Colon Cancer Guidelines Development Group Members

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The following institutions have participated in the elaboration or reviewing process of the guidelines:

- College of Oncology
- Belgian Society of Medical Oncology (BSMO)
- Belgian Group of Digestive Oncology (BGDO)
- College of Medical Imaging
- Belgian Society for Radiotherapy-Oncology (BVRO-ABRO)

This report was supported by the Belgian Healthcare Knowledge Centre.
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COLON CANCER

General algorithm

Clinical presentation
GP or specialist

Isolated cancerous polyp

Diagnostic procedure

Invasive cancer

Elective situation

Emergency

Clinical staging

MOC (optional)

Psychosocial help?

Patient consultation

Locally advanced

Surgery

Histology

MOC: final staging

Resectable Metastases

Unresectable Metastases

Metastases

Stage 4

Stage 3

Stage 2

Stage 1

Adjuvant chemotherapy

Follow up

Psychosocial help?

Patient consultation
# Staging

**TNM classification for colon cancer (UICC, 2002 Sixth Edition)**

<table>
<thead>
<tr>
<th>pT</th>
<th><strong>Primary Tumour</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: intraepithelial or invasion of lamina propria</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour directly invades other organs or structures or perforates visceral peritoneum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>pN</th>
<th><strong>Regional Lymph Nodes</strong> *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>No metastases in regional lymph nodes.</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases in 1 to 3 regional lymph nodes</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in 4 or more regional lymph nodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M</th>
<th><strong>Distant Metastasis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mx</td>
<td>Presence or absence of distant metastases cannot be determined</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases detected</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases detected</td>
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<table>
<thead>
<tr>
<th>G</th>
<th><strong>Histologic grade</strong></th>
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<tbody>
<tr>
<td>Gx</td>
<td>Grade cannot be assessed</td>
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<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

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* A tumour nodule in the pericolic or perirectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the **pN** category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the **T** category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.
## Staging

### TNM Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>0</td>
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<td>IIA</td>
<td>T3</td>
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<td>IIB</td>
<td>T4</td>
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<td>T1 or T2</td>
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<td>M0</td>
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<td>IIIB</td>
<td>T3 or T4</td>
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<td>M0</td>
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<td>Any T</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
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### Various chemotherapy regimens

<table>
<thead>
<tr>
<th>FOLFOX</th>
<th>FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin 85 mg/m IV over 2 hours, day 1</td>
<td>Irinotecan 180 mg/m IV over 2 hours, day 1</td>
</tr>
<tr>
<td>Leucovorin* 400 mg/m IV over 2 hours, days 1 and 2</td>
<td>Leucovorin* 400 mg/m IV over 2 hours prior to 5-FU, days 1 and 2</td>
</tr>
<tr>
<td>5-FU 400 mg/m IV bolus, then 600 mg/m IV over 22 hours continuous infusion, days 1 and 2</td>
<td>5-FU 400 mg/m IV bolus, then 600 mg/m IV over 22 hours continuous infusion, days 1 and 2</td>
</tr>
<tr>
<td>Repeat every 2 weeks</td>
<td>Repeat every 2 weeks</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>FOLFOX 5</th>
<th>FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin 100 mg/m IV over 2 hours, day 1</td>
<td>Irinotecan 180 mg/m IV over 90 minutes, day 1</td>
</tr>
<tr>
<td>Leucovorin* 400 mg/m IV over 2 hours, day 1</td>
<td>Leucovorin 400 mg/m IV over 2-hour infusion during Irinotecan, day 1</td>
</tr>
<tr>
<td>5-FU 400 mg/m IV bolus, then 2.4-3.0 g/m IV over 46 hours continuous infusion</td>
<td>5-FU 400 mg/m IV bolus, then 2.4-3 g/m IV over 46 hours continuous infusion</td>
</tr>
<tr>
<td>Repeat every 2 weeks</td>
<td>Repeat every 2 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>mFOLFOX 6</th>
<th>mFOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin 85 mg/m IV over 2 hours, day 1</td>
<td>Bevacizumab + 5-FU containing regimens:</td>
</tr>
<tr>
<td>Leucovorin 350-400 mg/m IV over 2 hours, day 1</td>
<td>Bevacizumab 5 mg/kg IV every 2 weeks + 5-FU and Leucovorin</td>
</tr>
<tr>
<td>5-FU 400 mg/m IV bolus, then 2.4 g/m IV over 46 hours continuous infusion</td>
<td>or IFL</td>
</tr>
<tr>
<td>Repeat every 2 weeks</td>
<td>or FOLFIRI</td>
</tr>
<tr>
<td></td>
<td>IFL In combination with bevacizumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FOLFOX 7</th>
<th>FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin 130 mg/m IV over 2 hours, day 1</td>
<td>Irinotecan 125 mg/m IV over 90 minutes, days 1, 8, 15, 22</td>
</tr>
<tr>
<td>Leucovorin 400 mg/m IV over 2 hours, day 1</td>
<td>Leucovorin 20 mg/m IV, days 1, 8, 15, 22</td>
</tr>
<tr>
<td>5-FU 400 mg/m IV bolus, then 2.4 g/m IV over 46 hours continuous infusion</td>
<td>5-FU 500 mg/m IV, days 1, 8, 15, 22</td>
</tr>
<tr>
<td>Repeat every 2 weeks</td>
<td>Repeat every 6 weeks</td>
</tr>
</tbody>
</table>
### Various chemotherapy regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Therapy Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capecitabine</strong></td>
<td>2,500 mg/m²/day PO in two divided doses, days 1-14, followed by 7 days rest. Repeat every 3 weeks.</td>
</tr>
<tr>
<td><strong>Protracted IV 5-FU</strong></td>
<td>5-FU 300 mg/m² protracted IV infusion followed by 7 days rest. Repeat every 3 weeks.</td>
</tr>
<tr>
<td><strong>Bolus or infusional 5-FU/leucovorin</strong></td>
<td>Mayo regimen: Leucovorin 20 mg/m² IV bolus, days 1-5; 5-FU 425 mg/m² IV bolus one hour after start of Leucovorin, days 1-5; Repeat every 4 weeks.</td>
</tr>
<tr>
<td></td>
<td>Irinotecan regimen: Irinotecan 125 mg/m² IV over 90 minutes, days 1, 8, 15, 22; Repeat every 6 weeks.</td>
</tr>
<tr>
<td></td>
<td>Mayo regimen: Leucovorin 20 mg/m² IV bolus, days 1-5; 5-FU 425 mg/m² IV bolus one hour after start of Leucovorin, days 1-5; Repeat every 4 weeks.</td>
</tr>
<tr>
<td></td>
<td>Irinotecan regimen: Irinotecan 300-350 mg/m² IV over 90 minutes, day 1; Repeat every 3 weeks.</td>
</tr>
<tr>
<td><strong>Roswell-Park regimen</strong></td>
<td>Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36; 5-FU 500 mg/m² IV bolus 1 hour after start of Leucovorin, days 1, 8, 15, 22, 29, 36; Repeat every 6 weeks.</td>
</tr>
<tr>
<td></td>
<td>Cetuximab ± irinotecan; Cetuximab 400 mg/m² 1st infusion, then 250 mg/m² weekly ± irinotecan 350 mg/m² every 3 weeks or 180 mg/m² every 2 weeks or 125 mg/m² every week for 4 weeks; Every 6 weeks.</td>
</tr>
<tr>
<td><strong>de Gramont</strong></td>
<td>Leucovorin* 400 mg/m² IV over 2 hours, days 1 and 2; 5-FU 400 mg/m² IV bolus, then 600 mg/m² IV over 22 hours continuous infusion, days 1 and 2; Repeat every 2 weeks.</td>
</tr>
</tbody>
</table>

*Leucovorin*
INTRODUCTION

The guidelines presented covers diagnosis, treatment and follow up of colon cancer. It is based on the existing international guidelines which have been critically appraised (Appendix 1) and on the consensus of national societies.

We will go through the following topics:

- Diagnosis
- Clinical Staging
- Multidisciplinary team meeting (optional)
- Treatment of non-metastatic disease
  - surgery
  - pathology
- Final staging - Multidisciplinary team meeting
  - follow up
  - adjuvant therapy
- Treatment of metastatic disease
  - resectable metastases
  - unresectable metastases

The grade of recommendation is stated in the text as follow:

**GR A** = Evidence derived from RCT or meta-analysis or systematic review of RCT

**GR B** = Evidence from non-randomised controlled trials or observational studies

**GR C** = Professional consensus, or case reports or case series

The key to evidence statements and grade of recommendations are presented in appendix 2.

SEARCH FOR EVIDENCE

First the existing guidelines were searched in October 2004 using as keywords “colon, rectum and colorectal with cancer and neoplasm”. The National Guideline Clearinghouse (114 references) and Pubmed (131 references, limit: practice guideline) were searched, without date limit or language restriction.

The websites of known agencies were systematically searched (Europe: ESMO, The Netherland: Oncoline, UK: NICE, The association of coloproctology of GB and Ireland, Scotland: SIGN, CANADA: Ontario Cancer care, USA: NCCN, NIC, ASCO, American Society of colon & rectal surgeons, France: ANAES, FNCLCC, Singapore: Ministry of Health). Two search engines were also searched (Google and Journalservice for medics) with the same keywords than mentioned earlier.

Finally a search for systematic reviews in the Cochrane database and in DARE (19 references) was performed.

DIAGNOSIS

Patient's history

A personal history has to be taken (GR C).

The diagnostic procedure is generally indicated for patients with the following symptoms [1-3] (GR B):
For all ages: rectal bleeding with change in bowel habits to looseness or increased frequency over a period of six weeks and/or palpable abdominal mass and/or iron-deficiency anaemia without overt cause.

Over 60 years: rectal bleeding without any symptoms, or change in bowel habits to looseness or increased frequency.

A family history has to be taken:
In order to determine the high risk groups, a family history of at least two generations should be taken to every patient with colon cancer [1,2] (GR B).
If there are 1 or 2 family members diagnosed with colon cancer, if the patient is less than 50 years old or if the patient has concomitant or previous ovarian or endometrium cancer, a 3 generations extensive family history is required (GR C).

Patients with suspected hereditary conditions should be oriented towards a Genetic Service [1] or a Familial Cancer Clinic (GR C).

**Examination**
A complete clinical examination has to be done (GR C).
Colonoscopy with biopsy is recommended for every patient with suspected colon cancer [1,2] (GR C). If not possible, an enema [4] has to be performed [1,2] (GR B).
Importance of good orientation of the specimen (quality criteria for endoscopist and pathologist). The biopsy must give answers to the following questions [1,2] (GR B):
- Malignant or benign?
- Is it a carcinoma within a polyp or an invasive cancer?
- What is the differentiation grade of the tumour?

**Diagnostic conclusion**
At the end of the diagnostic procedure, an answer must be given to the following questions:
- Is it an isolated cancerous polyp which has been completely resected? If the answer is yes (Tis stage), there is no other treatment except if there is histological evidence of tumour at, or within 1 mm of, the resection margin, there is lymphovascular invasion or the invasive tumour is poorly differentiated [1,5,6] (GR B). (All polyps have to be sent to the pathologist for analysis (GR C)).
- Is it a recurrence of a previous colon cancer [6] (GR C)?
- Is it an invasive cancer (GR C)?

**Emergency**
In case of emergency (bleeding, perforation, obstruction ) routine procedures may be neglected and immediate resection should be considered in optimal candidates [1,2,7,8] (GR B).
In that case, intraoperative liver ultrasound and postoperative imaging is necessary [1] (GR B).

**CLINICAL STAGING**
Following staging examinations are recommended:
- CEA level [6, 9] (GR C).
- In general, thoraco-abdominal contrast CT is recommended [2,9] (GR C).
Liver [1,2]: MRI is an alternative. US can be considered when contrast CT or MRI are not possible (GR B).

Chest [1,2]: CT scan [10] (GR B)

Lymph nodes: CT scan [2,9] (GR B)

cTNM: pre-treatment clinical classification, based on clinical examination, imaging, endoscopy, biopsy, surgical exploration or other.

FIRST MULTIDISCIPLINARY TEAM MEETING (MOC) – OPTIONAL

The objective of this first meeting is to decide on the therapeutic strategy based on the clinical staging [2] (GR C).

If possible, the general practitioner (GP) of the patient should attend this meeting [2]. Otherwise, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient (GR C).

Patients should be given clear information about the potential risks and benefits of treatment in order that they can understand adequately the therapeutic decision [1,2] (GR C). Information about local support services should be made available to both the patient and their relatives [1,2] (GR C). Healthcare professionals should respect patients' wishes to be involved in their own management [1,2] (GR B).

The need for psychosocial help must be evaluated and offered if required [2] (GR B).

PROCEDURE IF NON-METASTATIC DISEASE

Surgery

If no metastases are found, the patient is oriented to surgery which remains the only curative option [1,2,5,6,11] (GR C).

Preoperative preparation

A preoperative risk assessment should be performed according to the appropriate guidelines (www.kenniscentrum.fgov.be/fr/Publications.html).

Before undergoing surgery, the patient should have venous thromboembolism prophylaxis with anti-platelet therapy (GR B) and antibiotic prophylaxis (single dose of antibiotics providing both aerobic and anaerobic cover given within 30 minutes of induction of anaesthesia) [1,2,8,9,11] (GR A).

Surgery

There is little evidence relating to the radicality of colon cancer surgery [1]. Where a respectable organ (eg. kidney, ureter, duodenum, liver, stomach, bladder, uterus or vagina) is involved by the primary tumour, careful consideration should be given to removal (partial or total as appropriate) of that organ. Colon cancers adherent to adjacent structures should be resected en bloc [1,9,11] (GR C). Bilateral oophorectomy is advised when one or both ovaries are grossly abnormal or involved with contiguous extension of the colon cancer. However, prophylactic oophorectomy is not recommended [9] (GR C).

Lymph nodes at the origin of feeding vessel should be identified for pathologic examination (GR C).

Lymph nodes outside the field of resection considered suspicious should be biopsied or removed [6,9,11] (GR C).
Tumour tissue left behind indicates an incomplete (R2) resection. The surgery report must indicate if the resection was complete (R0 - R2) [2,6] (GR C).

The extent of resection of the colon should correspond to the lymphovascular drainage of the site of the colon cancer [9, 11] (GR C).

Synchronous colon cancers can be treated by two separate resections or subtotal colectomy [9, 11] (GR C).

**Histological procedure**

The exact procedure to examine a colon resection specimen is described in a consensus text made by the gastrointestinal pathologists [12].

The pathologist should search for lymph nodes in the resection specimen and the number found should be noted [2] (GR B). In patients with colon cancer who are treated with curative intent, 12 or more nodes should normally be examined; if the median number is consistently below 12, the surgeon and the pathologist should discuss their techniques [2] (GR B). Patients with inadequately sampled nodes could be offered adjuvant chemotherapy [13] (GR C).

All reporting of colon cancer specimens should contain gross description, histology type, differentiation by predominant area, margins (tumour involvement), metastatic spread, background abnormalities, staging [1,2] (GR B).

**FINAL STAGING**

Colon cancer should be staged following the TNM staging system [5,6,9] (GR B): pTNM: post-surgical histopathological classification (Staging).

The final staging is done during the second multidisciplinary meeting (MOC) on the basis of all results and reports available for a given patient [2,6] (GR C).

If possible, the general practitioner of the patient should attend this meeting. Otherwise, the staging has to be fully and clearly communicated to the GP and/or specialist of the patient [2] (GR C).

Depending on tumour stage, the further treatment options are decided [1,2,5,6,13-16] (GR A); A written report with staging and treatment options is mandatory for each patient [8] (GR C).

**TREATMENT**

A decision tree of the treatment in general is presented here.

Stage I: Follow up (GR A)

Stage II: Chemotherapy is discussed based on risk assessment (ev. Adjuv online) (GR A)

Stage III: Absolute indication for chemotherapy (if no major objection) (GR A)

Stage IV: See treatment of metastatic disease

**Adjuvant treatment**

As indicated in the final staging section, stage III colon cancer is an absolute indication for adjuvant chemotherapy (GR A). Different options, ie. infusional 5-fluorouracil in association with folinate, oral

**Treatment of metastatic disease**

**Treatment of resectable metastases**

Following therapeutic strategies can be proposed [1,2,5,9,30] (GR C):

- surgery of the primary tumour and the metastasis in the same procedure
- surgery of the primary tumour followed by:
  - surgery of the metastasis, or
  - chemotherapy and then surgery of metastasis

**Criteria for resectability of metastases [6]**

**Liver**

- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of noble hepatic function is required [6] (GR C).
- There should be no unresectable extrahepatic sites of disease [6] (GR C).
- The primary tumour must be controlled [6] (GR C).
- Re-resection can be considered in selected patients [6] (GR C).

Resection is the treatment of choice for resectable liver metastases. Other techniques such as radiofrequency might be optional or complementary [6] (GR C).

**Lung**

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required [6] (GR C).
- The primary tumour must be controlled [6] (GR C).
- Re-resection can be considered in selected patients [6] (GR C).

After resection, adjuvant chemotherapy can be considered [1,2,5,6,25-28,30] (GR C). The decision is made on individual basis.

The patient assessment and decision about treatment options should be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed [1,2] (GR C).

The need for a psychosocial help must be evaluated and, if required, the help has to be started [1,2] (GR B).

The follow up procedure is the same than that for patients without metastasis.

**Treatment of unresectable metastases**

- If the patient presents with symptoms related to the primary tumour (bleeding, obstruction): resection of primary tumour followed by chemotherapy [1,2,9,11] (GR B).
- If the patient has no symptoms related to the primary tumour: chemotherapy [29] (GR A).

Note: MRI with contrast agent has significantly superior sensitivity than CT for preoperative assessment of operability of liver metastasis [24] (GR B).
Each patient should receive an evaluation for first and second line chemotherapy [1,5,6,28] (GR C). Today, therapy with oral fluoropyrimidines in monotherapy or infusional 5-fluorouracil in combination with either Irinotecan or Oxaliplatin is considered as standard (GR C). The decision on which regimen for a given patient is especially based on the performance status [1,2,6] (GR A).

Reevaluation of patients under treatment for metastatic disease should include an every 2 to 3 month CT assessment, always performed with the same tools for comparison reasons (GR C). MRI can be considered in specific conditions (GR C). At every evaluation the different treatment options must be discussed (GR C).

The patient assessment and decision about treatment options should be done during the multidisciplinary team meeting, in presence of the patient's general practitioner. The role of the pain clinic in pain management has to be discussed [1,2] (GR C).

The need for a psychosocial help must be evaluated and, if required, the help has to be started [2] (GR B).

Patients with advanced colorectal cancer may benefit both from treatment of the cancer and from palliative care. These are concomitant approaches to management [1,2] (GR C).

Palliative care specialists should be members of, and integrated with, colorectal cancer multi-disciplinary teams; their role includes the provision of education and advice for other health professionals and direct patient management [2] (GR C).

A patient in good health status and progressive under standard therapy should be proposed a clinical trial protocol [2] (GR C).

FOLLOW-UP

Patients who have undergone curative resection for colorectal cancer should undergo formal follow up in order to facilitate the early detection of recurrence and/or metastatic disease [1,2,5,6,17-20] (GR A)

Although no absolute scientific prove of outcome benefit of an intensive follow up policy [19], we could recommend following strategy:

- Physician visit: every 3 to 6 months for the first 3 years after initial treatment, every 6 months during years 4 and 5 and then yearly for 5 years [10] (GR C)
- CEA every 3 months during 3 years if patient is candidate for surgery or systemic therapy [10] (GR C)
- CT thorax and abdomen at 3 months and every year during 3 years in patients at higher risk of recurrence [10,21] (GR C)
- Colonoscopy after 3 years and every 5 years in average risk patients [10] (GR C)

PET should be performed in patients with a high clinical suspicion of recurrent disease associated with negative or equivocal work up (high pre test probability):

- Suspicion of local recurrence of a colon cancer with equivocal CT, MRI and endoscopy.
- Exclusion or confirmation of metastasis in equivocal CT, MRI lesions (eg. indeterminate lymph nodes in the retroperitoneal space; a pulmonary or hepatic nodule).
- A rising CEA level.

(see KCE HTA report on PET scan: http://www.kenniscentrum.fgov.be/documents/D20051027330.pdf)
## Appendix 1: Evidence table

<table>
<thead>
<tr>
<th>Title</th>
<th>Country</th>
<th>Year</th>
<th>Scope</th>
<th>AGREE overall assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guidelines for the management of colorectal cancer - The association of coloproctology of GB and Ireland [8]</td>
<td>UK</td>
<td>2001</td>
<td>Colorectal</td>
<td>Recommend (with provisos or alterations)</td>
</tr>
<tr>
<td>Use of raltitrexed in management of metastatic colorectal cancer - Cancer care Ontario [26]</td>
<td>Canada</td>
<td>2002</td>
<td>Colorectal</td>
<td>Strongly recommend</td>
</tr>
<tr>
<td>Use of irinotecan combined with 5Fluorouracil and leucovirin as first line therapy for metastatic colorectal cancer - Cancer care Ontario [27]</td>
<td>Canada</td>
<td>2003</td>
<td>Colorectal</td>
<td>Strongly recommend</td>
</tr>
<tr>
<td>Follow up of patients with curatively resected colorectal cancer – Cancer care Ontario [17]</td>
<td>Canada</td>
<td>2004</td>
<td>Colorectal</td>
<td>Strongly recommend</td>
</tr>
<tr>
<td>Colon Cancer – NCCN[6]</td>
<td>USA</td>
<td>2004</td>
<td>Colon</td>
<td>Recommend (with provisos or alterations)</td>
</tr>
<tr>
<td>Colon cancer treatment – NCI [5]</td>
<td>USA</td>
<td>2004</td>
<td>Colon</td>
<td>Recommend (with provisos or alterations)</td>
</tr>
<tr>
<td>Colorectal cancer surveillance et Adjuvant chemotherapy for stage II colon cancer – American Society of clinical oncology [13]</td>
<td>USA</td>
<td>2000</td>
<td>Colorectal</td>
<td>Strongly recommend</td>
</tr>
<tr>
<td>Adjuvant chemotherapy for stage II colon cancer – American Society of clinical oncology [14]</td>
<td>USA</td>
<td>2004</td>
<td>Colon</td>
<td>Strongly recommend</td>
</tr>
</tbody>
</table>

Note: The assessment of the guidelines was made with the AGREE instrument which can be found on: [http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf](http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf)
Appendix 2: Key to evidence statements and grades of recommendations

directly applicable to the target population, and demonstrating overall consistency of results

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN) [1]

Levels of evidence

1++ High quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias
1+ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1- Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non analytic studies, e.g. case reports, case series
4 Expert opinion

Grades of recommendation

A At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; or body of evidence consisting principally of studies rated as 1++,

B A body of evidence including studies rated as 2++ , directly applicable to the target population, and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or
Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or
Extrapolated evidence from studies rated as 2+

NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE (NICE)

A Evidence derived from randomised controlled trials or systematic reviews of randomised trials
B Evidence from non-randomised controlled trials or observational studies
C professional consensus

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Level
I  Meta-analysis of multiple well designed, controlled studies; randomised trials with low false-positive and low false-negative errors (high power)

II  At least one well designed experimental study; randomised trials with high false-positive or high false-negative errors or both (low power)

III  Well designed, quasi-experimental studies, such as nonrandomised controlled, single-group, preoperative-postoperative comparison, cohort, time, or matched case-control series

IV  Well designed, non experimental studies such as comparative and correlational descriptive and case studies

V  Case reports and clinical examples

Grades

A  Evidence of type I or consistent findings from multiple studies of type II, III or IV

B  Evidence of type II, III or IV and generally consistent findings

C  Evidence of type II, III or IV but inconsistent findings

D  Little or no systematic empirical evidence

NATIONAL CANCER INSTITUTE (NCI)

Strength of study design

- Randomised controlled clinical trials
  - Double-blinded
  - Non blinded (allocation schema or treatment delivery)
- Non randomised controlled clinical trials
- Case series
  - Population-based, consecutive series
- Consecutive cases (not population-based)
- Non consecutive cases

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) [6]

Category 1  There is uniform NCCN consensus, based on high level evidence, that the recommendation is appropriate

Category 2A  There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate

Category 2B  There is non uniform consensus (but no major disagreement), based on lower level evidence including clinical experience, that the recommendation is appropriate

Category 3  There is major NCCN disagreement that the recommendation is appropriate

SINGAPORE MINISTRY OF HEALTH (SMOH)

Level IA  Evidence obtained from meta-analysis of RCT and systematic reviews of RCT

Level IB  Evidence obtained from at least one RCT

Level IIA  Evidence obtained from at least one well-designed controlled study without randomisation

Level IIB  Evidence obtained from at least one other type of well-designed quasiexperimental study

Level III  Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
Level IV Evidence obtained from expert committee or opinion and/or clinical experience of respected authorities without transparent proof.

Grades
A Requires at least one RCT, as part of the body of literature of overall good quality and consistency, addressing the specific recommendation (evidence levels Ia and Ib)
B Requires availability of well conducted clinical studies, but no RCT on the topic of recommendation (evidence levels IIa, IIb, III)
C Requires evidence obtained from expert committee reports or opinions, and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality (evidence level IV)
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