The value of PET/CT, MRI, ultrasonography and biochemical analyses for preoperative staging of endometrial cancer patients

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Abstract

The clinical challenge when handling endometrial cancer (EC) patients is the selection of patients to high- or low-risk groups. High-risk patients will receive extended radical surgery and lymphadenectomy while overtreatment should be avoided in low-risk patients. Accordingly, a non-invasive preoperative diagnostic method that is able to predict tumor aggressiveness and stage would be useful.

To assess this challenge we conducted this PhD project with the aim to evaluate PET/CT, MRI, 2D ultrasound and 3D ultrasound with power Doppler angiography (3D-PDA), SUVmax of FDG PET/CT, and biomarkers as preoperative diagnostic tools.

First, in paper I, we performed a study on the prevalence of undiagnosed EC in a nationwide cohort of Danish patients primarily diagnosed with atypical endometrial hyperplasia (AEH). We found that 59% of 773 patients preoperatively diagnosed with AEH actually had EC. Therefore, we decided to include patients primarily diagnosed with AEH in the subsequent studies.

Secondly, 318 women with EC were enrolled in the Danish Endometrial Cancer study, ENDOMET. The women went through PET/CT, MRI and 2D ultrasound (2D US) scans prior to surgical treatment at three Danish tertiary gynecological centers (Rigshospitalet and the University hospitals in Odense and Aalborg). Additionally, they had blood samples drawn less than 14 days before surgery as well as tissue collected at the time of surgery for translational studies.

For the imaging study (paper II), we found equal sensitivities for PET/CT (89%) and MRI (89%) in predicting myometrial invasion (MI). 2D US was less sensitive (69%) than the other modalities, but had higher or equivalent specificity and accuracy (specificity 46% (PET/CT), 57% (MRI), 74% (2D US)

and accuracy 64% (PET/CT), 67% (MRI), 73% (2D US)). For prediction of cervical involvement (CI) and lymph node metastases (LNM) we found PET/CT superior to MRI and 2D US. The imaging modalities were able to upstage patients, who would not have been recommended lymph node resection based on histology and grade alone. Furthermore, we found that all imaging modalities contributed to the preoperative staging, why they in combination can improve accuracy. Due to high specificities (93%) and negative predictive values (98% and 97%, respectively) in predicting LNM, PET/CT and MRI can additionally be useful in selected patients who are poor candidates for surgical staging.

During the evaluation of PET/CT images, the maximal standard uptake value (SUVmax) of the primary tumor was examined (paper III). We found significantly higher SUVmax values in patients with FIGO stage IB or higher compared to stage IA and for stage III–IV compared to stage I–II. Furthermore SUVmax was significantly higher in patients with MI $\geq$50% compared to MI <50%, CI compared to no CI, presence of LNM, and medium/high risk compared to low risk.

Besides conventional 2D gray scale transvaginal ultrasound, 61 patients were assessed by 3D-PDA (Paper IV). Endometrial thickness (ET) and -volume (EV) as well as power Doppler indices (Vascularization index, Flow index, Vascularization flow index) were evaluated as preoperative diagnostic tools. ET and EV were significantly higher in advanced FIGO stages, medium/high risk patients and tumors with CI. Vascularization index was significantly higher in medium/high-risk patients but there were no other significant differences in the 3D-PDA vascular indices even though the vascular indices were numerically higher in patients with deep MI, CI and advanced FIGO stages.

For the biomarker study (paper V), 371 patients were eligible. We found the levels of both HE4 and CA125 significantly positively correlated with histological grade (p<0.0001 and p=0.001, respectively), LNM (p<0.0001), MI (p<0.0001), and CI (p<0.0001). Significant increases in the levels of both biomarkers were found with increasing FIGO stage (p<0.0001). This study thus confirmed that the biomarkers are significantly elevated in patients characterized by clinical high-risk factors. The study showed that combining the biomarkers was beneficial for the preoperative evaluation of EC patients.

In conclusion, results from the investigated imaging modalities and biomarkers all contributed to further preoperative knowledge about EC patients. They may be used together or individually when planning treatment. However, none of the modalities can yet replace surgical staging as the sensitivities are not high enough. Gynecological oncology surgeons can use the imaging and biomarkers as a supplement to the clinical guidelines. Before implementation of imaging and biomarkers it is necessary to consider the cost-effectiveness in whole-body scans for low risk patients as well as the risk of missing extra-uterine disease in high-risk patients if not examined thoroughly enough preoperatively.

Papers:

I. **Patients with atypical hyperplasia of the endometrium should be treated in oncological centers**
Antonsen SL, Ulrich L, Høgdall C.
Gynecol Oncol. 2012 Apr;125(1):124-8.

II. **PET/CT, MRI and 2D ultrasound in the preoperative staging of endometrial cancer – a multicenter prospective comparative study**
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III. **SUVmax of ^{18}FDG PET/CT as a predictor of high-risk endometrial cancer patients**
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Gynecol Oncol. 2013 May;129(2):298-303

IV. **Three-dimensional ultrasound and power Doppler angiography for the preoperative evaluation of endometrial cancer**
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Under revision

V. **Preoperative HE4 and CA125 levels in the preoperative assessment of endometrial cancer patients: A Danish prospective multicenter study**
Antonsen SL, Høgdall E, Christensen IJ, Lydolph M, Tabor A, Loft A, Fagö-Olsen CL, Andersen ES, Jochumsen K, Høgdall C
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