COLLEGE OF ONCOLOGY

National Clinical Practice Guidelines

Colon Cancer

Version 1.2004

Continue

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Reference: Peeters M, Zlotta A, Roucoux F, De Greve J, Van Belle S, Haelterman M, Ramaekers D, Dargent G. Nationale Richtlijnen van het College voor oncologie: A. algemeen kader oncologish kwaliteitshandboek. B. wetenschappelijke basis voor klinische paden voor diagnose en behandeling colorectale kanker en testiskanker. Reports vol. 29A. Brussel: Federaal Kenniscentrum voor de gezondheidszorg (KCE) ; April 2006. KCERef. D/2006/10.273/12.

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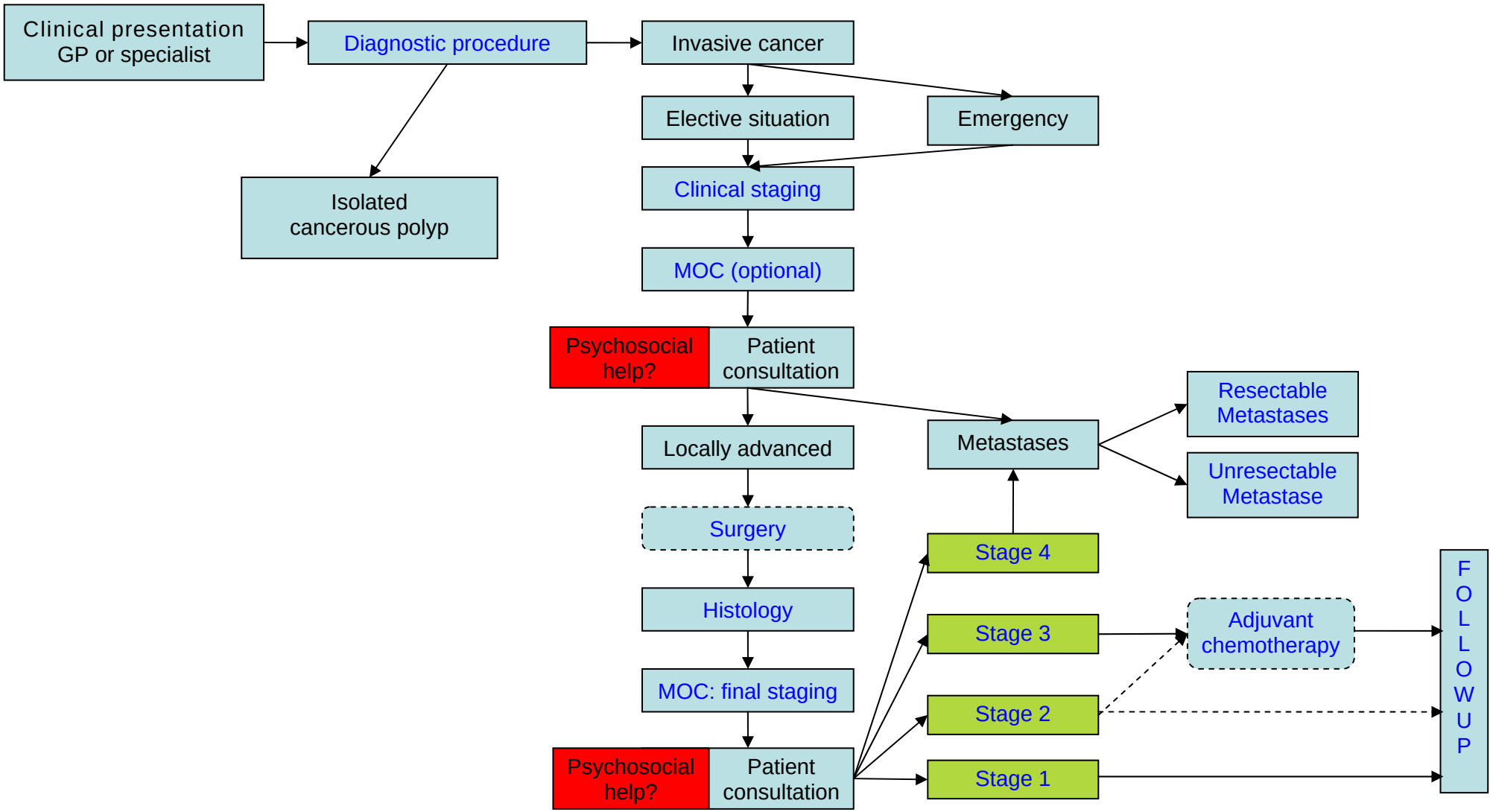

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Staging

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

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

pN	**Regional Lymph Nodes ***
Nx	Regional lymph nodes cannot be assessed.
N0	No metastases in regional lymph nodes.
N1	Metastases in 1 to 3 regional lymph nodes
N2	Metastasis in 4 or more regional lymph nodes

M	**Distant Metastasis**
Mx	Presence or absence of distant metastases cannot be determined
M0	No distant metastases detected
M1	Distant metastases detected

G	**Histologic grade**
Gx	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

* A tumour nodule in the pericolorectal 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.

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Staging

TNM Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1 or T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4	N0	M0
Stage IIIA	T1 or T2	N1	M0
Stage IIIB	T3 or T4	N1	M0
Stage IIIC	Any T	N2	M0
Stage IV	Any T	Any N	M1

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Various chemotherapy regimens

FOLFOX FOLFOX 4 Oxaliplatin 85 mg/m IV over 2 hours, day 1 Leucovorin* 400 mg/m IV over 2 hours, days 1 and 2 5-FU 400 mg/m IV bolus, then 600 mg/m IV over 22 hours continuous infusion, days 1 and 2 Repeat every 2 weeks	FOLFIRI Irinotecan 180 mg/m IV over 2 hours, day 1 Leucovorin* 400 mg/m IV over 2 hours prior to 5-FU, days 1 and 2 5-FU 400 mg/m IV bolus, then 600mg/ m IV over 22 hours continuous infusion, days 1 and 2 Repeat every 2 weeks
FOLFOX 6 Oxaliplatin 100 mg/m IV over 2 hours, day 1 Leucovorin* 400 mg/m IV over 2 hours, day 1 5-FU 400 mg/m IV bolus, then 2.4-3.0 g/m IV over 46 hours continuous infusion Repeat every 2 weeks	Irinotecan 180 mg/m IV over 90 minutes, day 1 Leucovorin 400 mg/m IV over 2-hour infusion during Irinotecan,day 1 5-FU 400 mg/m IV bolus, then 2.4-3 g/m IV over 46 hours continuous infusion Repeat every 2 weeks
mFOLFOX 6 Oxaliplatin 85 mg/m IV over 2 hours, day 1 Leucovorin 350-400 mg IV over 2 hours, day 1 5-FU 400 mg/m IV bolus, then 2.4 g/m IV over 46 hours continuous infusion Repeat every 2 weeks	Bevacizumab + 5-FU containing regimens: Bevacizumab 5mg/kg IV every 2 weeks + 5-FU and Leucovorin or IFL or FOLFOX or FOLFIRI IFL In combination with bevacizumab
FOLFOX 7 Oxaliplatin 130 mg/m IV over 2 hours, day 1 Leucovorin 400 mg/m IV over 2 hours, day 1 5-FU 400 mg/m IV bolus, then 2.4 g/m IV over 46 h continuous infusion Repeat every 2 weeks	Irinotecan 125 mg/m IV over 90 minutes, days 1, 8, 15, 22 Leucovorin 20 mg/m IV, days 1, 8, 15, 22 5-FU 500 mg/m IV, days 1, 8, 15, 22 Repeat every 6 weeks

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Various chemotherapy regimens

Capecitabine13
2,500 mg/m /day PO in two divided doses, days 1-14,
followed by 7 days rest
Repeat every 3 weeks

Protracted IV 5-FU
5-FU 300 mg/m /d protracted IV infusion

Bolus or infusional 5-FU/leucovorin
Mayo regimen
Leucovorin 20 mg/m IV bolus, days 1-5
5-FU 425 mg/m IV bolus one hour after start of Leucovorin,
days 1-5
Repeat every 4 weeks

Irinotecan
Irinotecan 125 mg/m IV over 90 minutes, days 1, 8, 15, 22
Repeat every 6 weeks

Irinotecan 300-350 mg/m IV over 90 minutes, day 1
Repeat every 3 weeks

Roswell-Park regimen
Leucovorin 500 mg/m IV over 2 hours,
days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m IV bolus 1 hour after start of Leucovorin,
days 1, 8, 15, 22, 29, 36
Repeat every 6 weeks

Cetuximab ± irinotecan
Cetuximab 400 mg/m 1st infusion, then 250 mg/m
weekly
±
Irinotecan
350 mg/m IV every 3 weeks

or

180 mg/m IV every 2 weeks
or
125 mg/m every week for 4 weeks
Every 6 weeks

de Gramont
Leucovorin* 400 mg/m IV over 2 hours, days 1 and 2
5-FU 400 mg/m IV bolus, then 600 mg/m IV over 22 hours
continuous infusion, days 1 and 2
Repeat every 2 weeks

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National Guideline
Colon Cancer

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 desicion 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

fluoropyrimidines, infusional 5-fluorouracil in association with folinate and oxaliplatine, [1, 2, 22, 23] **(GR A)** are available and reimbursed in Belgium (http://www.cbip.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm http://www.bcfi.be/ggr/index.cfm?ggrWelk=/GGR/MPG/MPG_J.cfm). The choice of a regimen for a given patient is based on his/her risk profile and the toxicity of the drugs ***(GR C)***. Various regimens are presented here.

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]

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

Note: MRI with contrast agent has significantly superior sensitivity than CT for preoperative assessment of operability of liver metastasis [24] **(GR B)**.

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required [6] ***(GR C)***.
- Resectable extra-pulmonary metastases do not preclude resection [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)**.

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)

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APPENDICES

Appendix 1: Evidence table

Titel	Country	Year	Scope	AGREE overall assessment
Management of colorectal cancer – SIGN [1]	Scotland	2003	Colorectal	Strongly recommend
Guidance on Cancer Services Improving Outcomes in Colorectal Cancer - NICE [2]	UK	2003	Colorectal	Strongly recommend
Guidelines for the management of colorectal cancer - The association of coloproctology of GB and Ireland [8]	UK	2001	Colorectal	Recommend (with provisos or alterations)
Adjuvant therapy for Stage II & IIIColon Cancer Following Complete resection – Cancer care Ontario [15]	Canada	2000	Colon	Strongly recommend
Use of irinotecan in treatment of metastatic colorectal carcinoma - Cancer care Ontario [25]	Canada	2000	Colorectal	Strongly recommend
Use of raltitrexed in management of metastatic colorectal cancer - Cancer care Ontario [26]	Canada	2002	Colorectal	Strongly recommend
Use of Irinotecan combined with 5Fluorouracil and leucovirin as first line therapy for metastatic colorectal cancer - Cancer care Ontario [27]	Canada	2003	Colorectal	Strongly recommend
Follow up of patients with curatively resected colorectal cancer – Cancer care Ontario [17]	Canada	2004	Colorectal	Strongly recommend
Colon Cancer – NCCN[6]	USA	2004	Colon	Recommend (with provisos or alterations)
Colon cancer treatment – NCI [5]	USA	2004	Colon	Recommend (with provisos or alterations)
Colorectal cancer surveillance et Adjuvant chemotherapy for stage II colon cancer – American Society of clinical oncology [13]	USA	2000	Colorectal	Strongly recommend
Adjuvant chemotherapy for stage II colon cancer – American Society of clinical oncology [14]	USA	2004	Colon	Strongly recommend
Colorectal cancer MOH Clinical practice guidelines [11]	Singapore	2004	Colorectal	Recommend (with provisos or alterations)
Coloncarcinoom - Oncoline (vereniging van Integrale kankercentra) : consensus based [30]	Netherlands	2000	Colon	Would not recommend

Note: The assessment of the guidelines was made with the AGREE instrument which can be found on: http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf

Appendix 2: Key to evidence statements and grades of recommendations

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

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)

Strenght 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 MINISTERY 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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