Pre-operative Diagnostic of Endometrial Cancer - based on a Combination of Clinical Database Information and Biobank Material

Sofie Leisby Antonsen, MD, PhD
Dept. of Gynecology and Obstetrics
The Juliane Marie Centre
Rigshospitalet, Copenhagen, Denmark
Endometriecancer

- Most common gynecological cancer
- The incidence in Denmark was 714 women in 2011
- Mostly postmenopausal
- Lifetime risk of developing EC is 2.6%
- Incidence is rising

DGCD 2011
Arora et al, best Prac Res Clin Obstet Gynecolclin
Engholm et al, NORDCAN, www.ancr.nu
Endometrial cancer stages in Denmark 2005-2011

- AEH
- Stage I
- Stage II
- Stage III
- Stage IV
- Sarcoma

DGCD Report 2011
Endometrial cancer survival divided between stages

- Stage I: 85%
- Stage II: 70%
- Stage III: 50%
- Stage IV: 19%

Survival days from the date of primary diagnosis

DGCD annual report 2008
Treatment of Endometriecancer

Total hysterectomy

- Ovary
- Uterus
- Fallopian tube
- Cervix
- Vagina

Total hysterectomy with salpingo-oophorectomy

- a
- OR
- b

Radical hysterectomy

- Nearby tissue

Low transverse incision
- Vertical incision

© 2009 Terese Winslow
U.S. Govt. has certain rights

Perspectives of Danish CancerBiobank 18.03.13
The treatment of EC implies two challenges

To remove all cancer tissue

Not to over-treat

Proper preoperative staging is important to select to low- and high-risk groups
To evaluate and compare the diagnostic performance of PET/CT, MRI, 2D- and 3D ultrasound in the preoperative staging of EC

To evaluate whether the biomarkers HE4 and CA125 correlate to known prognostic factors for EC
Patient population
Referred patient

Information/inclusion

MRI
PET/CT
US
Blood samples

1-31 days prior to surgery
1-14 days prior to surgery

Surgery
Pathology
Referred patient

Information/inclusion

MRI
PET/CT
US
Blood samples

1-31 days prior to surgery
1-14 days prior to surgery

Surgery
Pathology
Preoperative HE4 and CA125 levels in the preoperative assessment of endometrial cancer patients: a Danish prospective multicenter study (ENDOMET)

Sofie Leisby Antonsen, MD1, Estrid Høgdall, PhD2, Ib Jarle Christensen3,4, Magnus Lydolph, PhD5, Ann Tabor, MD, DMSc6,10, Annika Loft Jakobsen, MD, PhD7, Carsten L Fagø-Olsen, MD1, Erik Søgaard Andersen, MD8, Kirsten Jochumsen, MD, PhD9 & Claus Høgdall, MD, DMSc1

1Gynecologic Clinic, Rigshospitalet, Copenhagen University Hospital, Copenhagen
2Danish Cancer Biobank, Department of Pathology, Herlev University Hospital, Herlev
3Finsen Laboratory, Rigshospitalet, Copenhagen University Hospital
4Biotech Research and Innovation Centre (BRIC), University of Copenhagen, Copenhagen
5Department of Clinical Biochemistry and Immunology, Division of Microbiology and Diagnostics, Statens Serum Institute, Copenhagen
6Center of Fetal Medicine and Ultrasound, Rigshospitalet, Copenhagen University Hospital, Copenhagen
7Department of Clinical Physiology, Nuclear Medicine, & Positron Emission Tomography, Rigshospitalet, Copenhagen University Hospital, Copenhagen
8Department of Gynecology and Obstetrics, Aalborg University Hospital, Aalborg
9Department of Gynecology and Obstetrics, Odense University Hospital, Odense
10Faculty of Health Sciences, University of Copenhagen, Copenhagen

Provisionally accepted in Acta Obstetricia et Gynecologica Scandinavica
Biomarkers

CA125

- Elevated levels in EC patients
- Elevated levels predict extra-uterine disease

HE4

- Elevated levels are found in patients with serous and endometrioid epithelial ovarian and uterine cancer
- Correlation between HE4 and advanced FIGO stage
- Differentiate between malignant and benign lesions

Sood et al. Obstet Gynecol 197
Drapkin et al. Cancer Res 2005
Moore et al. Gynecol Oncol 2008
Material & Methods

Arrangement with Danish CancerBiobank

Blood samples automatically drawn, centrifuged, pipetted, and frozen

Serum were analyzed and results delivered when data collection was finished
Material & Methods

Preoperative HE4 and CA125 levels were measured in serum from 371 patients.

Biomarker levels were correlated to pathological characteristics of hysterectomy specimens.
Results

• HE4 and CA125 were moderately correlated ($r=0.49$, $p<.0001$)

• HE4 was correlated to age ($r=0.32$, $p<.0001$).

• HE4 and CA125 were significantly and positively associated with
  • Histological grade
  • Myometrial invasion
  • Cervical involvement
  • Lymph node metastases
  • FIGO stage
## Analyses of end-points

<table>
<thead>
<tr>
<th>End-point</th>
<th>Univariate</th>
<th></th>
<th></th>
<th>Multivariate</th>
<th></th>
<th></th>
<th></th>
<th>AUC (Index)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><strong>Univariate</strong></td>
<td><strong>Multivariate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>HE4</strong></td>
<td><strong>CA125</strong></td>
<td><strong>HE4</strong></td>
<td>CA125</td>
<td>Age</td>
<td>AUC (Index)</td>
<td></td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td>OR: 1.84(1.35–2.51)</td>
<td>OR: 1.67(1.26–2.20)</td>
<td>OR: 1.54(1.10–2.15)</td>
<td>OR: 1.47(1.09–2.00)</td>
<td>OR: 1.20(0.87–1.65)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>1B(n=43) vs. AEH/1A(n=225)</td>
<td></td>
<td><em>p=0.0001</em></td>
<td><em>p=0.0003</em></td>
<td><em>p=0.012</em></td>
<td><em>p=0.013</em></td>
<td><em>p=0.27</em></td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer</strong></td>
<td></td>
<td>OR: 1.47(0.91–2.38)</td>
<td>OR: 1.07(0.77–1.49)</td>
<td>OR: 1.42(0.81–2.48)</td>
<td>OR: 0.90(0.61–1.33)</td>
<td>OR: 1.48(0.92–2.39)</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>Cancer(n=344) vs. AEH(n=16)</td>
<td></td>
<td><em>p=0.12</em></td>
<td>AUC: 0.64</td>
<td>OR: 0.23</td>
<td>OR: 0.60</td>
<td>OR: 0.11</td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td><strong>Myometrial invasion</strong></td>
<td></td>
<td>OR: 1.96(1.58–2.44)</td>
<td>OR: 1.78(1.48–2.15)</td>
<td>OR: 1.55(1.21–2.0)</td>
<td>OR: 1.52(1.23–1.86)</td>
<td>OR: 1.04(0.83–1.31)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>MI ≥50% (n=134) vs. MI &lt;50% (n=213)</td>
<td></td>
<td><em>p=0.0001</em></td>
<td><em>p=0.0001</em></td>
<td>OR: 0.90</td>
<td>OR: 0.60</td>
<td>OR: 0.73</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph nodes</strong></td>
<td></td>
<td>OR: 1.61(1.23–2.10)</td>
<td>OR: 1.65 (1.31–2.08)</td>
<td>OR: 1.17(0.82–1.66)</td>
<td>OR: 1.53(1.15–2.04)</td>
<td>OR: 0.87(0.56–1.35)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>LNM (n=31) vs. no LNM(n=135)</td>
<td></td>
<td><em>p=0.0005</em></td>
<td><em>p=0.0001</em></td>
<td><em>p=0.38</em></td>
<td>OR: 0.0004</td>
<td>OR: 0.54</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td>OR: 1.35 (0.99–1.85)</td>
<td>OR: 1.22(0.90–1.67)</td>
<td>OR: 1.22(0.85–1.76)</td>
<td>OR: 1.10(0.77–1.57)</td>
<td>OR: 1.31(0.89–1.92)</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>High risk (n=30) vs. low+medium risk (n=215)</td>
<td></td>
<td><em>p=0.062</em></td>
<td>OR: 0.20</td>
<td>OR: 0.29</td>
<td>OR: 0.60</td>
<td>OR: 0.17</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td><strong>Cervical involvement</strong></td>
<td></td>
<td>OR: 1.67(1.35–2.08)</td>
<td>OR: 1.48(1.25–2.76)</td>
<td>OR: 1.39(1.07–1.81)</td>
<td>OR: 1.30(1.06–1.59)</td>
<td>OR: 1.08(0.84–1.40)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>CI (n=71) vs. no CI(n=291)</td>
<td></td>
<td><em>p=0.0001</em></td>
<td><em>p=0.0001</em></td>
<td>OR: 0.015</td>
<td>OR: 0.012</td>
<td>OR: 0.55</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>End-point No= (nn)</td>
<td>Sensitivity HE4 cut-off 70pM</td>
<td>Specificity HE4 cut-off 70pM</td>
<td>Sensitivity CA125 cut-off 35U/ml</td>
<td>Specificity CA125 cut-off 35U/ml</td>
<td>Sensitivity CA125 cut-off 20U/ml</td>
<td>Specificity CA125 cut-off 20U/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IB (42) vs. IA+AEH (220)</td>
<td>55.8</td>
<td>67.6</td>
<td>30.2</td>
<td>92.0</td>
<td>44.2</td>
<td>72.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer (353) vs. AEH (16)</td>
<td>44.6</td>
<td>76.5</td>
<td>19.5</td>
<td>88.5</td>
<td>42.1</td>
<td>70.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI &lt;50% vs. MI &gt;50%</td>
<td>60.0</td>
<td>66.8</td>
<td>34.1</td>
<td>90.8</td>
<td>61.5</td>
<td>70.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LNM (27) vs. no LNM (130)</td>
<td>77.4</td>
<td>48.1</td>
<td>61.3</td>
<td>80.0</td>
<td>83.9</td>
<td>53.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/med risk (204) vs. High risk (28)</td>
<td>50.0</td>
<td>66.9</td>
<td>16.7</td>
<td>88.5</td>
<td>40.0</td>
<td>69.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CI (71) vs. no CI (262)</td>
<td>62.0</td>
<td>61.9</td>
<td>31.0</td>
<td>85.2</td>
<td>64.8</td>
<td>65.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Plots and specificities for the index for three sensitivities

### End-point | Sensitivity | Specificity | False positive rate | False negative rate
--- | --- | --- | --- | ---
**Myometrial invasion** | 75 | 51.2 | 50.7 | 23.4
| 85 | 35.7 | 54.4 | 20.0
| 95 | 20.7 | 56.9 | 12.0
**Lymph node metastases** | 75 | 57.8 | 70.4 | 8.2
| 85 | 47.4 | 73.2 | 7.2
**Cervix involvement** | 75 | 47.1 | 74.4 | 11.6
| 85 | 35.1 | 75.9 | 9.7
| 95 | 10.7 | 79.5 | 11.4
Conclusions

The biomarkers HE4 and CA125 are significantly elevated in patients characterized by clinical high-risk factors.

In a combined index including HE4, CA125 and age, the diagnostic value increases.

These findings suggest that the markers may be used as an additional tool in combination with imaging and clinical information when planning the treatment of patients with EC.
Thank you

Questions?