Surgical Treatment of Patients with Lynch Syndrome & Familial Adenomatous Polyposis

V. Liana Tsikitis, MD MCR
Associate Professor of Surgery
Oregon Health & Science University
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Disclosures

No disclosures
Hereditary Colorectal Cancer
Lifetime Probability of Cancer by Site

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>All sites†</td>
</tr>
<tr>
<td>1 in 2</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>1 in 6</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Lung</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>1 in 13</td>
<td>1 in 17</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>1 in 17</td>
<td>1 in 18</td>
</tr>
<tr>
<td>Urinary bladder‡</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>1 in 28</td>
<td>1 in 38</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>1 in 46</td>
<td>1 in 55</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Ovary</td>
</tr>
<tr>
<td>1 in 52</td>
<td>1 in 68</td>
</tr>
<tr>
<td>Kidney</td>
<td>Melanoma</td>
</tr>
<tr>
<td>1 in 64</td>
<td>1 in 77</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Pancreas</td>
</tr>
<tr>
<td>1 in 67</td>
<td>1 in 79</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>Urinary bladder‡</td>
</tr>
<tr>
<td>1 in 73</td>
<td>1 in 88</td>
</tr>
<tr>
<td>Stomach</td>
<td>Uterine cervix</td>
</tr>
<tr>
<td>1 in 82</td>
<td>1 in 135</td>
</tr>
</tbody>
</table>

American Cancer Society: [www.cancer.org](http://www.cancer.org)
Hereditary Colorectal Cancer
Hereditary Component of Colorectal Cancer

Sporadic

Familial

Rare CRC syndromes

HNPCC (2-5%)

FAP (1%)

Adapted from Burt, RW. Inheritance and Genetic Testing for Colon Cancer
Syndromes associated with increased risk of CRC

• Lynch Syndrome
• FAP
• MYH associated polyposis (MAP)
• Serrated Polyposis
• Hamartomatous polyposis
• (Peutz Jeghers, juvenile polyposis)
Hereditary Colorectal Cancer- Lynch Syndrome

2-10% of all colorectal cancers

Mean age of CRC diagnosis: 41 (Range 19-83)

# Gene-Specific Cumulative Risks of Colorectal Cancer by Age 70 in Lynch Syndrome

<table>
<thead>
<tr>
<th>Gene mutation carriers</th>
<th>Risk %</th>
<th>Mean age at diagnosis, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sporadic cancer</td>
<td>5.5</td>
<td>69</td>
</tr>
<tr>
<td>MLH1/MSH2</td>
<td>Male: 27-74, Female: 22-53</td>
<td>27-46</td>
</tr>
<tr>
<td>MSH6</td>
<td>Male: 22, Female: 10</td>
<td>54-63</td>
</tr>
<tr>
<td>PMS2</td>
<td>Male: 20, Female: 15</td>
<td>47-66</td>
</tr>
</tbody>
</table>

Hereditary Colorectal Cancer- Lynch Syndrome

Inheritance pattern autosomal dominant
Gene penetrance approx. 85-90%

**Histology**

- Mucinous, signet-ring (30-40%)
- Poorly differentiated (23-39%)
- Tumor infiltrating lymphocytes

Lynch Syndrome

**Location**
- 2/3 Colon tumors proximal to the splenic flexure
- Increased risk for malignancy at certain extracolonic sites

**Prognosis**
- Better than for sporadic colon cancer
- Less response to traditional chemotherapy
- …. Add the latest with pembro and MSI high

Traditional testing strategy when family mutation known

- Clinically affected or at-risk family member
  - LS pedigree mutation known
  - Site-specific germline testing
    - Patient positive for LS mutation
    - LS
    - Lynch Syndrome surveillance
    - LS not excluded
    - Patient not tested
    - LS not excluded; follow average risk or CRC-specific surveillance depending on other family history

Traditional testing strategy when family mutation is unknown

- Pedigree mutation not known
  - Tumor tissue not available from other clinically affected pedigree members
    - See Figure 5. Tumor tissue NOT available
    - Yes
    - Gene test positive
    - Lynch Syndrome
    - LS surveillance
  - Tumor tissue available from other clinically affected pedigree member
    - Clinically affected family member available?
      - Yes
      - Consider germline testing of at-risk family member for MLH1, MSH2, MSH6, PMS2, EPCAM
      - Patient not tested, no mutation found, or VUS detected (inconclusive)
        - LS not excluded
    - No
      - See Figure 5. Tumor tissue available

Traditional testing strategy when patient is clinically affected and the family mutation is unknown

# Studies of Colorectal Screening in Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Subjects</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Jarvinen, 1995     | 252 at-risk persons from 20 of 22 families with MMR mutations | Observational; all invited for colonoscopy screening; 133 had every 3 y colonoscopy, 118 declined colonoscopy | 62% less CRC in screened (P = 0.03)  
Tumor stage more favorable in screened  
No deaths in screened vs 5 deaths in non-screened |
| Jarvinen, 2000     | 252 at-risk persons from 20 of 22 families with MMR mutations | Observational; follow-up reference 129 | 62% reduction in CRC in screened (P = 0.02)  
No deaths from CRC in screened vs 9 deaths in non-screened |
| de Vos tot Nederveen Cappel, 2002 | 857 members of 114 HNPCC or MMR-positive families | Observational- tumor stage with more frequent (≤ 2 y) vs less frequent colonoscopy; 10-y risk of CRC with partial vs subtotal colectomy | Earlier stage CRC with more frequent colonoscopy  
15.7% risk of CRC with partial vs 3.4% with subtotal colectomy at 10 y |
| Dove-Edwin, 2005   | 554 at-risk members of 290 families with HNPCC or MMR mutations | Prospective observational; evaluation of efficacy of colonoscopy surveillance | Estimated 72% disease in CRC death in screened individuals |
| Jarvinen, 2009     | 242 MMR mutation-positive and 367 mutation-negative subjects | Observational: cancer incidence/survival at 11.5 y follow-up of colonoscopy surveillance | No increase in cancer mortality in mutation positive vs negative persons |
| Stuckless, 2012    | 322 MSH2 mutation carriers | Observational: cancer incidence and survival in 152 screened vs 170 not screened by colonoscopy | Median age to CRC later in screened vs non-screened  
Survival statistically improved in screened vs non-screened |

Hereditary Colorectal Cancer- Lynch Syndrome

Progression from adenoma to cancer is accelerated

- Colon cancer 6% vs 16%
- Relative risk of CRC 0.377 (reduction of cancer by 62%)
- Death due to CRC 0 vs 9%

Hereditary Colorectal Cancer- Lynch Syndrome

Figure 1. Cumulative proportion of subjects free of CRC. \(^aP = 0.019\) between the screening and control groups including all subjects. \(^bP = 0.034\) between mutation-positive subjects of the screening and control groups.

Figure 3. Cumulative overall survival. \(^aP = 0.003\) between the screening and control groups including all subjects. \(^bP = 0.05\) between mutation-positive subjects of the screening and control groups.

Lynch Syndrome

**Endometrial Cancer**

- Most common extracolonic cancer
- More common with MSH6 (73% risk)
- MLH1 (31% risk) & MSH2 (29%)
- Average age at diagnosis: 54.6 (63 in sporadic)
- “Sentinel cancer” in over half of women w/ HNPCC

Lynch Syndrome

**Muir-Torre**
- Sebaceous adenomas, carcinomas, and keratoacanthomas
- Frequently w/colorectal malignancy
- Demonstrates MSI-H (MLH1 and MSH2)

**Turcot’s Syndrome** (Glioblastoma multiforme)

Lawes et al., BJS. 2002:89: 1357-1369
Muir-Torre

Sebaceous hyperplasia

keratoacanthoma

Sebaceous adenocarcinoma
### Studies of Endometrial and Ovarian Cancer Screening and Prophylactic Surgery in Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Subjects</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dove-Edwin, 2002</td>
<td>292 women from HNPCC or HNPCC-like families</td>
<td>Observational: all offered transvaginal ultrasound</td>
<td>2 cases of EC presented with symptoms, neither detected by ultrasound</td>
</tr>
<tr>
<td>Rijcken, 2003</td>
<td>41 women with MMR mutations or fulfilled Amsterdam I criteria followed for median of 5 y</td>
<td>Observational: all offered annual pelvic examination, transvaginal ultrasound, CA-125</td>
<td>17 of 179 ultrasounds gave reason for endometrial sampling with 3 premalignant lesions noted; 1 interval EC presented symptomatically</td>
</tr>
<tr>
<td>Renkonen-Sinisalo, 2007</td>
<td>175 women with MMR mutations</td>
<td>Observational: all offered transvaginal ultrasound and endometrial biopsy</td>
<td>14 cases of EC; 11 diagnosed by surveillance. Biopsy diagnosed 8 of 11 ECs and 14 cases of premalignant hyperplasia. Ultrasound indicated 4 EC cases but missed 6 others. 4 cases of ovarian cancer, none found by ultrasound</td>
</tr>
<tr>
<td>Lécuru, 2008</td>
<td>62 women (13 with MMR mutation, 49 met Amsterdam II criteria)</td>
<td>Observational: annual hysteroscopy and endometrial biopsy</td>
<td>3 malignancies in 3 patient with abnormal bleeding; 3 cases of hyperplasia in asymptomatic patients; hysteroscopy 100% sensitive for cancer or hyperplasia</td>
</tr>
<tr>
<td>Gerritzen, 2009</td>
<td>100 women from families with MMR mutation</td>
<td>Observational: annual transvaginal ultrasound, CA-125, endometrial sampling</td>
<td>3 atypical hyperplasias and 1 endometrial cancer diagnosed 1 stage III ovarian cancer developed despite ultrasound</td>
</tr>
<tr>
<td>Stuckless, 2013</td>
<td>174 women with MSH2 gene mutation</td>
<td>Case-control: Cases: 54 patients with at least 1 screening examination (transvaginal, endometrial biopsy or CA-125 test) Controls: matched women without screening</td>
<td>Stage I/II cancer diagnosed in 92% of screened patients compared with 71% in control group ((P = .17)). 2 of 3 deaths in the screened group from ovarian cancer</td>
</tr>
<tr>
<td>Schmeler, 2006</td>
<td>315 women with MMR mutation with and without gynecologic surgery</td>
<td>Retrospective: risk of uterine and ovarian cancer in patients with and without prophylactic/clinically indicated gynecologic surgery</td>
<td>No uterine or ovarian cancer in surgery group vs 33% and 5% cancer, respectively, in nonsurgery group</td>
</tr>
</tbody>
</table>

Lynch Syndrome

- 887 with gene defect and/or met Amsterdam
- Surveillance interval of < 2yrs vs. > 2yrs
- < 2 yrs (6 cancers)
  Dukes A (1), B (5)
- >2 yrs (16 cancers)
  Dukes A (4), B (7), C (5)

**Cumulative Risk for Mutation Carriers**
10.5% at 10 years

Nederveen Cappel et al, DCR 2002
Lynch Syndrome

**Prophylactic total colectomy**
- Unable to have colonoscopic surveillance
- Patients overly fearful of developing cancer

**Prophylactic TAH-BSO**
- If needed for benign disease
- Strongly consider at the time of colectomy

Lynch Syndrome

116 HNPCC patients (10-yr follow up)
- 24% metachronous lesion after segmental resection

39 families fulfilling Amsterdam criteria (13 yr follow up)
- 23% after right hemicolecotomy
- 31% after left hemicolecotomy
- 0% after TC + IRA

## Risk of Metachronous Colorectal Cancer in Lynch Syndrome Patients With Colectomy

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Subjects</th>
<th>Design</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Vos tot Nederveen Cappel, 2002</td>
<td>110 patients with MMR gene mutation or meet HNPCC criteria with CRC and partial colectomy; 29 MMR gene mutation patients with colorectal cancer and total colectomy</td>
<td>Observational; risk of colorectal cancer in patients with partial vs subtotal colectomy</td>
<td>10-y cumulative risk of colorectal cancer 15.7% with partial colectomy and 3.4% after subtotal colectomy</td>
</tr>
<tr>
<td>Win, 2013</td>
<td>79 patients with MMR gene mutation and proctectomy for rectal cancer undergoing post surgical surveillance by colonoscopy on average every 1.6 y</td>
<td>Observational; retrospective cohort study of risk of metachronous colon cancer after surgery</td>
<td>Cumulative risk of colon cancer was 19%, 47%, 69% at 10, 20, and 30 y, respectively</td>
</tr>
<tr>
<td>Parry, 2001</td>
<td>332 MMR gene mutation carriers with CRC and partial colectomy; 50 patients with CRC and extensive colectomy</td>
<td>Observational; retrospective cohort study of risk of colorectal cancer in patients with partial vs subtotal colectomy</td>
<td>Cumulative risk of colon cancer was 16%, 41%, 62%, at 10, 20, and 30 y, respectively. None of patients with extensive surgery diagnosed with CRC</td>
</tr>
<tr>
<td>Kalady, 2012</td>
<td>55 HPNCC patients with proctectomy for rectal cancer undergoing postsurgical surveillance by colonoscopy</td>
<td>Observational; retrospective cohort study of risk of advanced neoplasia (cancer and severe dysplasia) in patients with proctectomy</td>
<td>55% advanced neoplasia (15.2% developed colon cancer at median of 6 y)</td>
</tr>
</tbody>
</table>

Lynch Syndrome

*Patients with CRC or Advanced Adenoma*

- Total colectomy and ileorectal anastomosis (IRA)

- The choice of IRA assumes the anal sphincter and rectum function normally

- Hemicolecctomy and yearly colonoscopy

Patients with rectal cancer

- Total proctocolectomy and IPAA
- Anterior resection, assuming that sphincter can be saved

Rectal cancer risk after IRA?

- 71 pts followed for 13 years
- 11% developed rectal cancer
- Only 1 advanced CA (no surveillance)
- Overall risk = 12% at 12 years

Risk of Colonic Neoplasia After Proctectomy for Rectal Cancer in Hereditary Nonpolyposis Colorectal Cancer

Of the 33 patients followed after proctectomy, 13 had metachronous high-risk adenomas and five patients had metachronous cancer. One of these patients developed two high-risk adenomas before the cancer. Thus, 17 patients (51.5%) developed either metachronous high-risk adenomas or cancer after proctectomy.

Risk of Colonic Neoplasia After Proctectomy for Rectal Cancer in Hereditary Nonpolyposis Colorectal Cancer

Kaplan-Meier curves for:
(A) survival without formation of either a high-risk adenoma or colon cancer following proctectomy
(B) colon-cancer free survival following proctectomy.

Risk of Colonic of Ovarian Ca –Lynch Syndrome

**Figure 1.** Cumulative Incidence of Endometrial Cancer among Women with the Lynch Syndrome Who Underwent Prophylactic Hysterectomy and Those Who Did Not.

<table>
<thead>
<tr>
<th>Years</th>
<th>No. at Risk</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hysterectomy</td>
<td>210</td>
<td>106</td>
<td>52</td>
<td>28</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>61</td>
<td>39</td>
<td>28</td>
<td>25</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Cumulative Incidence of Ovarian Cancer among Women with the Lynch Syndrome Who Underwent Prophylactic Bilateral Salpingo-Oophorectomy (BSO) and Those Who Did Not.

<table>
<thead>
<tr>
<th>Years</th>
<th>No. at Risk</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>No BSO</td>
<td>223</td>
<td>131</td>
<td>83</td>
<td>65</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>BSO</td>
<td>47</td>
<td>28</td>
<td>19</td>
<td>16</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

# Cumulative Risks of Extracolorectal Cancer by Age 70 in Lynch Syndrome

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Risk general population %</th>
<th>Risk in LS, %</th>
<th>Mean age at diagnosis, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrium</td>
<td>2.7</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>MLH1/MSH2</td>
<td>14-54</td>
<td>48-62</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>17-71</td>
<td>54-57</td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td>15</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>&lt;1</td>
<td>0.2-13</td>
<td>49-55</td>
</tr>
<tr>
<td>Ovary</td>
<td>1.6</td>
<td>4-20</td>
<td>43-45</td>
</tr>
<tr>
<td>Hepatobiliary tract</td>
<td>&lt;1</td>
<td>0.02-4</td>
<td>54-57</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>&lt;1</td>
<td>0.2-25</td>
<td>52-60</td>
</tr>
<tr>
<td>Small bowel</td>
<td>&lt;1</td>
<td>0.4-12</td>
<td>46-49</td>
</tr>
<tr>
<td>Brain/central nervous system</td>
<td>&lt;1</td>
<td>1-4</td>
<td>50</td>
</tr>
<tr>
<td>Sebaceous neoplasm</td>
<td>&lt;1</td>
<td>1-9</td>
<td>NA</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1.5</td>
<td>0.4-4.0</td>
<td>63-65</td>
</tr>
<tr>
<td>Prostate</td>
<td>16.2</td>
<td>9-30</td>
<td>59-60</td>
</tr>
<tr>
<td>Breast</td>
<td>12.4</td>
<td>5-18</td>
<td>52</td>
</tr>
</tbody>
</table>

NA, not available

Lynch Syndrome

5-FU-based chemoadjuvant therapy benefits patients with stage II-III CRC and MSS, but not those with MSI-H.

MLH1 and MSH2 expression provides useful prognostic information for the management of stage II &III colorectal cancer patients.

Ribic, et al. NEJM 2003;349:247-257
Lanza et al. J Clin Oncol 2006;24:2359-2367
Quality of Life After Surgery For Colon Cancer in Patients With Lynch Syndrome: Partial vs Subtotal Colectomy

Haanstra JF et al. DCR 2012;55:653-659
Quality of Life After Surgery For Colon Cancer in Patients With Lynch Syndrome: Partial vs Subtotal Colectomy

Results SF-36. A higher score represents a higher level of functioning. Error bars, ±1 SD. SF-36 = Short Form-36 health survey.

Haanstra JF et al. DCR 2012;55:653-659
Quality of Life After Surgery For Colon Cancer in Patients With Lynch Syndrome: Partial vs Subtotal Colectomy

Results EORTC QLQ CR-38. A, Functional scales and single items (sexual enjoyment and future perspective): A higher score indicates better functioning. Error bars, ±1 SD. B, Symptom scales and the single item weight loss: A higher score indicates a higher level of symptomatology. Error bars, ±1 SD. EORTC QLQ CR-38 = European Organization for Research and Treatment of Cancer Colorectal Cancer-specific Quality of Life Questionnaire Module.

Haanstra JF et al. DCR 2012;55:653-659
Quality of Life After Surgery For Colon Cancer in Patients With Lynch Syndrome: Partial vs Subtotal Colectomy

Results COREFO. Higher scores represent a higher level of symptomatology. Error bars, ± 1 SD. COREFO = Colorectal Functional Outcome.

Haanstra JF et al. DCR 2012;55:653-659
Familial Adenomatous Polyposis (FAP)

- Inherited, non sex-linked, Mendelian dominant disease
- Clinical diagnosis on histologic confirmation of at least 100 adenomas
- Genetic defect of APC gene 5q21-22.

Vasen HF et al, Gut 2008;57:704
Treatment for FAP

• Treatment should include thorough counseling about the nature of the syndrome, its natural history, its extra-colonic manifestations and the need for compliance with recommendations for management and surveillance.

Clinical Guidelines for the management of Inherited Polyposis Syndromes” prepared by the Clinical Practice Guidelines Committee 2017 DCR Sep;60(9):881-894
Extracolonic Manifestations

- Duodenal adenomas (>90% of FAP pts)
- EGD as screening
- (114 pts 26% increase in size, 32% in number and 11% in grade-histology)
- Screening q1-q3 years
- Tx: Duodenectomy or pancreatoduodenectomy

Extracolonic Manifestations

- Desmoid tumors (cumulative risk is 21%)
- Gardner Syndrome (osteomatosis, epidermoid cysts & fibromas of the skin)
- Turcot’s (medulloblastoma)

Treatment for FAP

- Proctocolectomy with ileostomy or ileal pouch-anal anastomosis is the treatment of choice for patients with large number of rectal adenomas, but the optimal timing should be individualized.

- IPAA standard procedure (very few exceptions: 20 rectal adenoma less than total 1000 colonic polyps mutations not at 0-200 codons or>1500)

Clinical Guidelines for the management of Inherited Polyposis Syndromes 2017 DCR
Sep;60(9):881-894
Surgical Management

• Total proctocolectomy with rectal mucosectomy and ileoanal pouch
Ileorectal anastomosis versus Ileoanal anastomosis (IPAA)
Ileorectal anastomosis versus Ileoanal anastomosis (IPAA)

10-year for IRA or IPAA group were 0.87 (95% CI 0.83-0.90) vs. 0.83 (95% CI 0.77-0.90), respectively.

Cumulative rectal cancer risk 4.0%, 5.6%, 7.9%, and 25% at 5, 10, 15 and 20 years after IRA.

Very small risk for adenocarcinoma after IPAA
AZT neoplasia – risk of adenoma at 10 years ranges 10-22% after mucosectomy vs 31-51% after stapled anastomosis.

Clinical Guidelines for the management of Inherited Polyposis Syndromes” 2017 DCR
Sep;60(9):881-894
Van Duijvendijk etal:J Gastrointest.Surg.1999;3:325
Ileoanal anastomosis (IPAA)

• Annual endoscopic surveillance of the remaining rectal and ATZ mucosa and ileal pouch must be performed

• Total proctocolectomy with end ileostomy considered for poor sphincter function, incontinence, distal rectal cancer cancers requiring radiation.

Clinical Guidelines for the management of Inherited Polyposis Syndromes” 2017 DCR Sep;60(9):881-894
MYH associated polyposis

- Timing and type of surgery in patients with biallelic MYH mutation depend on the ability to maintain clearance of polyps, the rectal polyp burden, and the presence of malignancy.
- 28-fold increased risk of CRC over the geneal population.
- 19% by age 50, 43% by age 60, 80% by age 80.

QUESTIONS?

Thank you!
Hereditary Colorectal Cancer
Hereditary Component of Colorectal Cancer

Hereditary Colorectal Cancer
Hereditary Component of Colorectal Cancer

**Relative risk**
First degree relative with adenoma: 1.78
(Lifetime risk: 11%)

First degree relative with cancer: 2.62
(Lifetime risk 16%)

Amsterdam I and II Criteria for Diagnosis of Hereditary Nonpolyposis Colorectal Cancer

Amsterdam I criteria
1. Three or more relatives with histologically verified colorectal cancer, 1 of which is a first-degree relative of the other two. Familial adenomatous polyposis should be excluded.
2. Two or more generations with colorectal cancer.
3. One or more colorectal cancer cases diagnosed before the age of 50 years.

Amsterdam II criteria
1. Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), 1 of which is a first-degree relative of the other 2. Familial adenomatous polyposis should be excluded.
2. Cancer involving at least 2 generations.
3. One or more cancer cases diagnosed before the age of 50 years.

Revised Bethesda Guidelines

1. CRC diagnosed at younger than 50 years.
2. Presence of synchronous or metachronous CRC or other LS-associated tumors.
3. CRC with MSI-high pathologic-associated features (Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old.
4. Patient with CRC and CRC or LS-associated tumor diagnosed in at least 1 first-degree relative younger than 50 years old.
5. Patient with CRC and CRC or LS-associated tumor at any age in 2 first-degree or second-degree relatives.

*LS-associated tumors include tumor of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and keratoacanthomas.

Lynch Syndrome

**Colon**
Colonoscopy at age 25; repeat every 1-2 yrs annually after age 40.

**Uterus/ovaries**
Transvaginal U/S and/or endometrial aspiration and/or CA-125 at age 25-35; repeat every 1-2 yrs.

Lynch Syndrome

**Stomach**
Upper endoscopy, repeated annually if family history of gastric tumor

**Kidney/ureter/bladder**
Urine cytology and renal U/S if family history of urothelial tumor

**Pancreas/small bowel/brain**
No practical screening/surveillance