Colorectal cancer: diagnosis, staging and therapy

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CONFLICT OF INTEREST DISCLOSURE

Receipt of honoraria or consultation fees for speaker, consultancy or advisory roles:
Amgen, Bayer, Merck Serono, Roche, Servier, Astra Zeneca, Pierre Fabre
Epidemiology of CRC

International Agency for Research on Cancer

Estimated age-standardized incidence and mortality rates (World) in 2018, worldwide, males, all ages

- Lung
- Prostate
- Colorectum
- Stomach
- Liver
- Bladder
- Oesophagus
- Non-Hodgkin lymphoma
- Leukaemia
- Kidney

Data source: Globocan 2018
Graph production: GlobalCancer Observatory (http://gco.iarc.fr)
Epidemiology of CRC

Estimated age-standardized incidence and mortality rates (World) in 2018, worldwide, females, all ages

Breast
Colorectum
Lung
Cervix uterus
Thyroid
Corpus uterus
Stomach
Ovary
Liver
Non-Hodgkin lymphoma

Incidence
Mortality

Data source: Globocan 2018
Graph production: Global Cancer Observatory (http://gco.iarc.fr)
CRC

Sporadic 80%

Familial  ~15%

Hereditary  ~5%
  HNPCC
  FAP
Risk factors

• Intrinsic and genetic factors
  – Age
  – Personal history of adenoma, colorectal cancer or Inflammatory bowel disease
  – significant family history of CRC
  – Hereditary syndromes:
    • FAP
    • HNPCC

• Behavioural factors:
  – Diet: red meat, processed meat, decreased fibre and fruit, physical inactivity
  – Obesity
  – Smoking
  – Alcohol
  – Type II diabetes

Red meat cancer risk assessed

Evaluation of 800 studies on cancer by the International Agency for Research on Cancer (IARC)

- Red meat: Probably carcinogenic to humans
- Processed meat: Carcinogenic to humans

Risk compared to annual cancer deaths by causes:
- Global Burden of Disease Project
- Tobacco: 1,000,000
- Air pollution: 200,000
- Alcohol: 600,000
- Processed meat: 36,000
- Red meat: 50,000

Should we stop eating meat?
Meat has known health benefits. Many national health recommendations advise people to limit intake of processed and red meat.
Genes alteration and colon carcinoma progression
Risk of malignant transformation of adenoma

1. DIAMETER (< 1 cm: 1-2%; > 2 cm: 35-65%);

2. ISTOTYPES (tubular: 5%; villous 40%)

3. MORFOLOGY

4. NUMBERS;

5. SITE (right versus left)
Symptoms:
Weight loss, weakness, rarely obstruction.

Signs:
Iron -deficiency anaemia.

Symptoms:
Obstruction, tenesmus, bleeding.

Signs:
Palpable mass on rectal exam, bright red blood per rectum.

Symptoms:
Constipation, alternating bowel patterns, abdominal pain, decreased stool caliber, rectal bleeding.

Signs:
Bright red blood per rectum, large bowel obstruction.
Colonoscopy
Colonoscopy

Polyps

Cancer

Provided by Dr A. Cuomo
Tumor spread

- Paracolic
- Epicolic
- Principal nodes
- Internal iliac glands
- Upper zone
- Middle zone
- Lower zone
- To inguinal glands

Diagram showing tumor spread to the lungs and lymph nodes.
Radiological staging of the CRC

• Physical examination and medical history

• Laboratory test: CEA

• CT chest and abdominal for distant staging

• FDG-PET not recommended

• Bone scan and brain for patients with according symptoms
Colorectal cancer therapy

Multidisciplinary team

My decision is...

Our decision is...
Colonic resection

For stage I, stage II, stage III, laparotomy or laparoscopy (left side)
Colorectal cancer: staging
TNM system

T category describes the primary tumor site
N category describes the regional lymph node involvement
M category describes the presence or otherwise of distant metastatic spread

Decision making on treatment management
Patient individual prognosis
**Primary Tumor (T)**

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ: intraepithelial or invasion of lamina propria*
- **T1**: Tumor invades submucosa
- **T2**: Tumor invades muscularis propria
- **T3**: Tumor invades through the muscularis propria into pericolorectal tissues
- **T4a**: Tumor penetrates to the surface of the visceral peritoneum**
- **T4b**: Tumor directly invades or is adherent to other organs or structures**,***
Regional Lymph Nodes (N)

NX  Regional lymph nodes cannot be assessed
N0  No regional lymph node metastasis
N1  Metastasis in 1–3 regional lymph nodes
N1a Metastasis in one regional lymph node
N1b Metastasis in 2–3 regional lymph nodes
N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2  Metastasis in four or more regional lymph nodes
N2a Metastasis in 4–6 regional lymph nodes
N2b Metastasis in seven or more regional lymph nodes
**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastases in more than one organ/site or the peritoneum</td>
</tr>
<tr>
<td>Stage</td>
<td>T</td>
</tr>
<tr>
<td>-------</td>
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</tr>
<tr>
<td>0</td>
<td>Tis</td>
</tr>
<tr>
<td>I</td>
<td>T1</td>
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<tr>
<td></td>
<td>T2</td>
</tr>
<tr>
<td>IIA</td>
<td>T3</td>
</tr>
<tr>
<td>IIB</td>
<td>T4a</td>
</tr>
<tr>
<td>IIC</td>
<td>T4b</td>
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<tr>
<td>IIIA</td>
<td>T1–T2</td>
</tr>
<tr>
<td></td>
<td>T1</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3–T4a</td>
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<tr>
<td></td>
<td>T2–T3</td>
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<td></td>
<td>T1–T2</td>
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<tr>
<td>IIIC</td>
<td>T4a</td>
</tr>
<tr>
<td></td>
<td>T3–T4a</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
</tr>
<tr>
<td>IVA</td>
<td>Any T</td>
</tr>
<tr>
<td>IVB</td>
<td>Any T</td>
</tr>
</tbody>
</table>
### CRC survival rate

**Stage (AJCC 6th edition)** | **5-year survival (%)**
---|---
I = T₁ or T₂ N₀ | 85-95
IIₐ = T₃ N₀ | 85
IIₜ = T₄ N₀ | 72
IIIₐ = T₁ or T₂ N₁ | 60-83
IIIₜ = T₃ or T₄ N₁ | 42-64
IIIₜ = Tₓ, N₂ | 27-44
CRC stage at diagnosis

<table>
<thead>
<tr>
<th>Stage (AJCC 6th edition)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I = T₁ or T₂ N₀</td>
<td>93</td>
</tr>
<tr>
<td>IIₐ = T₃ N₀</td>
<td>85</td>
</tr>
<tr>
<td>IIₐ = T₄ N₀</td>
<td>72</td>
</tr>
<tr>
<td>IIIₐ = T₁ or T₂ N₁</td>
<td>60-83</td>
</tr>
<tr>
<td>IIIₐ = T₃ or T₄ N₁</td>
<td>42-64</td>
</tr>
<tr>
<td>IIIₐ = Tₓ, N₂</td>
<td>27-44</td>
</tr>
</tbody>
</table>

SURGERY

Eligible for adjuvant treatment?

No adjuvant treatment

Eligible for adjuvant treatment?
The concept of Adjuvant therapy

“Adjuvant therapy is a systemic treatment administered after primary tumour resection with the aim of reducing the risk of relapse and death “

- It has to be started within 6-8 weeks after surgery
- Drugs commonly used: 5FU, capecitabine and oxaliplatin
Cured by adjuvant FOLFOX
Cured by surgery alone
Recur despite surgery and CT
Cured by adjuvant 5-FU/LV
Cured by adjuvant FOLFOX

Stage III
- 28% Cured by surgery alone
- 15% Recur despite surgery and CT
- 7% Cured by adjuvant 5-FU/LV
- 50% Cured by adjuvant FOLFOX

Stage II
- ~75% Recur despite surgery and CT
- 20-25% Cured by adjuvant CT after surgery
- 2-5% Cured by surgery alone

Stage II
- 7% Cured by surgery alone
- 20-25% Recur despite surgery and CT
- 50% Cured by adjuvant 5-FU/LV
- 15% Cured by adjuvant FOLFOX

...adjuvant CT: discussion with patients
Stage III Colon Cancer:

- Adjuvant chemotherapy:
  - 5FU, leucovorin, oxaliplatin (FOLFOX) (Mosaic Trial NSABP C-072)
  - Capecitabine, oxaliplatin (CAPOX)

Mosaic Study

Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer

Thierry André, M.D., Corrado Boni, M.D., Lamia Mounedji-Boudiaf, M.D., Matilde Navarro, M.D., Josep Tabernero, M.D., Tamas Hickish, M.D., Clare Topham, M.D., Marta Zaninelli, M.D., Philip Clingan, M.D., John Bridgewater, M.D., Isabelle Tabah-Fisch, M.D., and Aimery de Gramont, M.D., for the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators

Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial

Thierry André, Corrado Boni, Matilde Navarro, Josep Tabernero, Tamas Hickish, Clare Topham, Andrea Bonetti, Philip Clingan, John Bridgewater, Fernando Rivera, and Aimery de Gramont
Mosaic: study design

Primary end-point: disease-free survival
Secondary end-points: safety, overall survival

FOLFOX4 : LV5FU2 + OXALIPLATIN 85 mg/m²

N = 2246
Stage II: 40%
Stage III: 60%
## Mosaic Study

**Summary: DFS, final update**

<table>
<thead>
<tr>
<th></th>
<th>5-year DFS %</th>
<th>HR</th>
<th>[95% CI]</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>FOLFOX4</td>
<td>LV5FU2</td>
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<tr>
<td>ITT (overall population)</td>
<td>73.3</td>
<td>67.4</td>
<td>0.80</td>
<td>0.003</td>
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<td></td>
<td>[0.68–0.93]</td>
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<td></td>
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<tr>
<td>Stage III</td>
<td>66.4</td>
<td>58.9</td>
<td>0.78</td>
<td>0.005</td>
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<tr>
<td></td>
<td>[0.65–0.93]</td>
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<tr>
<td>Stage II</td>
<td>83.7</td>
<td>79.9</td>
<td>0.84</td>
<td>0.258</td>
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<tr>
<td></td>
<td>[0.62–1.14]</td>
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<tr>
<td>High-risk stage II n=576</td>
<td>82.1</td>
<td>74.9</td>
<td>0.74</td>
<td>—</td>
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<tr>
<td></td>
<td>[0.52–1.06]</td>
<td></td>
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<tr>
<td>Low-risk stage II n=323</td>
<td>86.3</td>
<td>89.1</td>
<td>1.22</td>
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<tr>
<td></td>
<td>[0.66–2.26]</td>
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</table>

*Data cut-off: June 2006*
Mosaic Study
OS: stage II and stage III patients

Improved Overall Survival With Oxaliplatin, Fluorouracil, and Leucovorin As Adjuvant Treatment in Stage II or III Colon Cancer in the MOSAIC Trial

Thierry André, Corrado Boni, Matilde Navarro, Josep Tabernero, Tamás Hickish, Clare Topham, Andrea Bonetti, Philip Clingan, John Bridgewater, Fernando Rivera, and Aimery de Gramont

<table>
<thead>
<tr>
<th></th>
<th>Stage II FL</th>
<th>Stage II FL + oxaliplatin</th>
<th>Stage III FL</th>
<th>Stage III FL + oxaliplatin</th>
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<tbody>
<tr>
<td>Probability of survival at 5 years (%)</td>
<td>86.8</td>
<td>86.9</td>
<td>68.7</td>
<td>72.9</td>
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<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00 (0.79 to 1.41)</td>
<td>0.80 (0.65 to 0.97)</td>
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<tr>
<td>P</td>
<td>0.986</td>
<td>0.023</td>
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<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Stage III FL + oxaliplatin</th>
<th>Stage III FL</th>
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<tr>
<td>672</td>
<td>655</td>
<td>633</td>
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<td>616</td>
<td>590</td>
<td>567</td>
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<td>548</td>
<td>531</td>
<td>516</td>
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<td>499</td>
<td>484</td>
<td>468</td>
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<td>432</td>
<td>298</td>
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<td>183</td>
<td>163</td>
<td>53</td>
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</table>

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Stage II FL + oxaliplatin</th>
<th>Stage II FL</th>
</tr>
</thead>
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<tr>
<td>451</td>
<td>448</td>
<td>443</td>
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<td>437</td>
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<td>124</td>
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</table>

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Stage III FL + oxaliplatin</th>
<th>Stage III FL</th>
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<tbody>
<tr>
<td>448</td>
<td>442</td>
<td>436</td>
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<td>431</td>
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<td>331</td>
<td>221</td>
<td>130</td>
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<tr>
<td>130</td>
<td>41</td>
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</tr>
</tbody>
</table>
Stage II colon cancer: Is adjuvant CT beneficial?

- Recent recommendations - “standard risk” patients
  - ESMO – “adjuvant CT is not recommended in unselected pts” (ESMO guidelines)
  - ASCO “the routine use of adjuvant CT… is not recommended (JCO 2004)

...but in high risk pts?

- Inadequate staging (lymph node sampling <12)
- T4 lesions
- Bowel perforation/obstruction
- Lymphovascular and Perineural invasion
- Poorly differentiated histology
- MSS tumors
## Mosaic Study: Toxicity per patient

<table>
<thead>
<tr>
<th>NCI-CTC ≥ grade 3 (%)</th>
<th>FOLFOX4</th>
<th>LV5FU2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>41.0 (Gr 4, 12.2)</td>
<td>4.7</td>
</tr>
<tr>
<td>Neutropenia with fever or infection</td>
<td>1.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.9</td>
<td>1.4</td>
</tr>
<tr>
<td>Allergy</td>
<td>3.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Alopecia (grade 2)</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Neuropathy (grade 3)</td>
<td>12.4</td>
<td>0.0</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

- **Long-term safety**

  Second cancer (%) | 5.5 | 6.1
Mosaic Study: *neuropathy*
5FU/Irinotecan is not superior to 5FU/FA

**CALGB 89803**
- OS by Arm
- 1263 Stage III pts
- 5-FU/LV vs CPT-11/5-FU/LV
- p=0.81
- Saltz et al, 2004

**PETACC-3**
- DFS - Stage III
- 3500 Stage II and III pts

**ACCORD-02**
- DFS
- 2246 Stage II and III pts
- 3-year DFS: 60% vs 51%
- HR=1.19, 95% CI [0.90-1.59]
- FNCLCC Accord-02/ITCD 9803, 2005

**Van Custem et al, 2005**
- IF vs (IF+5-FU)
- 3-year DFS
- IF: 65.2, 95% CI [0.740-0.831], p=0.021
- observed: 63.3, 95% CI [0.77-1.11], p=0.091
Adjuvant stage III colon cancer

- Randomized trials support 6 months of post-operative fluorouracile and leucovorin or capecitabine plus oxaliplatin

- Adjuvant therapy appears to be equally effective in older and younger pts

- Current data do not support the use of irinotecan, bevacizumab or cetuximab in adjuvant treatment programs
Adjuvant treatment: what is new in 2017?

Is Three Months a Good IDEA?

Discussion of Abstracts 3500, 3501, 3502

Jeffrey Meyerhardt, MD, MPH
Dana-Farber Cancer Institute
Boston, MA

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17
Adjuvant treatment: what changed from in 2017?

Study Schema
The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration

Total planned accrual ≥ 10,500

Stage III Colon Cancer Patients

1:1

3 months

Investigator’s choice FOLFOX or CAPOX

6 months

FOLFOX: 5FU/LV + Oxaliplatin

CAPOX: Capecitabine + Oxaliplatin

Presented By Qian Shi at 2017 ASCO Annual Meeting
Adjuvant treatment: what changed from in 2017?

Primary DFS Analysis (mITT)

Duration 3-yr DFS
3m 74.6 %
6m 75.5 %
3-yr DFS diff. = -0.9 %,
95% CI, (-2.4 to 0.6 %)

DFS HR = 1.07
95% CI, 1.00 to 1.15

Presented By Qian Shi at 2017 ASCO Annual Meeting
Low risk tumors 3 months are equally to 6 months

DFS Comparison by Risk Groups

T1-3 N1 (58.7%)

Interaction p-value = 0.11
Treatment in 1\textsuperscript{st} Line mCRC

- **Tumour characteristics**
  - Clinical presentation (tumour burden, tumour localisation)
  - Tumour biology
  - RAS mutation status
  - BRAF mutation status

- **Patient characteristics**
  - Age
  - Performance status
  - Organ function
  - Comorbidities
  - Patient preference

- **Treatment characteristics**
  - Toxicity profile
  - Flexibility of administration
  - Quality of life
Treatment in 1st Line mCRC

Presented by Van Cutsem E. At ESO-ESMO masterclass 2015

Overall Survival (months)

*KRAS wild type tumors; **Extended RAS wild type population. Note: Informal comparison as these are not head-to-head clinical trials.

Monoclonal antibodies in CRC

- Murine Ab “momab”
- Chimeric Mouse-Human Ab “ximab”
- Humanized Ab “zumab”
- Human Ab “mumab”

EGFR
- Cetuximab
- Panitumumab

VEGF
- Bevacizumab

Modified by A. Grothey
EGFR and anti EGFR MoAbs

Only in RAS WT population

Main toxicities: Diarrhea, Skin toxicity, Infusion reactions, hypomagnesemia

Interstitial lung disease

Anti-angiogenic drugs

Toxicities: Bleeding, Thrombosis, Hypertension, Proteinuria, Wound dehiscence, Bowel perforation

New drugs in 3\textsuperscript{rd}-4\textsuperscript{th} line CRC

Regorafenib

\*Additional targets of regorafenib include RAF, BRAF, RET and KIT.

Cellular Signalling

ANGIOGENESIS
TUMOR MICROENVIRONMENT

TAS102

F\textsubscript{3}dThd (FTD)
Inhibition of tumor growth

F\textsubscript{3}dTMP
Alteration of DNA

F\textsubscript{3}dTDP

Incorporazione della FTD nel DNA

Molar ratio = 1 : 0.5

FTD: Trifluorothymidine
TPI: Tipiracil-HCl
The future: Immune checkpoint inhibitors?

Pembrolizumab
Cancer immunotherapy with mAb to PD-1

Avelumab
Atezolizumab

Mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab (anti-PD1)

Le et al, NEJM 2015
The future of precision medicine in CRC: treatment according to molecular subtypes

New possible target
Colorectal cancer Follow-up

- Clinical examination every 3 months for the first two years then every 6 months for a further three years
- TC / EUS abdomen every 6 months for the first two years, then annually for three more years
- Endoscopy every year in the first 5 years, then every 3 years
<table>
<thead>
<tr>
<th>CRC Cancer PREVENTION</th>
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<tbody>
<tr>
<td>High Quality Colonoscopy every 10 years, or</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy (FSIG) every 5 years*, or</td>
</tr>
<tr>
<td>Double contrast barium enema (DCBE) every 5 years*, or</td>
</tr>
<tr>
<td>CT colonography (CTC) every 5 years*</td>
</tr>
<tr>
<td>Annual guaiac-based fecal occult blood test (gFOBT) with high test sensitivity for cancer *, ** or</td>
</tr>
<tr>
<td>Annual fecal immunochemical test (FIT) with high test sensitivity for cancer*,**, or</td>
</tr>
<tr>
<td>Stool DNA test (sDNA), with high sensitivity for cancer*, interval uncertain</td>
</tr>
</tbody>
</table>

* Colonoscopy should be done if test results are positive.
** For gFOBT or FIT used as a screening test, the take-home multiple sample method should be used. gFOBT or FIT done during a digital rectal exam in the doctor's office is not adequate for screening.
Thank you for your attention!