics.

The establishment of new imaging markers also gives an opportunity to relate these novel biomarkers to established biomarkers and create a diagnostic algorithm aiming to more accurately identify high-risk patients preoperatively and thereby tailor therapy coherently. In line with this, the tumor measurement cut-offs from **Paper III** will be included in the MoMaTEC2 trial as part of a risk stratification model.

Furthermore, it would be interesting to investigate the relation between tumor volumes measured on MRI (**Paper III**) and the metabolic tumor volumes measured on FDG-PET (**Paper IV**). We currently do not know how much the morphologic tumor volume contributes to the measured metabolic tumor volume, and further studies are due on this matter.

9. References

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STUDY 3

III

OPEN

Preoperative Tumor Size at MRI Predicts Deep Myometrial Invasion, Lymph Node Metastases, and Patient Outcome in Endometrial Carcinomas

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Objective: The aim of this study was to explore the relation between preoperative tumor size based on magnetic resonance imaging (MRI) and the surgical pathologic staging parameters (deep myometrial invasion, cervical stroma invasion, and metastatic lymph nodes) and to assess the prognostic impact of tumor size in endometrial carcinomas. Interobserver variability for the different tumor size measurements was also assessed.

Methods/Materials: Preoperative pelvic MRI of 212 patients with histologically confirmed endometrial carcinomas was read independently by 3 radiologists. Maximum tumor diameters were measured in 3 orthogonal planes (anteroposterior, transverse, and craniocaudal planes [CC]), and tumor volumes were estimated. Tumor size was analyzed in relation to surgical staging results and patient survival. The multivariate analyses were adjusted for preoperative risk status based on endometrial biopsy. Intraclass correlation coefficients and receiver operating characteristics curves for the different tumor measurements were also calculated.

Results: Anteroposterior tumor diameter independently predicted deep myometrial invasion ($P < 0.001$), whereas CC tumor diameter tended to independently predict lymph node metastases ($P = 0.06$). Based on receiver operating characteristic curves, the following tumor size cutoff values were identified: anteroposterior diameter greater than 2 cm predicted deep myometrial invasion (unadjusted odds ratio [OR], 12.4; $P < 0.001$; adjusted OR, 6.7; $P < 0.001$) and CC diameter greater than 4 cm predicted lymph node metastases (unadjusted OR, 6.2; $P < 0.001$; adjusted OR, 4.9; $P = 0.009$). Large tumor size was associated with reduced progression/recurrence-free survival ($P \leq 0.005$ for all size

parameters), and CC diameter had an independent impact on survival (adjusted hazards ratio, 1.04; $P = 0.009$). The interobserver variability for the different size measurements was very low (intraclass correlation coefficient, 0.78–0.85).

Conclusions: Anteroposterior tumor diameter greater than 2 cm predicts deep myometrial invasion, and CC tumor diameter greater than 4 cm predicts lymph node metastases. Tumor size is a strong prognostic factor in endometrial carcinomas. Preoperative tumor measurements based on MRI may potentially improve preoperative risk stratification models and thus enable better tailored surgical treatment in endometrial cancer.

Key Words: Endometrial carcinoma, Tumor size, Magnetic resonance imaging, Prognosis

Endometrial cancer is the most common gynecologic malignancy in industrialized countries, and the incidence is increasing.[1] Surgical treatment is planned based on preoperative assessment of histological subtype, grade, and depth of myometrial invasion. Surgical International Federation of Gynecology and Obstetrics (FIGO) stage is documented to be the strongest prognostic factor in endometrial carcinoma, thus guiding adjuvant therapy in addition to the assessment of histologic subtype and grade in the hysterectomy specimen.[1–3]

Magnetic resonance imaging (MRI) has long been considered the diagnostic imaging method of choice for preoperative staging of endometrial carcinomas.[4–6] The presence of deep myometrial invasion and cervical stroma invasion could be visualized, and enlarged lymph nodes could be detected. However, conventional pelvic MRI has reportedly limitations in accuracy in the detection of the staging parameters, in particular for detecting lymph node metastases.[6,7] Interobserver variation between radiologists for all staging parameters also represents a source of inaccuracy.[8]

As opposed to the cervical cancer FIGO staging system,[6] FIGO staging for endometrial cancers does not include tumor size measurements. Nevertheless, large macroscopic tumor size, assessed in the hysterectomy specimen, has long been known to predict lymph node metastasis and poor survival in patients with endometrial carcinomas.[9–13] Recent publications support that tumor volume based on preoperative MRI predicts lymph node metastases and has prognostic impact in endometrial cancer.[14,15] However, the reproducibility of MRI-based tumor measurements has, to our knowledge, not yet been explored. Furthermore, the optimal cutoff value for risk assessment based on tumor size is not yet defined.

The primary objective of this study was to explore the relationship between different preoperative tumor size measurements using MRI and the surgical pathologic staging parameters deep myometrial invasion, cervical stroma invasion, and metastatic lymph nodes in endometrial carcinoma patients. The secondary objectives were to assess the interobserver variability for the different tumor measurements and to explore the value of these preoperative tumor size measurements to identify patients with poor outcome.

MATERIALS AND METHODS

Patient Series, Study Setting, and Clinical Outcome

This prospective study was conducted under institutional review board–approved protocols with informed consent from all patients. From April 2009 to November 2013, preoperative pelvic MRI was performed in 212 patients in whom the diagnosis of endometrial carcinoma was histologically verified at surgical staging. All patients were diagnosed and treated at the same university hospital serving a population of ~1 million inhabitants.

Follow-up data regarding recurrence, progression, and survival have been collected from patient records and from correspondence with the responsible primary physicians or gynecologists. The date of the last follow-up was July 2014, and the mean (range) follow-up for survivors was 25 (0–58) months.

Histological Diagnosis

All patients were surgically staged according to the 2009 FIGO staging criteria.[2] The responsible surgeon decided the extent of sampling, balancing preoperatively known histologic risk factors and the patient's comorbidity. The patient group without lymph node sampling is typically older with more myometrial invasion, otherwise not different from the sampled group.[16] Surgical specimens were sectioned along the longitudinal plane of the uterus, and myometrial invasion and cervical stromal invasion were estimated grossly and confirmed microscopically according to standard procedures.[17] Routine histopathology reports were generated without knowledge of preoperative MRI findings. The pathologists documented number and size of metastatic lymph nodes.

MRI Protocol

Contrast-enhanced (CE) MRI was performed on a 1.5-T Siemens Avanto Running Syngo MR B17 (Erlangen, Germany) using a 6-channel body coil[8] in accordance with the guidelines of European Society of Urogenital Imaging.[5] The mean (range) interval between MRI examination and surgical staging was 11.3 (0–98) days.

Data Analysis

All images were deidentified and read independently by 3 observers who were blinded for tumor stage, histological diagnosis, and patient outcome. Observer 1 and 2 are consultants with more than 10 years of experience with pelvic MRI. Observer 3 included 2 junior radiologists (both having more than 4 years of experience with pelvic MRI); one read the first 105 MRI examinations, and the other read the following 111 examinations.

All observers reported imaging findings on a standardized form. Presence of deep myometrial invasion (tumor invading half or more of the myometrial wall), cervical stroma invasion (disruption of the low-signal intensity cervical stroma on T2-weighted images), and enlarged pelvic or para-aortic lymph nodes (largest short-axis diameter >10 mm) were recorded. Maximum tumor diameters were measured in 3 orthogonal planes: anteroposterior (AP) and transverse (TV) diameters on axial CE T1-weighted oblique images (perpendicular to the long axis of the uterus) as well as craniocaudal (CC) diameters on sagittal T2-weighted images (Fig. 1). Tumor volume was then estimated based on these measurements of maximum tumor diameter in 3 orthogonal planes using the following equation: tumor volume = AP diameter × TV diameter × CC diameter/2.

To establish the overall imaging findings based on the recordings by all 3 observers, we also computed a new data set ("consensus reading") in which the value given by the majority of the observers was recorded for categorical variables, and the median value was recorded for continuous variables.

Statistical Analysis

Estimation of sample size was done by χ^2 test using software East4 2005 (Cytel Software Corp). To achieve 90% power of detecting a 20% higher occurrence of positive markers in patients with metastatic lymph nodes (5% vs 25%) at a 5% significance level, 101 patients were needed for inclusion, defining the minimum number of patients to be included in the MRI study. To reach 90% power detecting a 30% difference in 5-year survival (90% for patients with markers within reference range vs 60% with pathologic markers) at a 5% level of significance, 65 patients were needed, assuming a positive to negative ratio of the markers of 1:3.

Clinical and histopathology staging parameters were analyzed in relation to tumor size measurements using Mann-Whitney U test, Kruskal-Wallis H test, Jonckheere-Terpsta trend test, χ^2 test, and binary logistic regression analysis. Intraclass correlation coefficient was used to assess the consistency and reproducibility of tumor size measurements, and minimal detectable change (1.96 × standard error of the mean × square root of 2) for the measured diameters was also calculated.

Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic value of the different tumor size measurements in identifying deep myometrial invasion, cervical stroma invasion, and lymph node metastases. The optimal cutoff values (rounded to centimeters) were determined for which the best separation in Youden index between groups was achieved.

Differences in time to recurrence (for patients considered cured by primary treatment) or progression (for patients known to have residual disease after primary treatment) were assessed by the Mantel-Cox (log-rank) linear trend test. The Cox proportional hazards model was used to study the effect on survival of continuous variables. The prognostic value of different tumor size categories was explored with univariate analyses using Kaplan-Meier, and groups with similar survival were merged. McNemar test was used for pairwise analysis for differences in sensitivity, specificity, and accuracy. The data were analyzed using SPSS 22.0 (Chicago, IL) and Stata 12.1 (College Station, TX). All reported P values were 2-sided and considered to indicate statistical significance when less than 0.05.

RESULTS

Patients

The median (mean) patient age in the study sample (n = 212) was 66 (66) years (range, 32-93), and 91% (193/212) of the patients were postmenopausal. Applying the FIGO 2009 staging criteria, 55% (116/212) were stage IA (<50%
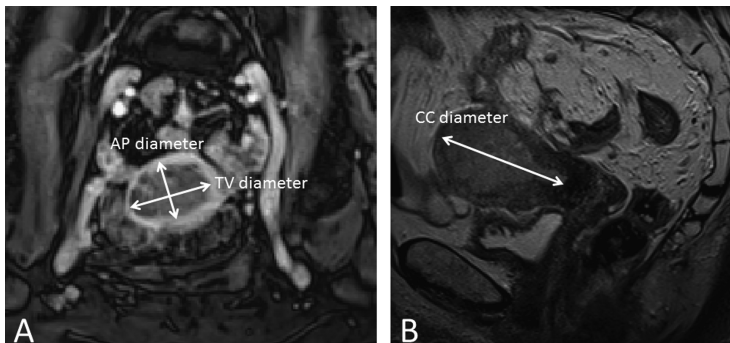

FIGURE 1. Axial oblique CE T1-weighted image (A) and sagittal T2-weighted image (B) for measurements of maximum tumor diameters in 3 orthogonal planes. AP and maximum TV diameters were measured on the axial oblique image (A), whereas CC diameters were measured on the sagittal image (B).

myometrial invasion), 23% (48/212) stage IB (≥50% myometrial invasion), 11% (23/212) stage II (cervical stroma invasion), 11% (24/212) stage III (local or regional tumor spread), and 0% (1/212) stage IV. The histological subtype was endometrioid in 81% (171/212) of which 50% (86/171) were grade 1, 29% (50/171) grade 2, and 17% (29/171) grade 3; whereas 4% (6/171) were ungraded. Clear cell histology was detected in 3% (6/212), serous in 10% (21/212), carcinosarcoma in 4% (9/212), and undifferentiated in 2% (5/212). Metastatic lymph nodes were more frequent in patients with deep myometrial invasion, cervical stroma invasion, high histologic grade, aneuploidy, and body mass index (BMI) greater than 25 (Table 1).

All patients were primarily treated with hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymph node sampling was performed in 85% (181/212) as part of the routine surgical staging procedure. Adjuvant therapy was given to 33% (70/212), chemotherapy in 28% (59/212), pelvic radiation in 5% (10/212), and hormonal treatment in 0% (1/212).

Tumor Size Is Correlated to Surgicopathologic Findings

The mean (median, range) preoperative tumor diameters were 28 (26, 0–113) mm for axial TV diameter, 18 (16, 0–77) mm for axial AP diameter, and 35 (31, 0–102) mm for sagittal CC diameter. The mean (median, range) estimated tumor volume was 19 (6, 0–444) mL. Tumor volume was significantly higher in patients with deep myometrial invasion, cervical stroma invasion, and lymph node metastases at surgical staging and in patients with aneuploidy and high histologic grade (Table 2).

Tumor measurements in the 3 orthogonal planes and tumor volume did all predict the presence of deep myometrial invasion at surgical staging (unadjusted odds ratios [ORs], 1.06–1.13; $P < 0.001$ for all); however, AP tumor diameter was the only size variable independently predicting deep myometrial invasion (adjusted OR, 1.14; $P < 0.001$). Craniocaudal tumor diameter was the only variable predicting cervical stroma invasion (adjusted OR, 1.04; $P = 0.008$). Although all size parameters predicted lymph node metastases in the univariate analyses (unadjusted ORs, 1.02–1.05; $P ≤ 0.004$ for all), only CC tumor diameter tended to independently predict lymph node metastases (adjusted OR, 1.04; $P = 0.06$).

Receiver operator characteristic curves for the different size parameters in the prediction of deep myometrial invasion (Fig. 2A), cervical stroma invasion (Fig. 2B), and lymph node metastases (Fig. 2C) showed that AP diameter had the highest area under the curve (AUC, 0.82) for deep myometrial invasion, whereas CC diameter had the highest AUC for cervical stroma invasion (AUC, 0.66) and for lymph node metastases (AUC, 0.76). Based on these ROC curves, the following cutoff values were identified: AP tumor diameter greater than 2 cm predicts deep myometrial invasion yielding sensitivity/specificity of 66%/86% and an OR of 12.4, and CC tumor diameter greater than 4 cm predicts lymph node metastases yielding sensitivity/specificity of 70%/73% and an OR of 6.2, whereas CC tumor diameter greater than 3 cm tends to predict cervical stroma invasion yielding sensitivity/specificity of 66%/51% and an

TABLE 1. Clinical characteristics and MRI findings in relation to the presence of metastatic lymph nodes at surgical staging in 181 endometrial carcinoma patients

Variable	n	LN+ n = 20 n (%)	LN− n = 161 n (%)	P*
Low-risk group†	72	0 (0)	72 (46)	<0.001
Intermediate-risk group†	51	10 (50)	41 (26)	
High-risk group†	54	10 (50)	44 (28)	
Myometrial invasion				< 0.001
<50%	109	4 (20)	105 (65)	
≥50%	72	16 (80)	56 (35)	
Cervical stroma invasion				0.001
Yes	27	8 (40)	19 (12)	
No	154	12 (60)	142 (88)	
Histologic subtype				0.14
Endometrioid	141	13 (65)	128 (80)	
Nonendometrioid	40	7 (35)	33 (20)	
Histological grade among endometrioid subtype				0.007
Grade 1	70	2 (15)	68 (55)	
Grade 2	42	5 (38)	37 (30)	
Grade 3	25	6 (46)	19 (15)	
Ploidy				0.014
Diploid	77	6 (50)	71 (82)	
Aneuploid	22	6 (50)	16 (18)	
Age, y				0.10
<66	95	7 (35)	88 (54)	
≥66	86	13 (65)	73 (45)	
BMI				0.03
<25	66	3 (15)	63 (40)	
≥25	113	17 (85)	96 (60)	
Tumor size at MRI				<0.001
AP ≤2 cm and/or CC ≤4 cm	136	8 (40)	128 (80)	
AP >2 cm and CC >4 cm	45	12 (60)	33 (20)	
Enlarged lymph nodes at MRI				<0.001
Enlarged lymph nodes	13	9 (45)	4 (2)	
Normal lymph nodes	168	11 (55)	157 (98)	

Significant *P* values are presented in boldface.
*χ^2 Test.
†Risk groups defined in European Society for Medical Oncology guidelines[26]: low risk, endometrioid grade 1/2 with myometrial invasion <50%; intermediate risk, endometrioid grade 1/2 with myometrial invasion ≥50% or endometrioid grade 3 with myometrial invasion < 50%; high risk, endometrioid grade 3 with myometrial invasion ≥50% or nonendometrioid histology

LN+, patients with lymph nodes metastases at surgical staging; LN−, patients without lymph node metastases at surgical staging.

TABLE 2. Tumor volume in relation to clinical and histologic characteristics in 212 endometrial carcinoma patients

Variable	n	Tumor Volume, mL Mean (95% CI)	P*
Myometrial invasion			**<0.001**
<50%	132	7.4 (5.2–9.7)	
≥50%	80	37.5 (23.4–51.6)	
Cervical stroma invasion			**0.049**
Yes	32	33.7 (5.2–62.2)	
No	180	16.1 (11.4–20.8)	
Lymph node metastases			**<0.004**
Yes	20	62.7 (12.0–113.5)	
No	161	13.9 (10.2–17.6)	
Histologic subtype			0.27
Endometrioid	171	13.4 (10.2–16.6)	
Clear cell	6	20.6 (0.0–50.4)	
Serous	21	21.0 (4.9–37.1)	
Carcinosarcoma	9	65.5 (0.0–135.8)	
Undifferentiated/others	5	107.8 (0.0–345.6)	
Histological grade among endometrioid subtype			**<0.001**
Grade 1	86	8.9 (5.6–12.1)	
Grade 2	50	14.7 (9.4–19.9)	
Grade 3	29	26.5 (13.2–39.8)	
Ploidy			**0.015**
Diploid	91	24.7 (12.8–36.7)	
Aneuploid	23	41.1 (21.4–60.7)	
Age, y			0.21
<66	106	15.6 (7.0–24.3)	
≥66	106	22.0 (14.2–29.8)	
BMI			0.38
<25	74	15.1 (9.1–21.1)	
≥25	134	20.9 (12.4–29.4)	

Significant *P* values are presented in boldface.

*Mann-Whitney *U* test for 2 categories and Kruskal-Wallis H test or Jonckheere-Terpsta trend test for multiple categories.

CI, confidence interval.

OR of 2.0 (Table 3). When adjusting for risk status based on preoperative endometrial biopsy and for conventional imaging findings (consensus reading) suggesting deep myometrial invasion, cervical stroma invasion, and lymph node metastases, respectively, AP diameter greater than 2 cm independently predicted deep myometrial invasion (adjusted OR, 6.7), and CC diameter greater than 4 cm independently predicted lymph node metastases (adjusted OR, 4.9), whereas CC diameter greater than 3 cm did not predict cervical stroma invasion (Table 3).

Tumor Size Predicts Progression/Recurrence-Free Survival

The 3 tumor diameter measurements and tumor volume did all predict progression/recurrence-free survival ($P \leq 0.01$ for all size parameters) in endometrial carcinoma patients. In a multivariate analysis including all size parameters and preoperative risk status based on endometrial biopsy, only CC tumor diameter had an independent impact on survival (Table 4, Supplemental Digital Content, http://links.lww.com/IGC/A270). When stratifying patient groups according to the proposed cutoff values for size variables defined by the ROC analyses, patients with AP tumor diameter greater than 2 cm and patients with CC tumor diameter greater than 4 cm had significantly reduced progression/recurrence-free survival ($P \leq 0.03$ for both; Figs. 3A, B). Combining these 2 size criteria yielded similar survival curves among patients with both or 1 size criterion below the cutoff values (the 2 survival curves are thus merged in Fig. 3C), whereas patients with both AP tumor diameter greater than 2 cm and CC tumor diameter greater than 4 cm had significantly reduced progression/recurrence-free survival ($P = 0.004$; Fig. 3C).

Interobserver Variability for Tumor Measurements

The interobserver variability for tumor diameter measurements by the 3 observers was low with intraclass correlation coefficients of 0.78 to 0.85 and minimum detectable change of 14 to 26 mm for the different tumor diameter measurements (Table 5, Supplemental Digital Content, http://links.lww.com/IGC/A270). Furthermore, the AUC values of the ROC curves for prediction of deep myometrial invasion, cervical stroma invasion, and lymph node metastases were not significantly different between observers (Figs. 2D-F).

DISCUSSION

In this large population-based study, we demonstrate a significant predictive value of preoperative tumor size measurements based on MRI to identify deep myometrial invasion and lymph node metastases. Furthermore, tumor size had a significant independent impact on survival also when adjusting for preoperative risk status based on endometrial biopsy. Based on the present study, we propose a risk model with cutoff values of AP tumor diameter greater than 2 cm indicating high risk for deep myometrial invasion and CC tumor diameter greater than 4 cm indicating high risk for lymph node metastases. Having established that the interobserver variability for these different tumor measurements at MRI was very low, we infer that these preoperative tumor measurements with corresponding cutoff values may represent robust biomarkers aiding in the preoperative risk stratification and in planning of tailored surgical treatment in endometrial cancer patients.

Presence of deep myometrial invasion in hysterectomy specimen at surgicopathological staging is associated with an increased risk of lymph node metastases, tumor recurrence, and distant relapse in endometrial carcinoma patients.[3,18] We found that all size parameters predicted deep myometrial invasion, which is in accordance with the findings of Todo et al[14] reporting high volume indexes (defined as the product
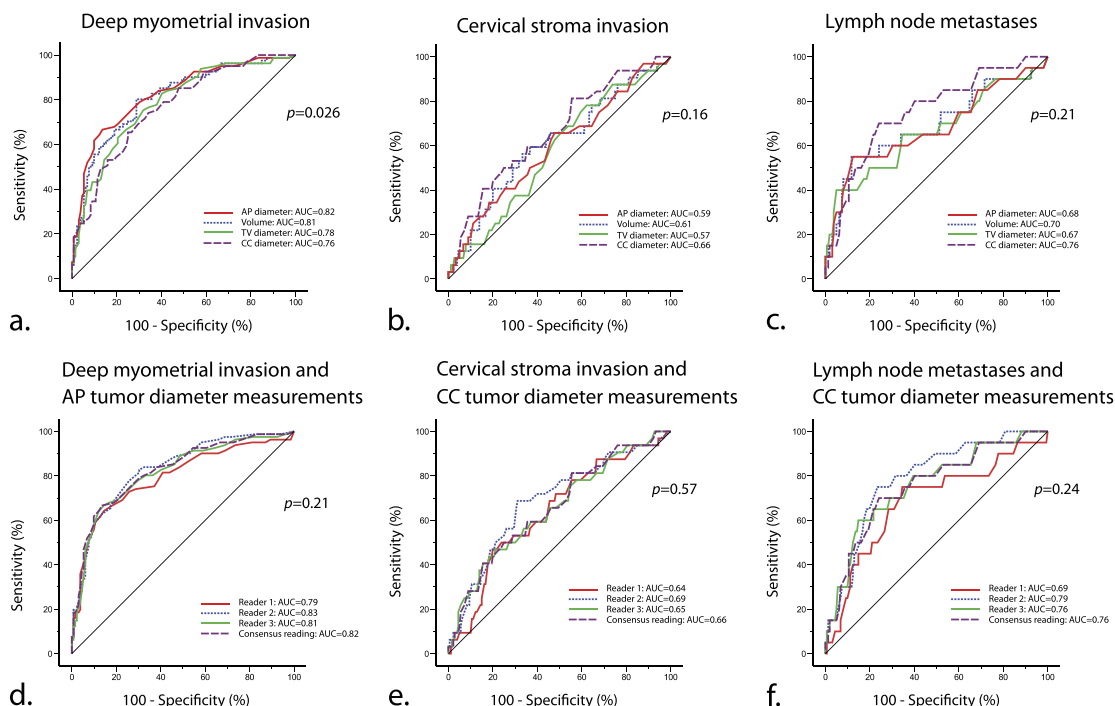
FIGURE 2. Receiver operator characteristic curves for the various tumor size measurements for identification of (A) deep myometrial invasion, (B) cervical stroma invasion, and (C) lymph node metastases and ROC curves for the different observers for (D) AP diameter to predict deep myometrial invasion, (E) CC diameter to predict cervical stroma invasion, and (F) CC diameter to predict lymph node metastases in patients with endometrial carcinoma. *P* values refer to the test of equal AUC values across tumor measurements.

TABLE 3. Sensitivity, specificity, LR+, LR−, and OR for the prediction of deep myometrial invasion (by AP tumor diameter >2 cm), cervical stroma invasion (by CC tumor diameter >3 cm), and lymph node metastases (by CC diameter >4 cm) using surgical staging as the criterion standard

	AP Tumor Diameter >2 cm and Deep Myometrial Invasion	CC Tumor Diameter >3 cm and Cervical Stroma Invasion	CC Tumor Diameter >4 cm and Lymph Node Metastases
Sensitivity, % (positive/total no. patients)	66 (53/80)	66 (21/32)	70 (14/20)
Specificity, % (positive/total no. patients)	86 (114/132)	51 (91/180)	73 (117/161)
LR+	4.9	1.5	2.6
LR−	0.39	0.68	0.41
Unadjusted and adjusted* OR (95% CI); *P* value† for deep myometrial invasion/cervical stroma invasion/lymph node metastases based on size cutoff values	12.4 (6.3–24.5) $P < 0.001$ 6.7 (3.1–14.4) $P < 0.001$	2.0 (0.9–4.3) $P = 0.10$ 1.1 (0.4–2.7) $P = 0.85$	6.2 (2.2–17.2) $P < 0.001$ 4.9 (1.5–15.8) $P = 0.009$

*Adjusted for risk status based on preoperative endometrial biopsy and conventional imaging findings (consensus reading) suggesting deep myometrial invasion, cervical stroma invasion, and lymph node metastases, respectively.

†Binary logistic regression analysis.

LR+, likelihood ratio for positive results: LR+ = sensitivity/(1 − specificity); LR−, likelihood ratio for negative results: LR− = (1 − sensitivity)/specificity.
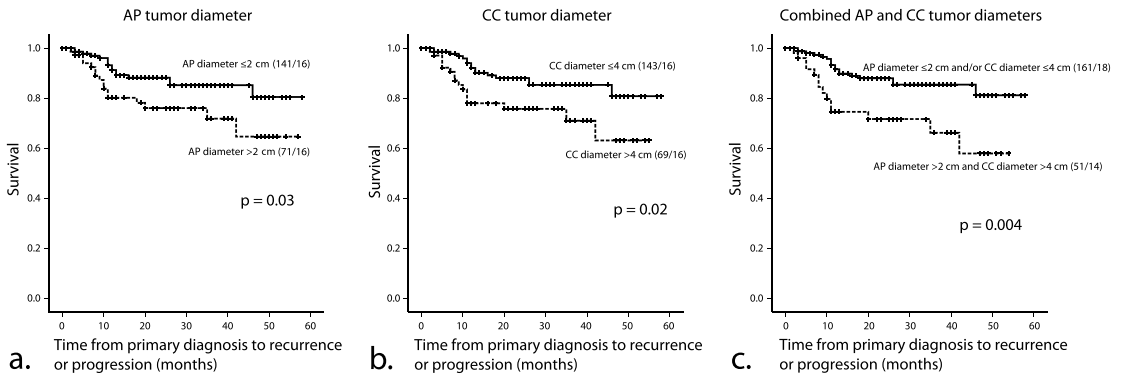
FIGURE 3. Kaplan-Meier survival curves depicting progression/recurrence-free survival according to (A) maximal AP tumor diameter ($\leq$2 vs >2 cm), (B) maximal CC tumor diameter ($\leq$4 vs >4 cm), and (C) a combination of AP and CC tumor diameters (AP $\leq$2 cm and/or CC $\leq$4 cm vs AP >2 cm and CC >4 cm). *P* values refer to the log-rank test for equality of survival distribution.

of maximum AP, TV, and CC tumor diameters at MRI) to be associated with deep myometrial invasion. As opposed to Todo et al,[14] we have also explored the independent impact of the different size variables in a multivariate model including preoperative risk status based on endometrial biopsy. Interestingly, AP diameter, which had the largest AUC (Fig. 2A), proved to be the only size variable independently predicting deep myometrial invasion.

Based on the ROC curve, the optimal cutoff value for prediction of deep myometrial invasion was AP diameter greater than 2 cm, and AP diameter greater than 2 cm independently predicted deep myometrial invasion even when adjusting for conventional imaging findings (consensus reading) suggesting the same. Interestingly, we found that AP diameter greater than 2 cm and MRI indicating deep myometrial invasion had comparable accuracy (sensitivity, specificity) for identification of deep myometrial invasion at surgical staging: 79% (66%, 86%) and 74% (70%, 77%), respectively, however, with significantly better specificity for AP diameter greater than 2 cm (86% vs 77%; *P* = 0.015, McNemar test). Thus, this relatively simple approach of measuring AP tumor diameter yields a diagnostic performance similar to or slightly better than conventional reading for prediction of deep myometrial invasion.

Several surgicopathological risk models for prediction of lymph node metastases have been proposed in endometrial cancer based on histologic grade, subtype, and tumor extent,[10,19,20] among which 1 model includes tumor greater than 2 cm based on the gross inspection of hysterectomy specimen.[10] These models are, however, limited by the fact that they rely on surgicopathological staging results, which are per definition not available preoperatively.

Tumor diameter greater than 2 cm in macroscopic fresh tissue has been reported to independently predict lymph node metastases and survival[9]; however, the independent impact on survival of tumor size greater than 2 cm has not been consistently reproduced in the literature.[10,13] Based on macroscopic gross inspection of the cut-up of the uterus, maximum tumor dimension greater than 3.75 cm was recently reported an independent predictor of deep myometrial invasion, distant recurrence, and death.[11] Because CC diameter was almost uniformly the largest tumor diameter in our study, our cutoff value for CC diameter greater than 4 cm seems to be in line with the proposed cutoff value of 3.75 cm. Direct comparison between tumor diameter measurements in macroscopic fresh tissue and preoperatively based on MRI is, however, difficult due to the differences in planes eligible for tumor measurements and the potential distortion and compression of tumor tissue in vivo compared with ex vivo. Thus, the optimal cutoff values for tumor size are not necessarily transferable from in vivo MRI-based assessment to the ex vivo gross section-based tumor measurements. Still, the metastatic potential and unfavorable prognostic impact of large tumor size in endometrial carcinomas is consistently supported by both in vivo and ex vivo studies.[9–15]

We found that the MRI-based parameters AP tumor diameter greater than 2 cm and CC tumor diameter greater than 4 cm both alone and combined are strongly associated with reduced progression/recurrence-free survival in endometrial carcinomas (Fig. 3). These tumor size parameters should in the future also be evaluated in relation to other preoperative biomarkers such as p53, hormone receptor, and DNA ploidy status in preoperative biopsies, prognostic markers assessed in blood samples,[21] and on functional imaging by MRI or PET/CT, which have been shown to yield prognostic information.[16,22–25]

For all risk stratification models, high accuracy and reproducibility of the variables included in the model are essential. To our knowledge, this is the first study assessing the interobserver variability for the different tumor size measurements at MRI in endometrial cancer. Interestingly, we found that tumor size was measured with very low interobserver variability and with no striking difference related to the readers' previous experience. Thus, tumor size measurements seem to represent robust biomarkers that are promising for potential inclusion in future risk stratification models in endometrial cancer.

This study has some limitations. First, the study was conducted in a single institution using a standardized imaging protocol. Thus, the potential impact of various imaging protocols on MRI-based tumor size measurements has not been assessed. However, our imaging protocol is based on the guidelines of the European Society of Urogenital Imaging and is thus expected to be quite similar to those applied at most centers treating endometrial cancer patients. Second, intraobserver variability was not assessed in this study. This is, however, expected to be lower than the observed interobserver variability, which was very low in this study, and the intraobserver variability is thus expected to be almost negligible.

In summary, tumor size assessed preoperatively by MRI predicts the presence of deep myometrial invasion and lymph node metastases and is a strong prognostic factor in endometrial carcinoma. Based on our findings, we propose cutoff values greater than 2 cm AP tumor diameter for predicting deep myometrial invasion and greater than 4 cm CC tumor diameter for predicting lymph node metastases, as well as poor survival for the combination of greater than 2 cm AP and greater than 4 cm CC tumor diameter. Preoperative tumor measurements at MRI may thus provide clinically relevant biomarkers for future risk stratification models guiding tailored surgical treatment in endometrial cancer.

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Appendix

MR registration form in endometrial cancer

Patient number   Images read by (initials)

Date of reading

Lesions are numbered consecutively according to decreasing size and primary location is specified: Fundus, **F**, Corpus **CO**, Istmus **I**, Cervix **CE**.

Lesions Number: **No Localis.**	Ax on uterus: (transverse diam rel. to uterus x AP) (mm) (VIBE+k)	Sag on uterus: CC diam (mm) (T2)	Maximum infiltr. depth myometr (mm) (VIBE+k)	Minimum distance tumor – serosa (mm) (VIBE+k)	Thickness myometr. cran or caud of tumor (mm) (sagT2)	Thickness myometr. contralat side (mm) (VIBE+k)	Primarily Right (R)/ Left (L)/ Midline (M) (select one only)	Primarily Ventral (V)/ Dorsal (D)/ Both (B) (one only)	Circumscr. Sharp(S)/ Moder. sharp (M)/ Diffuse (D) (VIBE+k)

Lesions No cont.	Signal (- i.v.k) lower (↓), same (→) or higher (↑) than normal myometrium		Homogeneous signal (- i.v. k.) (Y/N)		Contrast enhancement in tumor compared to normal myometrium (VIBE +k)			
	VIBE -k	T2	VIBE -k	T2	Less (↓) Same (→) More (↑)	Homo-geneous Y/N	Contr.defect Y/N	Ring-enhancem Y/N

Lesions No cont.	Tumor limited to uterus (Y/N)	Tumor limited to endometrium (E) / <50 % of myometrium (A) ≥ 50 % of myometrium (B)	Tumor in cervix (Y/N)	If Yes: Endo-cervix (E) Stroma (S)	Tumor growth serosa (Y/N)	Tumor growth adnex (Y/N)	Tumor growth vagina (Y/N)	Paraaortic or parailiac lymphadenopathy (largest short-axis diam ≥ 8 / 10 mm)(Y/N)

Lymph-nodes Numbered in decreasing size	Largest short-axis diam (mm)	Right (R)/ Left (L)/ Midline (M)	Close to ilica ext. (Y/N)	Close to ilica int. (Y/N)	Close to ilica comm. (Y/N)	Para-aortic (Y/N)	Tumor growth bladder (Y/N)	Tumor growth rectum (Y/N)	Distant metastases (Y/N); if yes, where

Other findings:	Free intraperitoneal fluid (Y/N)	If Yes: Small (↓) Moderate (→) Large (↑) quantities of fluid	**Other findings** (e.g. uterine myomas/cysts, ovarian lesions) List below:

PET/CT registration form in endometrial cancer

Patient number	Images read by (initials)
Date of reading	

Lesions are numbered consecutively according to decreasing size and primary location is specified: Corpus **CO**, Cervix **CE**.

Lesion No Localis.	Visually recogn. endom. tumor (Y/N)	Lightly/ moderately /intensely increased (L/M/I)	Tumor SUVmax ≥ 2,5 (Y/N)	SUV max	SUV mean (volume)	Volume ROI size (ml)	Visually recogn. tumor in cervix (Y/N)	If yes: FDG uptake in cervix (≥2,5) (Y/N)	If yes: SUV max cervix	SUV mean (volume) cervix	Volume ROI size (ml) cervix

Lesions No cont.	Visually recogn. l.n. (Y/N)	L.n. ≥10mm short axis (mm)	Lymph node uptake (≥2,5) (Y/N)	SUVmax l.n.	Close to iliaca ext. (Y/N)	Close to iliaca int. (Y/N)	Close to iliaca comm. (Y/N)	Para aortic (Y/N)	Left/right (L/R/M)

SUVmax liver	SUVmean liver	Distant metastases (Y/N) +loc.			Other findings/comments