COLORECTAL CANCER

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Dept of Gastroenterology & Hepatology
National University Hospital
## Cancer Incidence in Singapore 1993-97

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>3,158</td>
<td>Breast</td>
</tr>
<tr>
<td>Colorectal</td>
<td>2,570</td>
<td>Colorectal</td>
</tr>
<tr>
<td>Stomach</td>
<td>1,435</td>
<td>Lung</td>
</tr>
<tr>
<td>Liver</td>
<td>1,296</td>
<td>Cervix</td>
</tr>
<tr>
<td>NPC</td>
<td>1,121</td>
<td>Stomach</td>
</tr>
<tr>
<td>Prostate</td>
<td>903</td>
<td>Ovary</td>
</tr>
</tbody>
</table>

Singapore Cancer Registry
# Cancer Incidence in Singapore 1998-2002

Singapore Cancer Registry

**Preliminary Data for 1998-2002**

**TEN MOST FREQUENT CANCERS IN SINGAPORE, ALL RESIDENTS, 1998-2002.**

<table>
<thead>
<tr>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rank</td>
<td>Site</td>
</tr>
<tr>
<td>------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>1</td>
<td>Lung</td>
</tr>
<tr>
<td>2</td>
<td>Colo-rectum</td>
</tr>
<tr>
<td>3</td>
<td>Liver</td>
</tr>
<tr>
<td>4</td>
<td>Stomach</td>
</tr>
<tr>
<td>5</td>
<td>Prostate</td>
</tr>
<tr>
<td>6</td>
<td>Nasopharynx</td>
</tr>
<tr>
<td>7</td>
<td>Skin (Incl. melanoma)</td>
</tr>
<tr>
<td>8</td>
<td>Lymphomas</td>
</tr>
<tr>
<td>9</td>
<td>Bladder</td>
</tr>
<tr>
<td>10</td>
<td>Leukemias</td>
</tr>
</tbody>
</table>
Colorectal Carcinoma

Colorectal cancer (CRC) is:
- the commonest cancer in Singapore among men
- the second commonest cancer in Singapore among women

The average population risk for developing colorectal cancer in Singapore is among the highest in the world

The age-standardized rates (ASR) for the period 2002-2006 was:

MEN - 40.2 per 100,000 per year
WOMEN – 28.8 per 100,000 per year

Sources:
- Sung JJY et al, Lancet Oncol, 2005;6:871-76
- Sung JJY, Cancer Detection & Prevention, 2007;31:1-2
Figure 2: Incidence of cancer in the colon and rectum in Asian populations compared with US and UK populations (1993–97)

Data extracted from Cancer Incidence in Five Continents volumes I–VIII, IARC CancerBase number 7, Lyon, 2005.
Progression from polyp to cancer
Colon polyp
Colon Cancer
Colon polyp  Snaring of polyp  After polypectomy
Figure 114–3. Distribution of colorectal cancers within the large intestine. Only half of cancers are within reach of the flexible sigmoidoscope.
## Disease Distribution

<table>
<thead>
<tr>
<th>Site</th>
<th>No</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>12</td>
<td>16.7</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>13</td>
<td>18.1</td>
</tr>
<tr>
<td>Descending</td>
<td>11</td>
<td>15.3</td>
</tr>
<tr>
<td>Transverse</td>
<td>10</td>
<td>13.9</td>
</tr>
<tr>
<td>Ascending</td>
<td>16</td>
<td>22.2</td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>2</td>
<td>2.7</td>
</tr>
<tr>
<td>Caecum</td>
<td>8</td>
<td>11.1</td>
</tr>
</tbody>
</table>

**L-sided 50.1%**

**R-sided 49.9%**
# Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Table 114.7 · Risk Factors for Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-fat, low-bulk diet</td>
<td></td>
</tr>
<tr>
<td>Age &gt;40 yr</td>
<td></td>
</tr>
<tr>
<td>Personal history of</td>
<td></td>
</tr>
<tr>
<td>Colorectal adenomas (synchronous or metachronous)</td>
<td></td>
</tr>
<tr>
<td>Colorectal carcinoma</td>
<td></td>
</tr>
<tr>
<td>Family history of</td>
<td></td>
</tr>
<tr>
<td>Polyposis syndromes: familial polyposis coli; Gardner’s syndrome; Turcot’s syndrome (&gt;100 adenomas); Muir’s syndrome (scattered adenomas); Peutz-Jeghers syndrome; familial juvenile polyposis (from adenomas, not hamartomas)</td>
<td></td>
</tr>
<tr>
<td>Nonpolyposis inherited colon cancer; hereditary site-specific colon cancer; cancer family syndrome</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with colorectal cancer</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>Especialy with high-grade dysplasia or dysplasia-associated mass lesions</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td></td>
</tr>
</tbody>
</table>
Risk Factors

1. Personal history / risk
2. Family history / risk
3. Polyp type / features
1. Personal history and CA risk

- Personal history of CA
  - 1.5-3% cancer risk in 5 years

- Size of Polyp >1cm, multiple polyps and villous & tubullovillous polyp
  - RR 3.5-6.5

- Single small polyp – RR not increased
Risk Factors

2. Family history of polyps & CA risk

1° relative with polyp - RR 1.78
(1.1-2.67)

10 Siblings with polyp before 60 - RR 2.59 (1.46-4.58)

cf siblings with polyps after 60

Data from the US national polyp study
3. Family history of CA and CA risk

<table>
<thead>
<tr>
<th>Relative risk (95%CI)</th>
<th>Age adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>One 1° relative with CA</td>
<td>1.72 (1.34 – 2.19)</td>
</tr>
<tr>
<td>Age &lt;45</td>
<td><strong>5.37 (1.98-17.4)</strong></td>
</tr>
<tr>
<td>Age &gt;65</td>
<td>1.09 (0.52-2.28)</td>
</tr>
<tr>
<td>Two 1° relative with CA</td>
<td>2.75 (1.34-5.63)</td>
</tr>
<tr>
<td>One 1° relative &lt;50</td>
<td><strong>4.16 (2.83-5.91)</strong></td>
</tr>
<tr>
<td>Two 2° or 3° relative</td>
<td>Little increased</td>
</tr>
</tbody>
</table>

CS FuchsNEJM 1994,331:1669;  
Polyp type / features

Classifications of polyps and CA risk

- Polyps: Tubular, Tubulovillous, Villous
- Dysplasia:
  - Mild, Moderate dysplasia
  - High-grade / Severe dysplasia
- Polyp size: Large >1.0cm increased risk
  7.7x
Clinical Manifestations

- Abdominal pain — 44%
- Change in bowel habit — 43%
- Hematochezia or melena — 40%
- Weakness — 20%
- Anemia without other gastrointestinal symptoms — 11%
- Weight loss — 6%
Signs

- Abdominal mass on examination
- Low red blood cell (hemoglobin) count / Anemia - pale
- Blood in stools on anal examination
- Palpable anal mass on anal digital examination
Investigations

- Total Colonoscopy- synchronous lesions
- FBC
- Pre-operative CEA
- LFT
- CT abdomen & pelvis
- CXR
- Assess for Cardio-respiratory fitness
<table>
<thead>
<tr>
<th>Stage Duke’s</th>
<th>5-year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Limited to bowel wall)</td>
<td>94.3</td>
</tr>
<tr>
<td>B (Through bowel wall)</td>
<td>84.4</td>
</tr>
<tr>
<td>C (Regional nodes)</td>
<td>56.5</td>
</tr>
<tr>
<td>D (Distant metastases)</td>
<td>2.4</td>
</tr>
</tbody>
</table>
STAGING-TNM

5-year survival %

- Stage I (T1-2N0) — 93 %
- Stage IIA (T3N0) — 85 %
- Stage IIB (T4N0) — 72 %
- Stage IIIA (T1-2 N1) — 83 %
- Stage IIIB (T3-4 N1) — 64 %
- Stage IIIIC (N2) — 44 %
- Stage IV — 8 %
Treatment

- Surgical resection with end-to-end anastomosis (permanent colostomy)
- Adjuvant chemotherapy - 5FU/fluorouracil & levamisole in Dukes’ C (TNM stage III)
  - ie lymph node +ve
  - reduced risk of CRC recurrence by 42%
  - reduced overall death rate by 33% cf surgery alone
- Palliative chemotherapy for advanced disease - disappointing, 5FU & high-dose leucovorin
Post-surgery Follow up

- 80% of recurrences after CRC resection occur within the first 2 years post-surgery - therefore more intensive follow up during this period
- Colonoscopy surveillance 3-5 yearly
  - 5-10% of pts dev metachronous tumours
- CEA
- Liver imaging
- No final survival advantage demonstrated by randomized studies as of yet
Metastasis

- 15 to 20% pts have distant metastatic disease at the time of presentation.
- CRCs can spread by
  - lymphatic
  - hematogenous dissemination, as well as by
  - contiguous and transperitoneal routes.
- Most common metastatic sites
  - regional lymph nodes
  - Liver -10-25% pts
  - lungs
  - Peritoneum

Patients may present with signs or symptoms referable to any of these areas.
1.0 INTRODUCTION
There has been increasing recognition of the potential benefits of liver resection for colorectal metastases in the UK although this treatment has been established more widely in other Western countries. There are no randomised studies assessing outcome following resection compared with no treatment or other therapeutic modalities in patients with known resectable liver metastases as it is generally considered unethical not to offer surgery for resectable disease. There has been increased interest in more aggressive chemotherapy regimens that have been reported to not only control metastatic disease but also to render some advanced liver
### 5.5 Liver resection for colorectal metastases

- The aim of liver resection (resectability) is to remove all macroscopic disease with clear (negative) margins and leave sufficient functioning liver. (Category of evidence II; strength of recommendation B)

- Patients with solitary, multiple, and bilobar disease who have had radical treatment of the primary colorectal cancer are candidates for liver resection. (Category of evidence III; strength of recommendation C)

- The ability to achieve clear margins (R0 resection) should be determined by the radiologist and surgeon in the regional hepatobiliary unit. (Category of evidence III; strength of recommendation C)

- The surgeon should define the acceptable residual functioning volume, approximately one third of the standard liver volume, or the equivalent of a minimum of two segments. (Category of evidence III; strength of recommendation C)

- The liver surgeon and anaesthetist should take the clinical decision regarding fitness for surgery. (Category of evidence III; strength of recommendation C)

- If deemed medically unfit for surgery, patients should be considered for ablative therapy. (Category of evidence IV; strength of recommendation D)
Screening....WHY SCREEN?

- Common and lethal
- Long asymptomatic interval
  - Adenoma-carcinoma sequence 10-15 years
    - Polyp dwell time – Low rate of adenoma progression to Ca: 2.5 polyps /1000/ year.
- Safe, effective, feasible screening tests available
- Early detection & treatment improves survival
- Benefits from screening outweigh risks or adverse effects
Screening Recommendations

Population-based screening of AVERAGE RISK individuals (AGA, ACG, ACS etc)
Start at 50 yo, stop at 85 yo

1. Annual FOBT >50 yo and / or
2. Colonoscopy every 10 years
3. Flexible sigmoidoscopy every 5 yrs >50 yo
   A positive screen is an indication for colonoscopy
4. DCBE every 5-10 years
Current Recommendations

High risk groups

- 1° relative with CRC <55yo or polyp <60yo - start at 40 yo
- Large (>1cm) or multiple polyps
- colonoscopy in 3 years
Colorectal Cancer Screening in Singapore

Government policies

MOH Singapore Clinical Practice Guidelines

• Endorses colorectal cancer screening

• Recommendations for
  ▪ Average risk
  ▪ High risk
  ▪ Very High risk groups

• Clinical care eligible for public subsidies
## Screening for Colorectal Cancer

### Clinical Practice Guidelines, Ministry of Health, Singapore

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Screen Tool</th>
<th>Onset</th>
<th>Freq</th>
<th>Evidence</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Risk</strong></td>
<td>FOBT</td>
<td>50</td>
<td>Annually</td>
<td>Ia</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Fl sigmoidoscopy</td>
<td>50</td>
<td>Every 5y</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy</td>
<td>50</td>
<td>Every 10y</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Barium enema</td>
<td>50</td>
<td>Every 5-10y</td>
<td>IV</td>
<td>C</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>Colonoscopy</td>
<td>10y prior</td>
<td>Every 3y</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>1. CRC in 1st deg relative≤45 or two or more 1st deg rel</td>
<td>Colonoscopy</td>
<td>10y prior</td>
<td>Every 10y</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>2. CRC in 1st deg relative&gt;45</td>
<td>Colonoscopy</td>
<td>10y prior</td>
<td>Every 10y</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>3. Personal hx colon polyps</td>
<td>Colonoscopy</td>
<td>3y (hi risk) or 5y (lo risk)</td>
<td>Ib</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>4. Pers hx colorectal cancer</td>
<td>Colonoscopy</td>
<td>1y after resection</td>
<td>IIa</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td><strong>Very high risk</strong></td>
<td>Colonoscopy</td>
<td>1y after resection</td>
<td></td>
<td>IV</td>
<td>C</td>
</tr>
<tr>
<td>1. FH FAP</td>
<td>Fl sigmoid, genetic testing</td>
<td>12-14y</td>
<td>Annually</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>2. FH HNPCC</td>
<td>Colonoscopy, genetic testing</td>
<td>10y prior</td>
<td>Every 2y</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>3. IBD</td>
<td>Colonoscopy</td>
<td>15y (left-c) or 8y (pan)</td>
<td>IIb</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>
FOBT kit (Haemoccult Sensa / HOS)  
Guaiac based
FOBT kit
Immunochemical FOBT (IFOBT)

- Antibody to human Hb
- IFOBT is more specific and does not require dietary restrictions

- FOBT : 3 consecutive sample collection
- IFOBT : 2 consecutive sample collection
IFOBT kit

Green cap → Sampling Bottle → Sampling Probe → Sample feces at 6 places. → Cover groove Completely → Shake vigorously → For Assay
1. FOBT

- RCT Minnesota
- Follow up 13 yrs. Mainly rehydrated specimens

<table>
<thead>
<tr>
<th>Freq</th>
<th>13yr cum †/1000</th>
<th>† reduction %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual</td>
<td>5.88</td>
<td>33 Signif</td>
</tr>
<tr>
<td>Biennial</td>
<td>8.33</td>
<td>6 NS</td>
</tr>
<tr>
<td>Control</td>
<td>8.83</td>
<td></td>
</tr>
</tbody>
</table>

*Mandel JS et al NEMJ 93;328:1365-71*
## RESULTS OF FOBT TRIALS

<table>
<thead>
<tr>
<th>STUDY</th>
<th>N</th>
<th>Mortality</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minnesota</td>
<td>46,551</td>
<td>36%</td>
<td>Improved</td>
</tr>
<tr>
<td>New York</td>
<td>12,479</td>
<td>43%</td>
<td>Improved</td>
</tr>
<tr>
<td>Denmark</td>
<td>61,993</td>
<td>18%</td>
<td>Improved</td>
</tr>
<tr>
<td>England</td>
<td>150,251</td>
<td>15%</td>
<td>Improved</td>
</tr>
<tr>
<td>Sweden</td>
<td>68,308</td>
<td>33%</td>
<td>Improved</td>
</tr>
</tbody>
</table>
Flexible Scope
Scope room setup
Colonoscopy

Risks / Complications

- 0.1 – 0.3% intestinal perforation
- 0.1% bleeding
- 0.01% mortality / death
COLONOSCOPY
National Polyp Study

- 1418 pts colonoscopy: ≥1 adenoma, no prior polypectomy.
- F-up 5.9 years-97% pts, 8401 person-yrs
- 76% reduced incidence of CRC by colonoscopic removal of polyps

Canadian study: Database of nearly 2.4 million patients who were undergoing colonoscopy and looked at cancer reduction.

- They showed that for every 1% increase in utilization of colonoscopy, there was a 3% reduction in colon cancer death.

Normal DCBE
Polyps – 2 polyps
Cancer – large irregular filling defect, extent of tumour indicated by arrows
Colorectal Cancer Screening in Singapore

Which Screening Test for Population screening?

Cost-effectiveness analysis using decision model

Target population 50-70y, 495,000 people

- FOBT
- Colonoscopy
- DCBE
- Screen
- Flex Sig
- Colonoscopy
- DCBE

FOBT annually
Rpt Colonoscopy 10y
Rpt DCBE 5y
Rpt Flex Sig 3y

Yeoh
Simulation Model for Population screening in Singapore

Target population 50-70y, n=495,000

Offered FOBT screening

Compliance assumed 50%

FOBT uptake

2%

FOBT + ve

4950

Colonoscopy

4950

FOBT - ve

242550

Annual FOBT

Colonoscopy 3yrly

Annual FOBT

Surgery / Other Rx

Hospitalisation 1/7 Transfusion

Barium enema

Hospitalisation 4/7 Laparotomy

Minor eg bleeding

Major eg perf

Death

Complication, Minor eg bleeding

Complication, Major eg perf

Normal

Adenoma >1cm

Small polyp

Cancer

Incomplete

Complication, Minor eg bleeding

Complication, Major eg perf

Total cost $7,593,400

Yeoh
Which Screening Test is Cost-Effective?

Cost-effectiveness analysis using decision model

Conclusions:

FOBT has the lowest cost-per-life year gained

Calculated cost $2,681,008 (20% compliance)

$8,043,024 (60% compliance)
Population survey 2000 adults
- 1000 tel (85% compliance), 1000 mail (21.5% compliance),
- 1067 respondents

20 questions on knowledge of disease, symptoms, screening

Eg
- “What tests are available to detect colorectal cancer?“
- “What are the symptoms of Colorectal Cancer?“

Wong NY et al. Adults in a high risk area are unaware of the importance of Colorectal cancer. Dis Colon Rectum 2002; 45:946
**Population Awareness of CRC in Singapore**

- Awareness of screening as a important measure:
  - T 11%, M 35.8%

- Unable to name even one symptom of CRC:
  - T 46.5%, M 34.9%

- Poor general knowledge on CRC and screening
  - Higher education level (> college)
  - Positive family history
  - Newspapers and popular magazines > effective than TV or Drs

*Wong NY et al, Dis Colon Rectum 2002; 45:946*
SPECIAL ARTICLE

ACG Colorectal Cancer Prevention Action Plan: Update On CT-Colonography

Douglas K. Rex, M.D., F.A.C.G.¹ and David Lieberman, M.D., F.A.C.G.²
¹Indiana University School of Medicine, Indianapolis, Indiana; and ²Division of Gastroenterology, Oregon Health and Science University, Portland, Oregon

(Am J Gastroenterol 2006;101:1410–1413)

INTRODUCTION

As part of its Action Plan on Colorectal Cancer Prevention (1), the American College of Gastroenterology (ACG) will provide intermittent updates for clinicians on key developments on alternative colorectal cancer screening tests. This update provides a clinical perspective on the current status of computed tomography-colonography (CTC; virtual

Table 1. Results of the Four Largest Clinical Trials of CTC

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Sensitivity for Adenomas or Polyps ≥1 cm (Per Patient Basis) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1,233</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>703</td>
<td>48</td>
</tr>
<tr>
<td>9</td>
<td>615</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>614</td>
<td>59</td>
</tr>
</tbody>
</table>
CT Colonography

- 16 years since its introduction

**Advantages**
- Detection rates similar for >10mm polyp lesions
- No perforation risk
- Detects extracolonic lesions
- Useful when conventional /optical colonoscopy cannot be successfully completed
- “Prepless CTC” in trials, but not in clinical practice
CT Colonography

Disadvantages

- Unable to detect flat adenomas
- Learning curve for general radiologist reporting CTC
- Radiation risk (NB 1% of all cancer deaths in USA related to medical radiation!)
- Same problem as optical colonoscopy – no evidence that use of CTC will improve adherence to CRC screening

- De Gonzalez A et al Lancet 2004;363:345-51
CT Colonography

Disadvantages

CT colography was incredibly more costly, and less cost effective than any of the other modalities. In particular, in the head-to-head with colonoscopy,

Current ACG recommendations for CTC in clinical practice

1. Pts with any polyps ≥6mm in size or 3 polyps of any size should be offered colonoscopy and polypectomy

2. Findings of 1 or 2 polyps <5mm with moderate to high confidence should be reported and if pts are not offered polypectomy they should be informed of the findings

3. Pts undergoing CTC for screening should be informed of the risk of cancer assoc with radiation
CT Colonography

- Meta-analysis of published clinical trials – overall detection rates are inadequate for endorsement of CTC at this time
- Intervals between CTC examinations uncertain (if 6-9mm CTC repeated in 1-2 yr intervals)

Screening Recommendations

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