National Clinical Practice Guidelines of the College of Oncology : clinical practice guideline for colorectal cancer

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Federaal Kenniscentrum voor de gezondheidszorg
Centre fédéral d'expertise des soins de santé
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DISCLAIMER: It is by no means the intention that this report is applied literally or used as a standard for every individual patient. A standard is based on all available clinical evidence and can change according to the evolution of the scientific knowledge and technology. These recommendations are to be considered as a guideline only. The application of guidelines does not guarantee a successful result for every patient. Above this, guidelines cannot be considered as the only option and cannot lead to the exclusion of other generally accepted practices aiming at the same results. The ultimate decision to follow a certain clinical procedure is made by the care provider, taking into account the clinical data of the patient and the available diagnostic and therapeutic options. One can expect that these recommendations will be adopted and adapted after a local discussion within the clinical staff or other involved parties within the institution.

Scientific summary

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1 INTRODUCTION

An important part of the quality handbook in oncology is to bring together the guidelines used by the oncology care programmes. In order to help the oncology programmes to rest on high quality guidelines, the working party of the college of physicians for oncology has decided to review the existing guidelines for all tumours sites in the scientific literature, to make a critical appraisal based on the EBM and to adapt them to the Belgian situation. The final objective is to propose to the oncology programme a set of guidelines with recommendations based on the existing evidence. These guidelines represent the minimal criteria to be followed by the oncology programmes, taking into account the specific situation of each patient and will represent the basis for the development of clinical pathways. Every oncology programme will then have to add its own recommendations based on a local consensus when high level evidence doesn't exist in the scientific literature.

In order to review the existing guidelines, the college of Physicians for Oncology has requested the help of the KCE. It has been decided to start with colorectal tumour guideline, because it is a frequent cancer in the population and with testicular tumour because it is a tumour with a high percentage of recovery, when correctly managed. The expected health benefits of this work is to improve the general quality of cancer management for the topics covered, by spreading among all oncology programs high quality guidelines in a first step, and then by developing quality indicators based on these guidelines, in a second step.

The target population of these guidelines is made by all the physicians working in an oncology care programme. Despite the fact that is has not been developed in first instance for these professionals, it could surely be of interest for the non medical staff of the oncology programme and for the GPs. The expected health benefits of this work is to improve the general quality of cancer management for the topics covered, by spreading among all oncology programs high quality guidelines in a first step, and then by developing clinical pathways and quality indicators based on these guidelines, in a second step.

The College of Oncology represents all the medical disciplines involved in the diagnosis and treatment of cancers. The working party "guidelines development" of the College is in charge of developing high quality guidelines. For each tumour, the working party has appointed an expert to develop the guideline, with the help of the KCE. It has been decided to submit the draft of all the guidelines developed to the concerned scientific societies. There is no direct and specific involvement of other healthcare professionals in the development of this work. Nevertheless, the point of view of these professionals has been taken into account through the review of the guidelines reviewed to build up these presented here.

1.1 REVIEW BY EXPERTS

As stated before, the guidelines were reviewed by a physician expert in the concerned tumour and appointed by the working party of the College of oncology, by the different scientific societies concerned by the guidelines topic, by the College of oncology as a whole, and finally, validated by 3 experts.

1.2 UPDATING AND DISSEMINATION

No formal procedure to update the guidelines has been decided. However, the working party "guidelines development" of the college of oncology bears the responsibility to start an updating procedure anytime major changes in the scientific evidence occurs.

The guidelines will be sent in a paper format to all oncology programmes. Moreover, in order to develop the dissemination, an electronic version available on the internet will be proposed.

1.3 FINAL REMARKS

- The cost effectiveness of these guidelines recommended procedures have not been studied. It will be one of the objectives of the development of a clinical pathway.
- The different management options are presented in the flow chart presented at the beginning of each guideline. More details are presented in the text when necessary.
- The following institutions have participated in the elaboration or the reviewing process of the guidelines:
    - College of Oncology
    - College of Radiotherapy
    - Belgian Society of Medical Oncology (BSMO)
    - Belgian Group of Digestive Oncology (BGDO)
    - College of Medical Imaging
    - Belgian Association of Radiotherapy-Oncology (BVRO/ABRO)

The name, affiliation and potential conflict of interest of the persons involved in the development of this work are presented in the first page of this report.

2 CLINICAL QUESTIONS

The clinical questions of this guideline are the following:

- What is the evidence for colon and rectal cancers diagnosis management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for colon and rectal cancers therapy management? Are there various options and if so, what is the link between an option and a specific patient subgroup?
- What is the evidence for colon and rectal cancers follow up management?

3 METHODOLOGY

3.1 SEARCH FOR EVIDENCE

First the existing guidelines were searched in October 2004 using as keywords "colon, rectum and colorectal with cancer and neoplasm" (MESH terms and text). 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 Netherlands: 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 Journal service 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. An update of the search was performed in December 2005 but did not yield new significant publication.

3.2 SELECTION

The guidelines on diagnosis, treatment and follow up of colorectal cancers were reviewed. In order to exclude all opinions papers or narrative reviews, the guidelines with no mention of a clear evidence-based system to grade the recommendations, were excluded. The guidelines were selected and appraised by two experts, using the AGREE instrument. All disagreements were resolved by consensus. The results of the appraisal are presented in appendix. The guidelines with an overall assessment of "strongly recommended" or "recommended" were selected and used to develop a synthesis which was discussed and reviewed by the expert appointed by the working party of the College of Oncology, in order to adapt the recommendations to the Belgian situation. A special interest was brought to the methods used in all the reviewed guidelines to search and select the evidence (databases, search strategies, selection criteria, selection methods). The synthesis was build using the guidelines rated as "strongly recommended" as basis. For every point, the recommendations of the guidelines rated "recommended with provisos", if any, were also cited. In case of disagreement between different guidelines, the recommendations of the guidelines rated "strongly recommended" were always preferred on the others. For specific points for which no recommendations were found in the "strongly recommended" guidelines, the evidence of "recommended guidelines " or coming from good systematic reviews have been used.

3.3 GRADING OF RECOMMENDATIONS

Each guideline developer has his own evidence grading system. To synthesize the different systems, a correspondence table is presented hereunder. The key to evidence statements and grades of recommendations used in the selected guidelines are presented in the appendices.

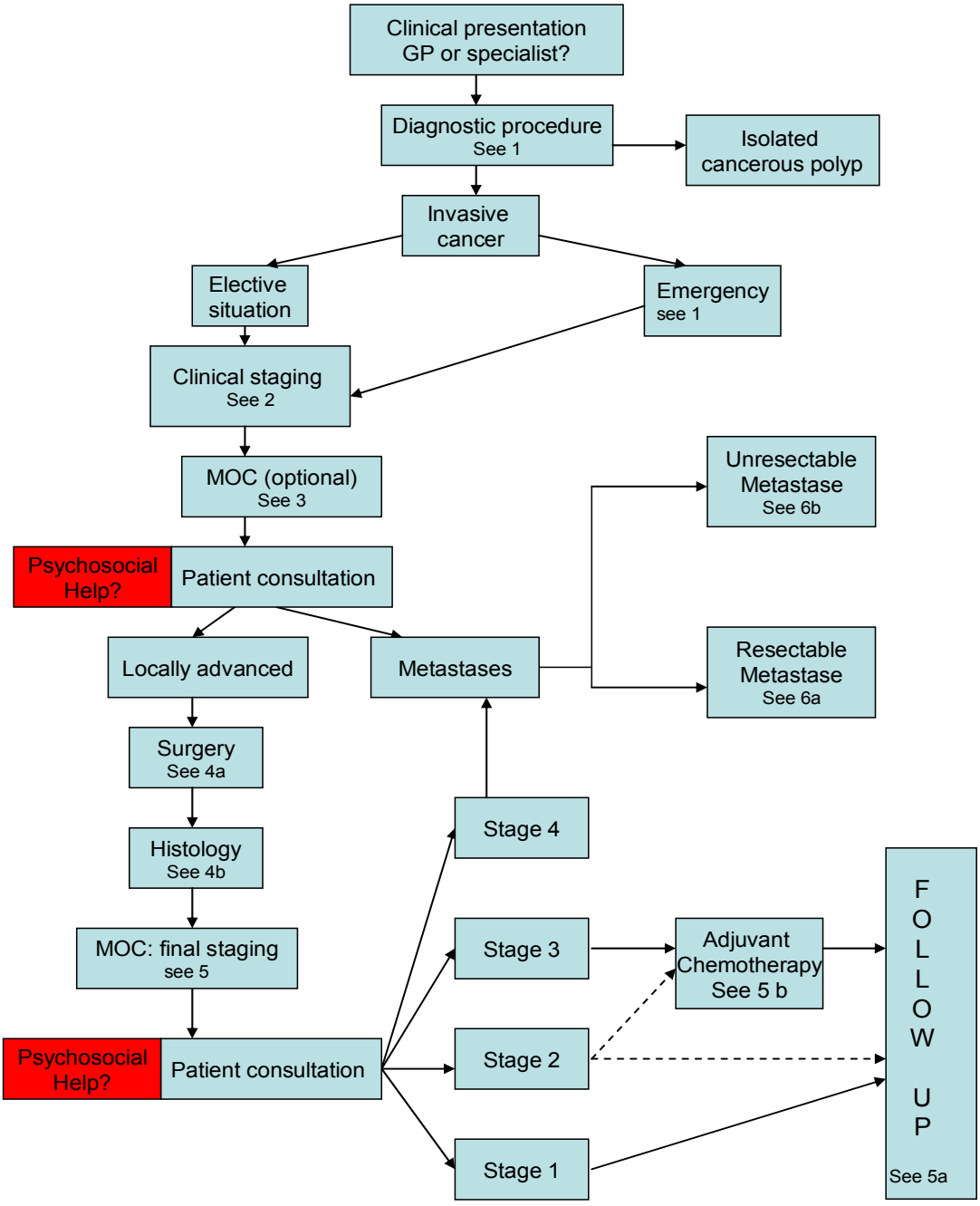
KCE grade	SIGN	NICE	ASCO	NCI	NCCN	SMOH
A	A	A	A	I		A
B	B & C	B	B	2 & 3i & 3ii		B
C	D	C	C & D	3iii	I & 2A	C

A = Evidence derived from RCT or meta-analysis or systematic review of RCT.
B = Evidence from non-randomised controlled trials or observational studies.
C = Professional consensus, or case reports, case series.

For presentation reasons, grade A recommendations, with a very high level of evidence, are put in bold letter; grade B recommendations with a high level of evidence are put in normal letters and grade C recommendations, principally based on consensus are put in italic letters. Due to their weak level of evidence, these last recommendations could be changed in a near future depending on the body of evidence. Nevertheless they are presented in this work because they are based on a large consensus within the scientific community.

4 COLON CANCER GUIDELINE

4.1 GENERAL ALGORITHM



4.2 INTRODUCTION

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

4.3 GUIDELINE

1. Diagnosis

Patient's history

A personal history has to be taken.

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 [2] or a Familial Cancer Clinic ***(GR C)***.

Examination

x a complete clinical examination***(GR C)***.

x 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)**.

x Importance of good orientation of the specimen (quality criteria for endoscopist and pathologist). The biopsy should 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 [2, 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 [5] ***(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 [7, 1, 2, 8] **(GR B)**.

In that case, intraoperative liver ultrasound and postoperative imaging is necessary [2] **(GR B)**.

2. Clinical staging

Following staging examinations are recommended:

- CEA level [9, 5] ***(GR C)***.
- In general, thoraco-abdominal Contrast CT is recommended [9, 1] ***(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 [9, 1] **(GR B)**

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

3. First Multidisciplinary Team Meeting (MOC) – optional

- The objective of this first meeting is to decide on the therapeutic strategy based on the clinical staging [1] **(GR C)**.
- If possible, the general practitioner (GP) of the patient should attend this meeting [1]. 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] **(GRC)**. 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 [1] **(GR B)**.

4. Treatment of non-metastatic disease

a. Surgery:

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

- x preoperative preparation:

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

Before undergoing surgery, the patient should have venous thromboembolism prophylaxis with LMW Heparin**(GR B)** and antibiotic prophylaxis (single dose of antibiotics providing both aerobic and anaerobic cover given within 30 minutes of induction of anaesthesia) [7, 9, 1, 2, 11] **(GR A)**.

- x surgery:

There is little evidence relating to the radicality of colon cancer surgery [2]. 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 [9, 2, 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 [9, 11, 5] **(GR C)**.

Tumour tissue left behind indicates an incomplete (R2) resection. The surgery report must indicate if the resection was complete (R0 - R2) [1, 5] **(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)**.

b. Histology procedure: (see pathologists guideline)

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 [1] **(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 [1] **(GR B)**. Patients with inadequately sampled nodes could be offered adjuvant chemotherapy [13] ***(GRC)***.

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)**.

5. Final Staging

Colon cancer should be staged following the TNM staging system [9, 5, 6] (GR B) :

pTNM: post-surgical histopathological classification.

T - 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 pericoloc or perirectal tissues
T4	Tumour directly invades other organs or structures or perforates visceral peritoneum

N – Nodal status

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

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.

M – Distant metastases

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

TNM Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1 or T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T4	N0	M0
Stage III A	T1 or T2	N1	M0
Stage III B	T3 or T4	N1	M0
Stage III C	Any T	N2	M0
Stage IV	Any T	Any N	M1

The final staging is done during the second multidisciplinary meeting (MOC) on the basis of all results and reports available for a given patient [1, 5] **(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 [1] **(GR C)**.

Depending on tumour stage, the further treatment options are decided [13, 14, 1, 2, 15, 16, 5, 6] (GR A):

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 point 6 (metastatic disease)

A written report with staging and treatment options is mandatory for each patient [7] **(GR C)**.

a. Follow up procedure

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 [17, 18, 1, 2, 19, 5, 6, 20] **(GR A).**

Although no absolute scientific prove of outcome benefit of an intensive follow up policy [21], 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 [22, 10] ***(GR C)***.
- Colonoscopy still to be done for those patients who did not have complete colonoscopy preoperatively (to perform within 6 months after operation [1, 2] ***(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 (without clear positive conclusion) 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.

For detection and localization of local, hepatic and extra-hepatic recurrence, the diagnostic efficacy includes changes in patient management and therapeutic decision. In addition, there is limited evidence for cost-effectiveness. PET is indicated for localization of metastasis in case of increasing CEA level following surgery in a patient with colorectal cancer.

b. Adjuvant therapy

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, 23, 24] **(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 in the appendices.

6. Treatment of metastatic disease

a. Treatment of resectable metastases

Following therapeutic strategies can be proposed on the basis of the individual situation of the patient and his tumour [9, 1, 2, 5, 6] ***(GR C)***:

x surgery of the primary tumour and the metastasis in the same procedure,

x surgery of the primary tumour followed by:

- surgery of the metastasis, or
- chemotherapy and then surgery of the metastasis

CRITERIA FOR RESECTABILITY OF METASTASES [5]

Liver

Complete resection must be based on the anatomic location and the extent of disease, maintenance of hepatic function is required [5] ***(GR C)***

There should be no unresectable extrahepatic sites of disease [5] ***(GR C)***.

The primary tumour must be controlled [5] ***(GR C)***.

Re-resection can be considered in selected patients [5] ***(GR C)***.

Resection is the treatment of choice for resectable liver metastases. Other techniques such as radiofrequency might be optional or complementary [5] ***(GR C)***.

Note:

- MRI with contrast agent has significantly superior sensitivity than CT for preoperative assessment of operability of liver metastasis [25] **(GR B)**.
- PET scan is recommended in the preoperative evaluation of resectable liver metastases **(GR A)** [25].

Lung

Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required [5] ***(GR C)***.

Resectable extra-pulmonary metastases do not preclude resection [5] ***(GR C)***.

The primary tumour must be controlled [5] ***(GR C)***.

Re-resection can be considered in selected patients [5] ***(GR C)***.

After resection, adjuvant chemotherapy can be considered [26-28, 1, 29, 2, 5, 6]. The decision is made on individual basis depending on the risk profile and health status ***(GR C)***.

The patient assessment and decision about treatment options should preferably 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 as for patients without metastasis.

b. Treatment of unresectable metastases

If the patient presents with symptoms related to the primary tumour (bleeding, obstruction…): resection of primary tumour followed by chemotherapy [9, 1, 2, 11] **(GR B).**

If the patient has no symptoms related to the primary tumour: chemotherapy [30] **(GR A).**

Each patient should receive an evaluation for first and second line chemotherapy [26, 2, 5, 6] **(GR A).** 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, NCCN, 2004 #28, 2] **(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 preferably 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] **(GR B).**

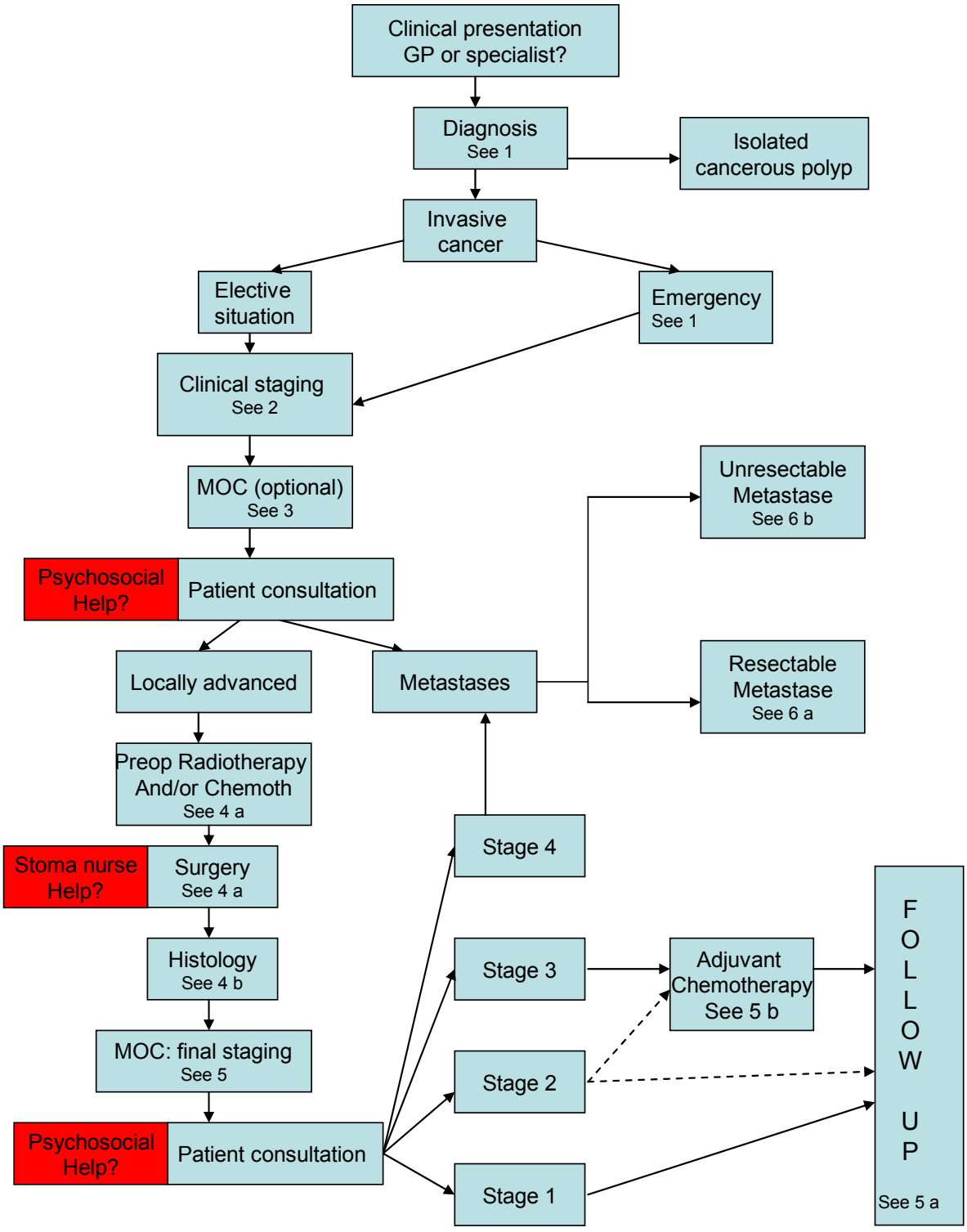
Patients with advanced colorectal cancer may benefit both from treatment of the cancer and from palliative care. These are concomitant approaches to management [1, 2] ***(GR C).***

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 [1] ***(GR C).***

A patient in good health status and progressive under standard therapy should be proposed a clinical trial protocol [1] ***(GR C).***

5 RECTUM CANCER GUIDELINE

5.1 GENERAL ALGORITHM



5.2 INTRODUCTION

The guidelines presented covers diagnosis, treatment and follow up of rectum cancer. It is based on the existing international guidelines which have been critically appraised (see appendix) and on the consensus of national societies. These guidelines are in concordance with the ongoing national, multidisciplinary project on rectal cancer, PROCARE.

The definition of rectal tumours in this guideline is: tumours whose distal edge is seen within 16 cm from the anal verge as measured with a rigid recto-sigmoidoscope (PROCARE guideline)

We will go through the following topics:

- Diagnosis
- Clinical Staging
- Multidisciplinary team meeting (optional)
- Treatment of non-metastatic disease
    - a. surgery with or without (neo)adjuvant therapy
    - b. pathology
- Final staging - Multidisciplinary team meeting
    - a. follow up
    - b. adjuvant therapy
- treatment of metastatic disease
    - a. resectable metastases
    - b. 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

5.3 GUIDELINE

1. Diagnosis

Patient's history

A personal history has to be taken.

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 [2] or a Familial Cancer Clinic ***(GR C).***

Examination

x A complete clinical examination ***(GR C).***

x Colonoscopy with biopsy is recommended for every patient with suspected rectal cancer[1, 2] ***(GR C).*** If not possible, an enema [4] has to be performed [1, 2] **(GR B).**

x Importance of good orientation of the specimen (quality criteria for endoscopist and pathologist). The biopsy should 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 totally 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[2, 5, 6] **(GR B)** (All polyps have to be sent to the pathologist for analysis ***(GR C)***).
- Is it a recurrence of a previous rectal cancer [5] ***(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 [7, 1, 2, 8] **(GR B**).

In that case, intraoperative liver ultrasound and postoperative imaging is necessary [2] **(GR B)**.

2. Clinical staging

Following staging examinations are recommended:

If local excision and/or radiotherapy is considered, pelvic MRI and ultrasound endoscopy can be considered, although this is not based on clinical evidence ***(GR C).***

To detect metastases, the following examinations are recommended:

- CEA level [9, 5] ***(GR C).***
- For staging, the primary choice is thoraco-abdominal Contrast CT [9, 1] ***(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).**
- Adenopathy: CT scan [9, 1] **(GR B).**

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

3. First Multidisciplinary Team Meeting (MOC) - optional

- The objective of this first meeting is to decide on the therapeutic strategy based on the clinical staging [1] **(GR C)**.

- If possible, the general practitioner of the patient should attend this meeting [1]. If not, 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 when making plans about their own management [1, 2] **(GR B)**.
- The need for psychosocial help must be evaluated and offered if required [1] **(GR B)**.

4. Treatment of non-metastatic disease

a. Surgery

If no metastases are found, the patient is oriented to surgery which remains the only curative option [31, 1, 2, 11, 5] ***(GR C).***

x preoperative radio/chemotherapy:

- Preoperative radiotherapy, planned with 3 or 4 fields (and not parallel opposed fields), should be considered in patients with operable rectal cancer [32-34, 1, 2] *(Chemotherapy could be given synchronously with radiotherapy [33, 31, 1, 2, 5]* ***(GR C).*** *The regimens usually used are bolus FUFA or continuous fluorouracil (Procare guideline)* ***(GR C).*** *The patient with T1-2 rectal cancer cStage I in whom an adequate TME procedure is performed does not need neoadjuvant therapy. Neoadjuvant therapy is recommended in all other cases, except for tumours located at less than 6 cm from the anal verge or with a Circumferential Resection Margin less than 5 mm (Procare guideline)* ***(GR C)****)*

  Note: a more detailed discussion on the indications of radiotherapy and the addition of chemotherapy will be provided in the updated PROCARE guideline.

  Postoperative radiotherapy should be considered in patients with rectal cancer who did not receive preoperative radiotherapy (e.g. case of emergency) and who are at high risk of local recurrence [32, 33, 2] ***(GR C).***
    - YTNM: classification after induction therapy;

x preoperative preparation:

- A preoperative risk assessment should be performed according to the appropriate guidelines (see http://www.kenniscentrum.fgov.be/fr/Publications.html).
- Before undergoing surgery, the patient should have venous thromboembolism prophylaxis with LMW Heparin **(GR B)** and antibiotic prophylaxis (single dose of antibiotics providing both aerobic and anaerobic cover given within 30 minutes of induction of anaesthesia) [7, 9, 1, 2, 11] **(GR A).**

x surgery: (see Procare guideline)

- The safe margin between the lower end of the tumour and the rectal stump must be greater than or equal to 2 cms [33] **(GR B)**. An appropriate mesorectal excision, depending on the localization of the tumour, has an impact on the rate of local recurrences [31, 2, 5] **(GR B)**.

  Note: a more detailed discussion on the excision margin will be provided in the updated PROCARE guideline.
- There is currently no indication for extensive pelvic nodal clearance [33].Lymph nodes at the origin of feeding vessel should be identified for pathologic

examination. Lymph nodes outside the field of resection considered suspicious should be biopsied or removed [9, 11, 5] ***(GR C)***.

- Tumour tissue left behind indicates an incomplete (R2) resection. The surgery report must indicate if the resection was complete (R0 R2[1, 5] ***(GR C)***.

b. Histological procedure: (see pathologists guideline)

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 as many lymph nodes as possible in the excised specimen and the number found should be noted [1] **(GR B).** In patients with rectum cancer who are treated with curative intent, 6 or 8 nodes should normally be examined; if the median number is consistently below 8, the surgeon and the pathologist should discuss their techniques[1] **(GR B).** Patients with inadequately sampled nodes could be offered adjuvant chemotherapy [13] ***(GR C).***

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

5. Final Staging:

Rectum cancers should be staged using the TNM staging system [9, 31, 5] (**GR B):**

pTNM: post-surgical histopathological classification

T - 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 pericoloc or perirectal tissues
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum

N – Nodal status

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

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.

M – Distant metastases

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

TNM Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1 or T2	N0	M0
Stage II A	T3	N0	M0
Stage II B	T4	N0	M0
Stage III A	T1 or T2	N1	M0
Stage III B	T3 or T4	N1	M0
Stage III C	Any T	N2	M0
Stage IV	Any T	Any N	M1

The final staging is done during the second multidisciplinary meeting (MOC) on the basis of all results and reports available for a given patient [1] ***(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 [1] ***(GR C).***

Depending on the tumour stage, the further treatment options are decided [13, 31, 1, 2, 5] **(GR A):**

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 point 6 (metastatic disease)

A written report with staging and treatment options is mandatory for each patient [7] ***(GR C).***

a. Follow up procedure

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 [17, 18, 1, 2, 19, 5, 6, 20] **(GR A)**

Although no absolute scientific prove of outcome benefit of an intensive follow up policy [21], 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 [22, 10] ***(GR C).***
- Colonoscopy still to be done for those patients who did not have complete colonoscopy preoperatively (to perform within 6 months after operation [1, 2] ***(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 (without clear positive conclusion) 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

For detection and localization of local, hepatic and extra-hepatic recurrence, the diagnostic efficacy includes changes in patient management and therapeutic decision. In addition, there is limited evidence for cost-effectiveness. PET is indicated for localization of metastasis in case of increasing CEA level following surgery in a patient with colorectal cancer.

b. Adjuvant therapy

As indicated in the final staging section, stage III rectal 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, 23, 24] **(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). Various regimens are presented in the appendices.

The choice of a regimen for a given patient is based on his/her risk profile and the toxicity of the drugs.

Adjuvant radiotherapy combined with chemotherapy could be an option, although there is no clear evidence that this combination improves survival [35] ***(GR C).***

6. Treatment of metastatic disease

a. Treatment of resectable metastases:

Following therapeutic strategies can be proposed on the basis of the individual situation of the patient and his tumour [9, 1, 2, 5, 6]] ***(GR C):***

- x surgery of the primary tumour and the metastasis in the same procedure, with or without (neo)adjuvant therapy for the primary tumour (although this is not based on solid clinical evidence)
- x surgery of the primary tumour followed by:
    - surgery of the metastasis, or
    - chemotherapy and then surgery of metastasis

CRITERIA FOR RESECTABILITY OF METASTASES [5]

Liver

- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of noble hepatic function is required [5] ***(GR C)***.
- There should be no unresectable extrahepatic sites of disease [5] ***(GR C)***.
- The primary tumour must be controlled [5] ***(GR C)***.
- Re-resection can be considered in selected patients[5]

Resection is the treatment of choice for resectable liver metastases. Other techniques such as radiofrequency might be optional or complementary [5] ***(GR C).***

Note:

- MRI with contrast agent has significantly superior sensitivity than CT for preoperative assessment of operability of liver metastasis [25] **(GR B).**
- PET scan is recommended in the preoperative evaluation of resectable liver metastases **(GR A)** [25].

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required [5] ***(GR C)***.

- Resectable extra-pulmonary metastases do not preclude resection [5] ***(GR C)***.
- The primary tumour must be controlled [5] ***(GR C)***.
- Re-resection can be considered in selected patients [5] ***(GR C).***

After resection, adjuvant chemotherapy can be considered [26-28, 1, 29, 2, 5, 6]. The decision is made on individual basis depending on the risk profile and health status ***(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 [1, 2] **(GR B).**

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

b. Treatment of unresectable metastases

If the patient presents with symptoms related to the primary tumour (bleeding, obstruction…): resection of primary tumour with or without (neo)adjuvant therapy for the primary tumour [9, 1, 2, 11] **(GR B)**, or radiotherapy (in case of bleeding), or stenting (in case of obstruction)**.**

If the patient has no symptoms related to the primary tumour: chemotherapy [30] **(GR A)**. Each patient should receive an evaluation for first and second line chemotherapy [26, 2, 5, 6] ***(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, 5] **(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 [1] **(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 [1] ***(GR C).***

A patient in good health status and progressive under standard therapy should be proposed a clinical trial protocol[1] ***(GR C).***

6 QUALITY CONTROL

The good utilization of a guideline has to be evaluated. Therefore, a guideline has to be accompanied with quality control criteria.

These criteria should at least assess the following steps of the algorithm:

- clinical staging process
- surgery process
- histology process
- adjuvant chemotherapy and other treatments

For each step, quality indicators will be developed. In 2006, the KCE will start a project with the objective to develop and test quality indicators for rectal cancer. It will be the first tumour for which these kind of indicators will be tested and others will follow.

7 APPENDICES

APPENDIX 1: EVIDENCE TABLE COLORECTAL GUIDELINES

Titel	Country	Year	Scope	AGREE overall assessment
Management of colorectal cancer – SIGN [2]	Scotland	2003	Colorectal	Strongly recommend
Guidance on Cancer Services Improving Outcomes in Colorectal Cancer - NICE[1]	UK	2003	Colorectal	Strongly recommend
Guidelines for the management of colorectal cancer - The association of coloproctology of GB and Ireland[7]	UK	2001	Colorectal	Recommend (with provisos or alterations)
Adjuvant therapy for Stage II & IIIColon Cancer Following Complete resection – Cancer care Ontario [14]	Canada	2000	Colon	Strongly recommend
Use of irinotecan in treatment of metastatic colorectal carcinoma - Cancer care Ontario[27]	Canada	2000	Colorectal	Strongly recommend
Use of raltitrexed in management of metastatic colorectal cancer - Cancer care Ontario [28]	Canada	2002	Colorectal	Strongly recommend
Use of Irinotecan combined with 5Fluorouracil and leucovirin as first line therapy for metastatic colorectal cancer - Cancer care Ontario[29]	Canada	2003	Colorectal	Strongly recommend
Follow up of patients with curatively resected colorectal cancer – Cancer care Ontario [20]	Canada	2004	Colorectal	Strongly recommend
Postoperative adjuvant Radiotherapy and/or Chemotherapy for Resected Stage II & III Rectal Cancer – Cancer care Ontario[35]	Canada	2001	Rectum	Strongly recommend
The use of Preoperative radiotherapy in the management of patients with Clinically respectable Rectal cancer - Cancer care Ontario[34]	Canada	2004	Rectum	Strongly recommend
Colon Cancer – NCCN[5]	USA	2004	Colon	Recommend (with provisos or alterations)
Rectal Cancer - NCCN [5]	USA	2004	Rectum	Recommend (with provisos or alterations)

Titel	Country	Year	Scope	AGREE overall assessment
Colon cancer treatment – NCI[6]	USA	2004	Colon	Recommend (with provisos or alterations)
Rectal cancer treatment – NCI[31]	USA	2003	Rectum	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 [15]	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[36]	Netherlands	2000	Colon	Would not recommend
Rectumcarcinoom – Oncoline (vereniging van Integrale kankercentra) : consensus based[37]	Netherlands	2001	Rectum	Would not recommend

COLORECTAL CANCER AGREE Key items	SIGN	NICE	NCCN	NCI	Singapore MOH	Assoc Coloproct GB	Cancer Care Ontario	ASCO	Oncoline
Scope and Purpose									
1	4	4	4	4	4	4	4	4	4
2	4	4	4	4	4	4	4	4	4
3	4	4	4	4	4	4	3	4	4
Stakeholder involvment									
4	4	4	4	1	4	4	3	1	2
5	3	3	1	3	1	4	3	1	1
6	4	4	3	4	4	4	4	4	4
7	2	2	2	2	1	2	2	2	2
Rigour of development									
8	4	4	2	2	1	1	4	4	1
9	4	4	4	4	4	4	4	4	1
10	4	4	4	4	1	4	4	4	1
11	4	4	4	4	4	4	4	4	1
12	4	4	4	4	4	4	4	4	1
13	4	4	2	2	1	2	4	2	1
14	4	3	3	1	4	1	4	4	1
Clarity and Presentation									
15	4	4	4	4	4	4	4	4	4
16	4	4	4	4	4	4	4	4	4
17	4	4	4	4	4	4	4	3	4
18	4	2	4	4	4	2	2	1	1
Applicability									
19	2	1	1	1	1	1	1	1	1
20	1	4	1	1	1	1	1	1	1
21	4	4	1	1	1	1	1	1	1
Editorial independance									
22	4	4	4	2	1	4	4	4	4
23	4	4	2	2	1	1	4	1	1
Overall assessment	SR	SR	R	R	R	R	SR	SR	NR

The assessment of the guidelines was made with the AGREE instrument.

All details can be found on the AGREE collaboration website:

http://www.agreecollaboration.org/

The AGREE instrument can be found on: http://www.agreecollaboration.org/pdf/agreeinstrumentfinal.pdf

APPENDIX 2: KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS COLORECTAL GUIDELINE

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

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
A 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

Grade

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)

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)

Levels of evidence

Ia Evidence obtained from meta-analysis of RCTs
Ib Evidence obtained from at least one RCT
IIa Evidence obtained from at least one well designed controlled study without randomisation
IIb Evidence obtained from at least one other type of well designed quasi-experimental study
III Evidence obtained from well designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

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)

APPENDIX 3: VARIOUS CHEMOTHERAPY REGIMENS

CHEMOTHERAPY REGIMENS	
FOLFOX	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
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	Capecitabine13 2,500 mg/m /day PO in two divided doses, days 1-14, followed by 7 days rest Repeat every 3 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	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
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	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
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	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
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	Protracted IV 5-FU 5-FU 300 mg/m /d protracted IV infusion
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	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 Cetuximab ± irinotecan Cetuximab 400 mg/m 1st infusion, then 250 mg/m weekly ±
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	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

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