Management of Gynaecological Cancer Risk in Lynch Syndrome

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obermair.info
Terminology

HNPCC - hereditary nonpolyposis colorectal cancer >> misleading ...

• Various other cancers are “forgotten”

Implication:
“I go and have my colonoscopies and I’ll be OK.”
Lynch Syndrome (LS) is...

- Autosomal dominant germline mutation in one of several DNA mismatch repair (MMR) genes
  - Inherited
    - Irrespective of gender
- Increases the risk of several cancers
  - Risk of *endometrial* cancer: 27% to 71% (exceeds the risk of bowel cancer)
  - Risk of *ovarian* cancer: 3% to 14%
- Genetic defect in 1 of 3100 people [1]

[1]. Dunlop et al., Br J Cancer 2000
### Lifetime cancer risk (females)

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>MLH1</th>
<th>MSH2</th>
<th>MSH6</th>
<th>PMS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Lynch cancer</td>
<td>50%‐76%</td>
<td>38%‐78%</td>
<td>65%</td>
<td>21%‐53%</td>
</tr>
<tr>
<td>Colorectal</td>
<td>50%‐53%</td>
<td>39%‐68%</td>
<td>18%‐30%</td>
<td>15%</td>
</tr>
<tr>
<td>Endometrial</td>
<td>60%</td>
<td>21%</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td>Ovarian</td>
<td>20%</td>
<td>24%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>Upper urologic tract</td>
<td>0.4%</td>
<td>9%</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td>6%</td>
<td>2%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Small bowel</td>
<td>6%</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary/Pancreatic</td>
<td></td>
<td></td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Brain tumors (gliomas)</td>
<td>1.7%</td>
<td>2.50%</td>
<td></td>
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</tbody>
</table>
Identification of LS carriers

• **Family history**
  – Revised Amsterdam Criteria by the International Collaborative Group on HNPCC
  – Revised Bethesda Criteria for testing colorectal tumours for MSI
  – 50% of LS patients have a negative family history

• **Sentinel cancer diagnosis – Tumour based**
  – E.g. dad had bowel cancer – was Lynch tested
  – Auntie had endometrial cancer – was Lynch tested
Risk Assessment
Family History & Pedigree

Easy to do

False negative
• Small families
• Adoption
• Paucity of female relatives
• Non-Paternity

*Inheritance*: Autosomal dominant - 50% chance of inheritance;
*Penetrance*: 80% breast ca, 40% ovarian ca), etc.

Prediction Models: use family/personal history
Tumour based Tests

• Immunohistochemistry
  – On cancer tissue
  – Is not a genetic test
  – Requires confirming genetic tests

• Microsatellite instability testing
  – Uses PCR to amplify a standard panel of DNA sequences containing nucleotide repeats
Benefits & Limitations of Genetic Testing

1. Information > Angst/Anxiety;
2. Identifies the individuals concerned;
3. If a mutation has been demonstrated on a relative, a negative result is most definite and is very reassuring;
4. If result is negative for a known mutation: Does it exclude a mutation?
Endometrial Cancer

- Majority of EC are non-Lynch related
- Lynch in only 2% to 5%
- A Lynch carrier very high risk of EC
- Mean age ~ 50 years (62 years in Non-Lynch)
  - 18% were diagnosed under the age of 50 years
- Cell types: majority are endometrioid cancers
- Location of tumour: Lower uterine segment
  - 10 of 35 patients
Risk factors for Endometrial cancer

<table>
<thead>
<tr>
<th>Lynch</th>
<th>Non-Lynch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young age at menarche</td>
<td>Young age at menarche</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>Nulliparity</td>
</tr>
<tr>
<td>No contraceptive pill</td>
<td>No contraceptive pill</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
</tr>
</tbody>
</table>
Diagnosis of Endometrial Cancer

- Abnormal bleeding = WARNING SIGN!
- Requires investigation:

  Hysteroscopy D&C

  Pipelle endometrial sampling
Endometrial Cancer

Treatment

- Hysterectomy
- Removal of ovaries
- ± Lymph nodes
- ± Radiation
- ± Chemotherapy
Risk of endometrial cancer finding Lynch

18% of patients who were 50 years of age or younger and were diagnosed with endometrial cancer had presumptive Lynch.

M Walsh et al: Clin Cancer Res 2008
Uterine cancer after bowel cancer

Obermair et al, Int J Cancer 2010
Ovarian Cancer

- Uterus
- Ligament
- Fallopian Tube
- Ovarian Carcinoma
- Healthy Ovary
Ovarian Cancer

- Life time risk is 3% to 14% in Lynch carriers
  - :: 1.3% in general population
- Patients are younger: 45 years
  - :: 62 years in general population
- Histological cell types: no difference between Lynch and Non-Lynch patients
  - Stage 3 & 4
  - Poor prognosis
- Risk groups: not identifiable
- Warning signs are unspecific
Treatment of Ovarian Cancer

• Epithelial Ovarian Cancers
  – Surgery + Chemotherapy

• Non-Epithelial Ovarian Cancer
  – Limited surgery + chemotherapy

• Borderline tumours
  – Surgery only
## Screening & Prevention

<table>
<thead>
<tr>
<th></th>
<th>Uterine Ca</th>
<th>Ovarian Ca</th>
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</thead>
<tbody>
<tr>
<td>Screening*</td>
<td>unreliable</td>
<td>unreliable</td>
</tr>
<tr>
<td>Chemoprevention</td>
<td>Unknown</td>
<td>50%</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>? Mirena</td>
<td>through OCP</td>
</tr>
<tr>
<td>Prophylactic surgery</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>(Risk reduction in %)</td>
<td></td>
<td></td>
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* Screening still recommended by some because of lack of effective alternatives
Surveillance – Endometrial Cancer

• Premenopausal women:
  – Endometrial sampling

  ??? RELIABLE ???

• Postmenopausal women:
  – Transvaginal ultrasound
Uterine Surveillance in Lynch/HNPCC

- 269 women with HNPCC
- Follow-up totalled 826 years of risk
- Pelvic US for a period of 13 years (annual or biennial)
- Two new cases of endometrial carcinoma –
- Neither case was detected by US
  – Both cases were early stage and presented with bleeding.

Dove-Edwin et al.: Cancer 2002
Uterine Surveillance in Lynch/HNPCC

- 41 women, median follow-up 5 years
  - 197 patients years at risk
- 179 patients had ultrasound examinations
  - 17 patients needed endometrial sampling
    - 3 patients endometrial hyperplasia with atypia
    - 1 interval cancer [not detected by US]
  - No ovarian cancers detected.

V.d. Zee et al.: Gynecol Oncol 2003
Surveillance vs. Prophylactic surgery for Lynch/HNPCC

<table>
<thead>
<tr>
<th></th>
<th>Prophylactic Surgery</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial Cancer</td>
<td>0</td>
<td>69 (33%)</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>0</td>
<td>12 (5%)</td>
</tr>
</tbody>
</table>

315 women with Lynch/HNPCC; Cases: 61 prophylactic hysterectomy, 47 BSO; 200+ patients for matched controls;

Boyd-Rogers et al.: NEJM 2006
Surveillance - Ovarian Cancer

- UNRELIABLE – UNPROVEN
- Nevertheless sometimes recommended by professional societies
- Transvaginal Ultrasound & CA125
Chemoprevention

• Ovarian Cancer:
  – Oral contraceptive pill – Risk reduction by 50%

• Endometrial Cancer:
  – Mirena
    • Endometrial polyps -90%*
    • Endometrial cancer -50%**

Mirena to treat endometrial carcinoma

Baker J et al: Gynecol Oncol 2012
Surgical Prevention
Prophylactic Surgery for Lynch

- Remove uterus = hysterectomy
- **Hysterectomy** is the most common gynaecological surgical procedure (~30,000 women in AUS every year)
  - 2,000 for cancer
  - 28,000 for abnormal bleeding, pain
- **Ovaries** should be removed.
Prophylactic Surgery for Ovarian Cancer

- Label them correctly – collaborate with pathology provider
- Collect samples from peritoneal lining
- Performed by someone with an interest in Oncology / Lynch
Timing of surgery

Age of onset of Lynch-related endometrial cancer

Prevalence (%) vs. Age group (years)

Lynch Neg
Lynch Pos

Age group:
- <25.0
- 25.0-29.9
- 30.0-34.9
- 35.0-39.9
- 40.0-44.9
- 45.0-49.9

Prevalence (%)
Pre-surgical assessment

• Medical check up
• Stop blood thinners + herbs/supplements (10 d)
• Gynaecological examination
• PAP smear
• Ultrasound
• Blood tests
• Bowel Prep is not required
Surgical Approach*

• Avoid laparotomy
  – Surgical complication rate is too high

• Avoid vaginal surgery
  – Ovaries cannot be removed
  – Unsafe in women who had previous surgery (cesarean section)

• Avoid morcellation of uterus

• Laparoscopic approach is recommended
  – Hospital stay 1 or 2 days

*Obermair.info
Risks of surgery

- Conversion from laparoscopic to open (2%)
- Medical and anesthetic risks
- Risk of organ injury (bowel, bladder, ureter, bleeding, nerves) (1%)
- Deep vein thrombosis, Pulmonary embolus
- Infection (<1%)
- Menopause
- Constipation (pain killers)
- Postoperative pain
- Vaginal discharge for 6 weeks, vault haematoma
- Shoulder pain
- Fatigue
- Failure – Development of cancer
- Sexual dysfunction (?)
LS Summary & Recommendations

• Lynch is autosomal dominant inherited
  – Inherited irrespective of gender
• Challenge is to identify LS carriers
  – Indicator patients >> identify LS carriers
  – Family history unreliable
  – Immuno-stain for all patients diagnosed with endometriai cancer
    • Cost effective
    • Not miss any LS carriers
Clinical Management (1)

Young women who have not completed family

- Plan your family & consider surgery as soon as the family is completed.
- Healthy lifestyle
- Chemoprevention
  - Oral Contraceptive Pill / Mirena
- Screening
  - No major organisation in AUS/US recommends screening for uterine or ovarian cancer.
  - Endometrial sampling (yearly) from age 30 years (or 5 years prior to earliest age of cancer)
- RR-Prophylactic Salpingectomy
Clinical Management (2)

Women who completed their family

Healthy lifestyle

Prophylactic surgery

– Total Laparoscopic Hysterectomy, BSO, washings
– Very effective to prevent cancer
– Screening is very unreliable
– Surgical risks are low
FUTURE: Genomic Treatment

Pembrolizumab is a Programmed Death -1 (PD-1) inhibitor.

41 patients with mismatch-repair deficiency (various cancers).

Mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab.

NEJM, June 2015
Prof. Obermair specializes in surgery for gynaecological cancer and complex pelvic surgery for benign conditions.

http://obermair.info/information/gynaecological-cancer/