Moving Endometrial Cancer into the Future

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Presenter Disclosure

- Robert Lotocki, BSc, MD, FRCSC

  - **Speaker’s bureau/honoraria:**
    - ✓ Merck & Co., Inc
    - ✓ International Center for Infectious Disease (ICID)

  - **Grants/research support:**
    - ✓ Merck & Co., Inc

  - **Advisory Committee:**
    - ✓ Roche Pharmaceuticals
Mitigating Potential Bias

Robert Lotocki, BSc, MD, FRCSC

- none
Moving Endometrial Cancer into the Future

Learning objectives:

1. List the clinico-pathological features of endometrial cancer
2. Review the diagnosis and work up of endometrial cancer
3. Describe the management of endometrial cancer
4. Define the genetic risk of Endometrial Cancer
Moving Endometrial Cancer into the Future

The incidence in Canada is 2.6/100,000 women

2014 estimates:

- Canada: 5600 new cases of endometrial cancer and 890 deaths
- Manitoba: 230 new cases of endometrial cancer and 30 deaths
## Risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>nulliparity</td>
<td>2-3</td>
</tr>
<tr>
<td>late menopause</td>
<td>2.4</td>
</tr>
<tr>
<td>21-50 lbs overweight</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 50 lbs overweight</td>
<td>10</td>
</tr>
<tr>
<td>diabetes</td>
<td>2.8</td>
</tr>
<tr>
<td>unopposed estrogen therapy</td>
<td>4-8</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>2-3</td>
</tr>
<tr>
<td>atypical endometrial hyperplasia</td>
<td>8-29</td>
</tr>
<tr>
<td>HNPCC</td>
<td>20</td>
</tr>
</tbody>
</table>
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Two different clinico-pathological subtypes of endometrial cancer:

- type I: the estrogen-related (endometrioid)
- type II: non-estrogen-related (serous and clear cell)
# Moving Endometrial Cancer into the Future

**Clinico-pathological Feature:**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type I - Endometrioid</th>
<th>Type II - serous and clear cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>63 years</td>
<td>67 years</td>
</tr>
<tr>
<td>Confined to Uterus</td>
<td>&gt; 70%</td>
<td>&lt; 50%</td>
</tr>
<tr>
<td>5-year survival</td>
<td>83%</td>
<td>Serous: 53%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clear cell: 62%</td>
</tr>
<tr>
<td>Genetic alterations</td>
<td>microsatellite instability mutations:</td>
<td>P53</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PIK3CA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>K-ras</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CTNNBI (β-catenin)</td>
<td></td>
</tr>
<tr>
<td>ER/PR receptors</td>
<td>Present</td>
<td>absent</td>
</tr>
</tbody>
</table>
What are the most common symptoms associated with endometrial cancer?

- abnormal uterine bleeding:
  - postmenopausal (80%)
  - perimenopausal (15%): (intermenstrual bleeding or menorrhagia)
  - premenopausal (5%): (irregular cycles)

- vaginal discharge

- Pyometra

- Asymptomatic

- Asymptomatic postmenopausal women with endometrial cells on a Papanicolaou test, particularly if they are atypical

- Patients who have advanced disease may have symptoms similar to those seen with advanced ovarian cancer, such as abdominal or pelvic pain, abdominal distension, early satiety, or change in bowel or bladder function
Pap test with Endometrial Cells

Dutch study of 29,144 asymptomatic postmenopausal women:

Prevalence rate of (pre-) malignant uterine disease when normal endometrial cells reported versus absence:

6.5% versus 0.2%

relative risk of 40.2 [95% confidence interval (CI) 9.4-172.2]

Pap test with Endometrial Cells

Morphologically abnormal endometrial cells found in the cervical smear, the prevalence rate of (pre-) malignant uterine disease

25% of women have endometrial carcinoma

What is your initial test to evaluate a nulli-parous woman presenting with postmenopausal bleeding?

1. Endovaginal ultrasound
2. Hysteroscopy and D± C
3. Endometrial suction aspiration
What is your initial test to evaluate a nulli-parous woman presenting with postmenopausal bleeding?

1. Endovaginal ultrasound

2. Hysteroscopy and D&C

3. Endometrial suction aspiration
Moving Endometrial Cancer into the Future

- meta-analysis of studies on the efficacy of several devices:
  - Pipelle has the best performance, with detection rates of:
    - 99.6% for endometrial cancer
    - 98% for endometrial hyperplasia
  

- hysteroscopic guidance remains the gold standard in the diagnostic evaluation

What is a Negative Biopsy?

“… strips of atrophic flattened columnar cells seen.

The sample is too scant for a histology diagnosis.

Suggest repeat biopsy or D&C…”

Is this sample Negative or Unsatisfactory??
What is a Negative Biopsy?

“… strips of atrophic flattened columnar cells seen. The sample is too scant for a histology diagnosis. Suggest repeat biopsy or D&C…”
Management of Abnormal Uterine Bleeding

Aspiration Suction Biopsy

- Positive
  - Unsatisfactory or Unable to do
    - Low risk
      - Appropriate management
        - Transvaginal ultrasound
          - Negative
            - Follow
          - Suspicious
            - Hysteroscopy and D&C
        - High risk
          - Follow
    - Negative
      - Further bleeding
        - Follow
      - No further bleeding
        - Follow

S O G C/GOC/SCC Clinical Practice Guideline
February 2000

The ‘Incidentoma’:

The endometrium is thickened to 9 mm and is heterogeneous and complex with cystic spaces. There is no enhanced flow associated. The ovaries are unremarkable and there is no free fluid in the pelvis.

Impression: Thick, complex appearing endometrium. Endometrial sampling is recommended.
Endovaginal Ultrasound (TVUS) to Exclude Endometrial Disease

**Definition of Endometrial Thickness:**

Width of the combined thickness of the anterior and posterior sides of the endometrium
Reliably of transvaginal ultrasonography to exclude endometrial cancer with postmenopausal bleeding

data from approximately 2900 patients collected from 13 published studies

<table>
<thead>
<tr>
<th>endometrial thickness cut-off</th>
<th>sensitivity</th>
<th>specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mm</td>
<td>90%</td>
<td>54%</td>
</tr>
<tr>
<td>3-mm</td>
<td>98%</td>
<td>35%</td>
</tr>
</tbody>
</table>

reduce the pretest probability of endometrial cancer from 10% to 0.7% in women with negative results

Management of women with uterine papillary serous cancer: A Society of Gynecologic Oncology (SGO) review

52 women with Type 2 endometrial cancer (24 with UPSC) ultrasound stripe

≤ 5mm in 35%

< 4mm in 17%
How thick is too thick?

When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding?

- In postmenopausal women without vaginal bleeding, the risk of cancer is approximately 6.7% if the endometrium is thick (> 11 mm)
- 0.002% if the endometrium is thin (≤ 11 mm)

Changes in the Sonographic Appearance of the Uterus With Tamoxifen Therapy

Endometrial thickness:

- Increased with increasing duration of tamoxifen use: rate of 0.75 mm/year

- Mean endometrial thickness after approximately 5 years of tamoxifen use: 12 mm (range, 6–21 mm)

- Decreased after discontinuation of tamoxifen: rate of 1.27 mm/year

Mindy Fishman, MD et al
What is the recommended metastatic assessment for newly diagnosed endometrial cancers

Imaging tests evaluating for metastasis is not necessary
(level of evidence: A)

Serum CA125
✓ may be useful in management planning of selected endometrial cancer patients

✓ cannot currently be recommended for routine clinical use
(level of evidence: C)
## Evaluation of Myometrial Invasion

<table>
<thead>
<tr>
<th></th>
<th>Accuracy</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ultrasound</td>
<td>60 to 84%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>61%</td>
<td>40%</td>
<td>75%</td>
</tr>
<tr>
<td>MRI</td>
<td>62.5%</td>
<td>50.6 to 87%</td>
<td>88 to 90%</td>
</tr>
</tbody>
</table>

Teefy, Am J Roent 166; 547, 1996
Arbo, J Ultrasound Med 19; 639, 2000
Kim, J Comput Asst Tomog 19; 766, 1995
Sawicki, Eur J Gynecol Oncol, 24; 293, 2003
Dessole, Am J Obstet Gynecol, 194; 362, 2006
Chung, Gynecol Oncol. 2007; 104:654-9
Rockall, J Gynecol Cancer, 2007;17: 188-96
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- Less is Better
- Focused Treatment
Endometrial Cancer – Risk Groups

Low Risk:
Stage IA or IB, grade 1 or 2
non-serous and non-clear cell carcinoma

Intermediate Risk:
Stage IC grade 1 or 2; Stage IIA grade 1 or 2
non-serous and non-clear cell carcinoma

High Risk:
Stage IC or IIA grade 3; Stage IIB
Stage III or IV
serous and clear cell carcinoma
“Routine” Lymphadenectomy

- Opinion remains divided

- Information gained by comprehensive
  - Offers prognostic pathologic staging
  - Used to individualize additional treatment
Endometrial Carcinoma
“Routine” Lymphadenectomy

<table>
<thead>
<tr>
<th>Stage IC, G1,2,3</th>
<th>2-year Survival</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical Group</td>
<td>97%</td>
<td>94%</td>
</tr>
<tr>
<td>(Pelvic XRT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical Staged</td>
<td>97%</td>
<td>95%</td>
</tr>
<tr>
<td>(No pelvic XRT)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rittenberg, 2002
Chemotherapy for advanced, recurrent or metastatic endometrial cancer

- More intense combination chemotherapy
  - significantly improves the disease-free survival
  - modest improvement in OS

- Cisplatin and anthracyclines (e.g. doxorubicin)
  or the taxanes [e.g. paclitaxel (Taxol)]

- Increased grade 3 and 4 myelosuppression and gastrointestinal toxicity

Eleven eligible RCTs were identified that recruited 2288 patients.
Endometrial Cancer

Inherited Genetic Factors: 5 to 10%

Hereditary non-polyposis colorectal cancer syndrome (HNPCC)
HNPCC and Gynecology

- higher risk of Endometrial Cancer
- higher risk of Ovarian cancer.
<table>
<thead>
<tr>
<th>Cancer</th>
<th>General Population Risk</th>
<th>HNPCC Risks</th>
<th>Mean Age of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>5.5%</td>
<td>80%</td>
<td>44 years</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2.7%</td>
<td>20-60%</td>
<td>46 years</td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1%</td>
<td>11-19%</td>
<td>56 years</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6%</td>
<td>9-13%</td>
<td>42.5 years</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1%</td>
<td>2-7%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1%</td>
<td>4-5%</td>
<td>~55 years</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1%</td>
<td>1-4%</td>
<td>49 years</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1%</td>
<td>1-3%</td>
<td>~50 years</td>
</tr>
</tbody>
</table>

Suggested Referral Criteria for CRC Genetic Screening in Manitoba

Affected individuals from families with:

- at least 3 affected relatives, one with CRC and the other two with any combination of CRC, endometrial, ovarian, gastric, small bowel, hepatobiliary, ureter, transitional cell kidney cancer, and/or sebaceous adenoma/carcinoma.

- 2 of the 3 family members must be in a 1st degree relationship.

- at least two successive generations.
EC/OC in a young women may indicate the presence of HNPCC

- 126 Women with dual malignancy (Amsterdam criteria)
- 57 (45%) EC/OC First.
- 47 (37%) Colon Cancer First.
- 22 (17%) CRC & EC/OC were diagnosed simultaneously

Lu K. et al 2004
EC/OC in a young women may indicate the presence of HNPCC

- EC/OC First, median age 44.9
  - CRC 57.9.

- CRC First, median age 40
  - EC/OC 49.2

- Mean interval between cancers 11.1 years.

Lu K. et al 2004
Endometrial Cancer and HNPCC

Options:

- Screening
  - Endometrial Bx, Current Study in MD Anderson

- Medical Prevention
  - HNPCC & Endometrial Cancer: Chemoprevention Using the Oral Contraceptive vs. Depo-Provera (Protocol #ID01-340)

- Surgical prevention
Take Home Message?
Transvaginal ultrasound should not be used as screening for endometrial cancer.

Endometrial sampling in a post menopausal woman without bleeding should not be routinely performed.

Indications for tissue sampling of the endometrium in bleeding postmenopausal women with an endometrial thickness >4-5mm should not be extrapolated to asymptomatic women.

A woman who has endometrial thickening and other positive findings on ultrasound, such as increased vascularity, inhomogeneity of endometrium, particulate fluid or thickened endometrium over 11mm, should be referred to a gynecologist for further investigations.

SOGC Clinical Practice Guideline; October, 2010
Decisions about further investigations should be made on a case-by-case basis in asymptomatic women with increased endometrial thickening and risk factors for endometrial cancer such as obesity, hypertension and late menopause.

In asymptomatic women on tamoxifen, a routine ultrasound for endometrial thickening should not be performed.

Not all postmenopausal women who have asymptomatic endometrial polyps require surgery. Women found to have asymptomatic polyps on ultrasound should be triaged for intervention according to the size of the polyp, age and other risk factors.
Questions?