

# CLINICAL PRACTICE GUIDELINES

2017

MOH/P/PAK/352.17(GU)

## MANAGEMENT OF



# COLORECTAL CARCINOMA



Ministry of Health  
Malaysia



Malaysian Society  
of Colorectal  
Surgeons



Malaysian Society  
of Gastroenterology  
& Hepatology



Malaysian  
Oncological Society



Academy of  
Medicine Malaysia

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Available on the following websites:

<http://www.moh.gov.my>  
<http://www.acadmed.org.my>  
<http://www.colorectalmy.org>  
<http://www.msgh.org.my>  
<http://www.malaysiaoncology.org>

Also available as an app for Android and IOS platform: MyMaHTAS

**STATEMENT OF INTENT**

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

## **UPDATING THE CPG**

These guidelines were issued in 2017 and will be reviewed in a minimum period of four years (2021) or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE	
Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

## FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

## KEY RECOMMENDATIONS

The following recommendations were highlighted by the guidelines Development Group as the key clinical recommendations that should be prioritised for implementation.

### Screening in Average Risk Population

- Screening of colorectal carcinoma (CRC) should be offered at the age of 50 years and continues until 75 years old for average risk population.
- Immunochemical faecal occult blood test (iFOBT) is the preferred method to screen for CRC in average risk population.
  - If iFOBT is positive, an early colonoscopy is necessary.
  - If iFOBT is negative, yearly test should be performed.

### Screening/Surveillance in Moderate and High Risk Groups

- Asymptomatic individuals with positive family history should be screened for colorectal carcinoma.
- All individuals whose family history is suggestive of a hereditary colorectal cancer syndrome should be referred to a clinical genetics service for genetic risk assessment, where accessible.

### Diagnostic and Radiological Investigations for Staging

- Computed tomography scan should be used for staging and surveillance of colorectal carcinoma.
  - Magnetic resonance imaging is the modality of choice in diagnosing and staging of rectal carcinoma.
- 
- In colorectal carcinoma, standardised histopathology reporting proforma incorporating tumour-node-metastasis (TNM) staging system should be used.

## Surgical Management

- Patients undergoing colorectal carcinoma surgery should have:
  - antibiotic prophylaxis
  - venous thromboembolism prophylaxis
  
- A thorough surgical exploration should be performed at the time of resection in colorectal carcinoma.
- Low rectal surgery should be performed by surgeons credentialed in the management of rectal carcinoma.
- Total mesorectal excision should be performed for middle and low rectal carcinoma.
- If abdominoperineal resection (APR) is required, it should be performed as cylindrical APR.

## Chemotherapy and Radiotherapy

- Adjuvant chemotherapy may be considered for stage II colon carcinoma with high risk features. Patient should be carefully selected and counselled.
- Fluorouracil/leucovorin (5-FU/LV) with oxaliplatin should be given in stage III colon carcinoma.
  
- Neoadjuvant chemoradiotherapy should be offered to T3-T4 or node positive rectal carcinoma.
  
- Palliative chemotherapy may be considered in metastatic colorectal carcinoma.
  - Combination chemotherapy is the preferred regime.

## GUIDELINES DEVELOPMENT AND OBJECTIVES

### GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these CPG were from the Ministry of Health (MoH) and Ministry of Higher Education (MoHE). There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: Guidelines International Network (G-I-N), Medline via Ovid, Cochrane Database of Systemic Reviews (CDSR) and Pubmed. Refer to **Appendix 1 for Example of Search Strategy**. The inclusion criteria are all patients with colorectal carcinoma regardless of study design. The search was limited to literature published in the last 20 years and on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 7 May 2015 to 28 January 2016. Literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 30 April 2017 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other guidelines as listed below:

- Scottish Intercollegiate Guidelines Network (SIGN) - Diagnosis and Management of Colorectal Cancer (December 2011)
- New Zealand Guideline Group (NZGG) - Management of Early Colorectal Cancer (May 2011)
- National Institute for Health and Clinical Excellence (NICE) - The Diagnosis and Management of Colorectal Cancer (November 2011)

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to it being used as reference.

A total of 14 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2 for Clinical Questions**. The DG members met 23 times throughout the development of these guidelines. All literatures retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meetings. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion are resolved consensually. The CPG was based

largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literatures used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001) while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of AGREE II.

On completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MoH Malaysia for review and approval. Details on the CPG development by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at: [http://www.moh.gov.my/penerbitan/mymahtas/CPG\\_MANUAL\\_MAHTAS.pdf](http://www.moh.gov.my/penerbitan/mymahtas/CPG_MANUAL_MAHTAS.pdf))

## OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on colorectal carcinoma (CRC) on these aspects:

- Screening in average risk population
- Surveillance of moderate and high risk groups
- Diagnosis and staging
- Treatment and follow-up

## CLINICAL QUESTIONS

Refer to **Appendix 2**

## TARGET POPULATION

### Inclusion Criteria

- Healthy population for screening programme
- High risk population for surveillance
- Lynch syndrome/Hereditary non-polyposis colorectal cancer (HNPCC)
- Familial adenomatous polyposis (FAP)
- Inflammatory bowel disease
- Peutz-Jegher syndrome
- MUTYH-associated polyposis (MAP)
- Juvenile polyposis
- All patients with CRC

### Exclusion criteria

CRC other than adenocarcinoma such as gastrointestinal stromal tumour (GIST), neuroendocrine tumour (NET) and lymphoma

## TARGET GROUP/USER

This CPG is intended to guide those involved in the management of CRC either in primary or secondary/tertiary care (all in public and private practice) namely:

- Medical officers and specialists
- Trainees and medical students
- Patients and their advocates
- Professional societies

## HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

## **DEVELOPMENT GROUP**

### **Chairperson**

Dr. Nil Amri Mohamed Kamil  
Consultant Colorectal Surgeon  
Hospital Sultanah Bahiyah, Kedah

### **Co-chairperson**

Dr. Hjh. Rosaida Hj. Md. Said  
Consultant Gastroenterologist  
Hospital Ampang, Selangor

### **Members (alphabetical order)**

Assoc. Professor Dr. Ahmad Najib Azmi  
Lecturer & Gastroenterologist  
Faculty of Medicine & Health Sciences  
Universiti Sains Islam Malaysia  
Negeri Sembilan

Dr. Ahmad Shanwani Mohamed Sidek  
Consultant Colorectal Surgeon  
Hospital Raja Perempuan Zainab II,  
Kelantan

Dr. Ch'ng Gaik Siew  
Consultant Clinical Geneticist &  
Paediatrician  
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Fauziah Jaya  
Consultant Gastroenterologist  
Hospital Raja Permaisuri Bainun, Perak

Dr. Hafizah Zaharah Ahmad  
Clinical Oncologist  
Institut Kanser Negara, Putrajaya

Dr. Hanin Farhana Kamaruzaman  
Senior Principal Assistant Director  
Health Technology Assessment Section  
Ministry of Health Malaysia, Putrajaya

Dr. Ibtisam Muhamad Nor  
Clinical Oncologist  
Hospital Kuala Lumpur,  
Kuala Lumpur

Dr. Mohd. Aminuddin Mohd. Yusof  
Head of CPG Unit  
Health Technology Assessment Section  
Ministry of Health Malaysia, Putrajaya

Dr. Noraini Abdul Rahim  
Consultant Radiologist  
Institut Kanser Negara, Putrajaya

Ms. Nik Nuradlina Nik Adnan  
Pharmacist  
Institut Kanser Negara, Putrajaya

Dr. Salahudin Baharom  
Consultant Colorectal Surgeon  
Hospital Selayang, Selangor

Dr. Salmi Abdullah  
Pathologist (Anatomic Pathology)  
Hospital Selayang, Selangor

Dr. Siti Aminah Akbar Merican  
Consultant Family Medicine  
Klinik Kesihatan Batu Rakit, Terengganu

Dr. Tee Hoi Poh  
Consultant Gastroenterologist  
KPJ Pahang Specialist Hospital,  
Pahang

Dr. Tengku Norita Tengku Yazid  
Consultant Pathologist  
(Chemical Pathology)  
Hospital Selayang, Selangor

Dr. Zalwani Zainuddin  
Consultant Gastroenterologist  
Hospital Sultanah Bahiyah, Kedah

## **REVIEW COMMITTEE**

The draft CPG was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the CPG.

### **Chairperson**

Dato' Dr. Fitjerald Henry  
Senior Consultant Colorectal Surgeon  
(National Head of Clinical Service Colorectal Surgery)  
Hospital Selayang, Selangor

### **Members (alphabetical order)**

Dato' Dr. Abdul Jamil Abdullah  
Senior Consultant General Surgeon  
Hospital Sultanah Nur Zahirah, Terengganu

Dr. Akhtar Qureshi  
Consultant Colorectal Surgeon  
Sunway Medical Centre, Selangor

Professor Dr. Azmi Md. Nor  
Dean & Consultant Colorectal Surgeon  
Kulliyah of Medicine  
International Islamic University Malaysia

Mr. Hamzan Arshad  
Patient Advocate  
(Survivor of Colorectal Carcinoma)

Dr. Junainah Sabirin  
Deputy Director  
Health Technology Assessment Section  
Ministry of Health Malaysia, Putrajaya

Dato' Dr. Mahendra Raj  
Consultant Gastroenterologist  
Hospital Pantai Kuala Lumpur, Kuala Lumpur

Dr. Manisekar Subramaniam  
Consultant Hepatobiliary Surgeon  
(National Head of Clinical Service Hepatobiliary Surgery)  
Hospital Sultanah Bahiyah, Kedah

Dato' Dr. Mohamed Yusof Abdul Wahab  
Senior Consultant General Surgeon  
(National Head of Clinical Service General Surgery)  
Hospital Tengku Ampuan Rahimah, Selangor

Dr. Mohd Roslan Haron  
Senior Consultant Clinical Oncologist  
Hospital Sultan Ismail, Johor

Dato' Dr. Muhammad Radzi Abu Hassan  
Senior Consultant Gastroenterologist  
(National Head of Clinical Service Gastroenterology & Hepatology)  
Hospital Sultanah Bahiyah, Kedah

Datin Dr. Nik Raihan Nik Mustapha  
Consultant Pathologist (Histopathology)  
Hospital Sultanah Bahiyah, Kedah

Dr. Ros Suzanna Ahmad Bustamam  
Consultant Clinical Oncologist  
(National Head of Clinical Service Oncology)  
Hospital Kuala Lumpur, Kuala Lumpur

Mdm. Rosminah Din  
Deputy Director  
Formulary & Pharmacoeconomics  
Pharmacy Practice & Development  
Ministry of Health, Selangor

Professor Dr. Tong Seng Fah  
Lecturer & Consultant Family Medicine Specialist  
Faculty of Medicine  
Universiti Kebangsaan Malaysia, Kuala Lumpur

Dato' Dr. Wan Khamizar Wan Khazim  
Senior Consultant Colorectal Surgeon  
Hospital Sultanah Bahiyah, Kedah

Dr. Yun Sii Ing  
Consultant Radiologist  
Hospital Sungai Buloh, Selangor

**EXTERNAL REVIEWERS (in alphabetical order)**

The following external reviewers provided feedback on the draft:

Professor Dr. Angelo Vanzulli  
Consultant Radiologist  
University of Milan, Italy

Professor Dr. Aw Tar Choon  
Senior Consultant in Laboratory Medicine  
Changi General Hospital, Singapore

Dr. Azura Deniel  
Consultant Oncologist  
KPJ Ampang Puteri Specialist Hospital, Kuala Lumpur

Dr. Baizury Bashah  
Consultant Family Medicine  
Klinik Kesihatan Kuala Lumpur, Kuala Lumpur

Adj. Assoc. Professor Dr. Charles Tsang Bih-Shiou  
Senior Consultant General Surgeon  
Yong Loo Lin School of Medicine  
National University of Singapore &  
Medical Director  
Colorectal Clinic Associates International, Singapore

Professor Dr. Chucheep Sahakitrungruang  
Consultant Colorectal Surgeon  
Bumrungrad International Hospital, Thailand

Dr. Clement Edward A/L Thaumanavar  
Head of Department & Consultant General Surgeon  
Hospital Tuanku Fauziah, Perlis

Professor Dato' Dr. Fuad Ismail  
Senior Consultant Oncologist  
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur

Dr. Leow Voon Meng  
Consultant Hepato-Pancreato-Biliary & General Surgeon & Lecturer  
Advanced Medical and Dental Institute  
Universiti Sains Malaysia, Pulau Pinang

Associate Professor Dr. Lim Kiat Hon  
Senior Consultant Pathologist  
Singapore General Hospital, Singapore

Dato' Dr. Meheshinder Singh  
President of Malaysian Society of Colorectal Surgeons &  
Consultant General & Colorectal Surgeon  
Pantai Medical Centre Kuala Lumpur, Kuala Lumpur

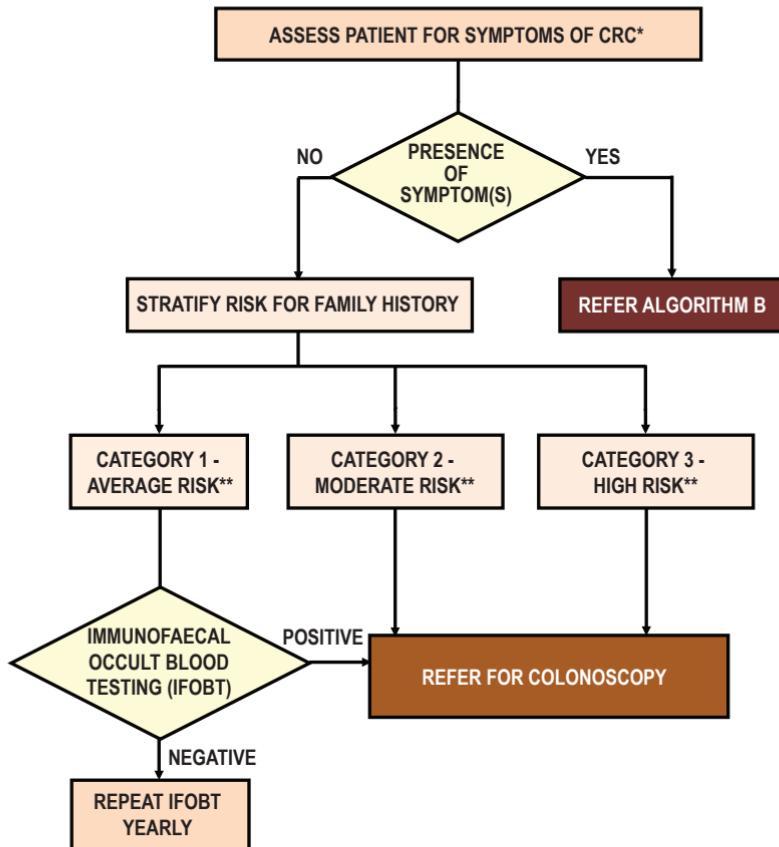
Dr. Narasimman Sathiamurthy  
Consultant Thoracic Surgeon  
Hospital Kuala Lumpur, Kuala Lumpur

Dr. Nazrila Hairizan Nasir  
Consultant Family Medicine  
Family Health Development Division  
Ministry of Health Malaysia, Putrajaya

Associate Professor Dr. Raja Affendi Raja Ali  
Consultant Physician & Gastroenterologist  
Pusat Perubatan Universiti Kebangsaan Malaysia, Kuala Lumpur

Professor Dr. Rajvinder Singh  
Professor of Medicine  
The University of Adelaide &  
Director of Gastroenterology  
The Lyell McEwin & The Modbury Hospitals, Australia

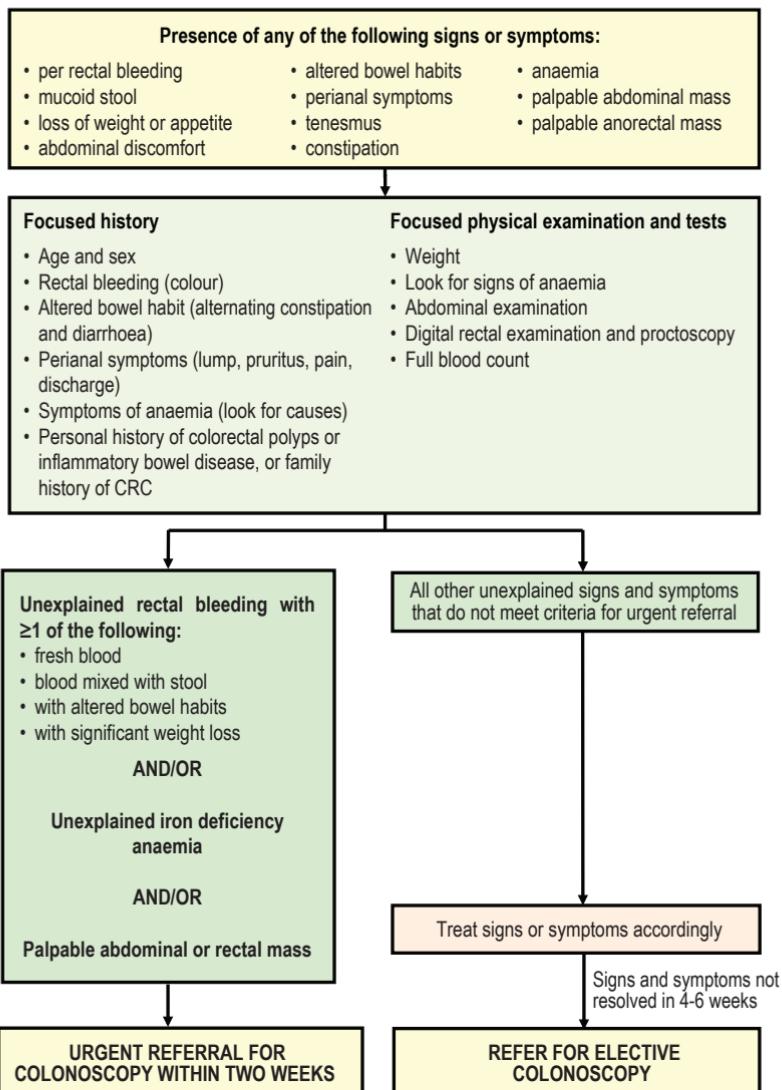
Professor Dr. Roger Barton  
Provost & CEO, Professor of Clinical Medicine &  
Consultant Gastroenterologist  
Newcastle University Medicine Malaysia, Johor

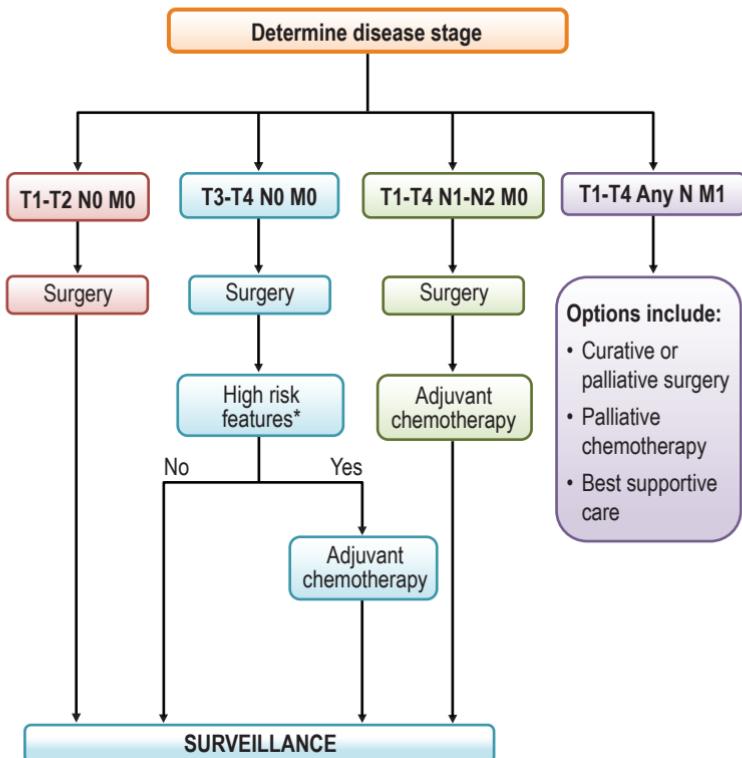
**ALGORITHM A: SCREENING FOR COLORECTAL CARCINOMA**

\*Symptoms as outlined in **Algorithm B**.

\*\*Refer to **Table 4** on Risk Categories for Family History with Colorectal Carcinoma.

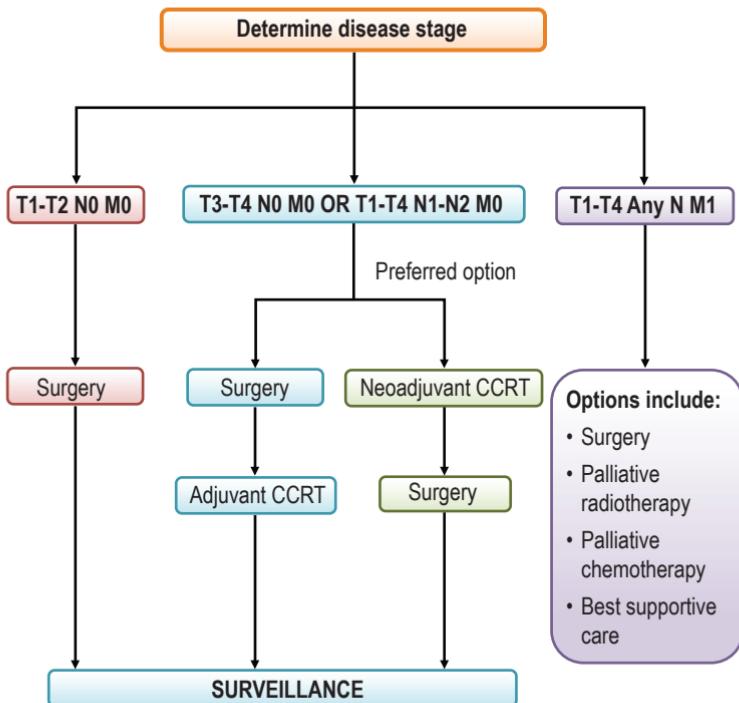
## ALGORITHM B: PRIMARY CARE REFERRAL FOR SYMPTOMS OF COLORECTAL CARCINOMA



**ALGORITHM C: TREATMENT FOR COLON CARCINOMA**

\*High risk features for stage II colon carcinoma are presence of any of the following:

- obstruction
- perforation
- T4 disease
- poorly differentiated tumour
- lymphovascular invasion
- perineural invasion
- inadequate lymph node sampling (<12)

**ALGORITHM D: TREATMENT FOR RECTAL CARCINOMA**

\*High risk features for stage II rectal carcinoma are presence of any of the following:

- obstruction
- perforation
- T4 disease
- positive CRM
- poorly differentiated tumour
- lymphovascular invasion
- perineural invasion
- inadequate lymph node sampling (<12)
- incomplete mesorectum

CCRT = Concurrent chemoradiotherapy

CRM = Circumferential resection margins



## 1. INTRODUCTION

Colorectal carcinoma (CRC) is the second most common cancer in Malaysia (13.2%) as reported in Malaysian National Cancer Registry Report 2007-2011.<sup>1, level III</sup> According to National Cancer Patient Registry on Colorectal Cancer 2008-2013, the overall incidence rate for CRC was 21.3 cases per 100,000 population. Age-adjusted incidence rate was 1.33 times higher among male than female. The incidence was highest in Chinese followed by Malay and Indian. Overall mortality rate was 9.8 cases per 100,000 population and age-adjusted mortality rate was 1.42 times higher in male than female.<sup>2, level III</sup>

The most common presenting symptoms of CRC are altered bowel habit (41.7%) followed by blood in stool (35.5%), abdominal pain (31.5%), weight loss (31.0%), anaemia (9.8%) and intestinal obstruction (9.3%).<sup>2, level III</sup>

Left-sided carcinoma is the commonest form and constitutes 81.8% of all notified cases. Majority of patients are at stage III and IV (54.36%) while only 8.4% are diagnosed at stage I according to the tumour-node-metastasis (TNM) staging.<sup>2, level III</sup>

The estimated societal cost of CRC management in government hospitals in Malaysia using conventional chemotherapy ranges between RM13,622 to RM27,163 based on different stages, with an average of RM21,377 per patient. The cost of treatment is higher when combined conventional chemotherapy and monoclonal antibody is used.<sup>3</sup> With increasing number of new cases detected every year, the economic burden of CRC management is escalating especially if the patients present in advanced stage.

Management of patients with CRC consists of a comprehensive strategy of screening, diagnosis, staging, appropriate treatment and follow-up. Hence, this first national CPG on CRC is developed to assist healthcare providers in the management of CRC.

## 2. SCREENING AND SURVEILLANCE

### 2.1 Screening in Average Risk Population

Average risk population is defined as population with no known risk for CRC. There is no retrievable evidence on the age to start CRC screening for average risk population. This section is written based on recommendation by existing guidelines on CRC and unpublished data from international and local cancer registries.

Most of the major CRC guidelines recommend screening of CRC to start at the age of 50 years old.<sup>4-5, level III</sup>

Depending on the method used, the following screening intervals for CRC among average risk population recommended by major guidelines are shown in the following **Table 1.**<sup>5, level III; 6, level II-2; 7-8, level III</sup>

**Table 1. Screening Intervals for CRC Based on Methods**

Methodology	Minimum interval
Faecal occult blood	Yearly
Stool DNA test	3-yearly
CT colonography	5-yearly
Colonoscopy	10-yearly

The US Preventive Task Force recommends screening for CRC to start at the age of 50 years and continues until age 75 years. The decision to screen for CRC in adults aged 76 to 85 years should be individualised, taking into account the patient's overall health and prior screening history.<sup>9, level III</sup>

## 2.2 Screening Modalities

Most CRC arise from adenomatous polyps that progress from small to large polyps and later to cancer. The slow transition from polyps to cancers in most patients gives the window of opportunity for screening and early cancer detection.

Multiple tests are available for CRC screening. Each test has its own strength and weakness in the attributes of an ideal screening tool.

### a. Faecal Tests

Faecal test is a non-invasive tool for screening CRC in general population. It can detect presence of blood, proteins e.g. enzyme M2-PK and DNA.

Faecal occult blood test (FOBT) has qualitative and quantitative testing methods. In a meta-analysis of fair to high quality evidence, the pooled sensitivity to detect CRC was 74% (95% CI 62 to 83) for quantitative test methods and 79% (95% CI 61 to 90) for qualitative test methods.<sup>9, level III</sup>

Immunochemical FOBT (iFOBT) and guaiac-based FOBT (gFOBT) are two methods of qualitative FOBT. The sensitivities of iFOBT and gFOBT are 0.67 (95% CI 0.61 to 0.73) and 0.54 (95% CI 0.48 to 0.60) respectively. The specificities of iFOBT and gFOBT are comparable at 0.85 (95% CI 0.83 to 0.87) and 0.80 (95% CI 0.78 to 0.82)

respectively.<sup>10, level I</sup> Screening with FOBT has a 16% reduction in the risk of CRC mortality (RR=0.84, 95% CI 0.78 to 0.90).<sup>11, level I</sup>

Faecal M2-PK test has a pooled sensitivity and specificity of 79% (95% CI 73 to 83) and 80% (95% CI 73 to 86) respectively.<sup>12, level I</sup> On the other hand, quantitative faecal DNA test has a higher sensitivity at 92% (95% CI 84 to 97) to detect CRC.<sup>9, level III</sup> These two faecal tests for CRC screening are, however, not widely used locally in screening for general population due to high cost incurred.

In a health technology assessment (HTA) report by MaHTAS, screening programme using iFOBT can be effective for prevention of advanced CRC (risk of developing advanced CRC was reduced by 28-46%) and reduced mortality by 23-60%. Regular iFOBT can detect pre-cancerous lesions and CRC in early stages and thus reduce mortality from CRC.<sup>13, level II-2</sup>

### **b. Sigmoidoscopy**

Flexible sigmoidoscopy needs less rigorous bowel preparation and can be performed as a clinic-based procedure without the need for sedation. Small polyps can be biopsied during procedure but excision of larger lesions (>1 cm) may be performed during subsequent colonoscopy.

Sigmoidoscopy reduces the CRC incidence by 18-32% and mortality by 26-38% in general population. There is low incidence of bowel perforations associated with it.<sup>14-17, level I</sup>

### **c. Colonoscopy**

Colonoscopy is the screening modality that has the ability to visualise the colonic mucosa directly, perform biopsy and excise polyps. It can detect proximal lesions that would be missed by screening sigmoidoscopy and has been shown to reduce risk of cancer in the right colon.<sup>18, level II-2; 19, level II-3</sup>

Screening colonoscopy reduces overall CRC incidence significantly by 56% and death by 68%.<sup>20, level II-2</sup> For those who has had colonoscopy especially for screening, the risk of CRC is strongly reduced by 91% up to 10 years.<sup>18, level II-2</sup>

Colonoscopy is a safe modality for colorectal screening in general population with low incidence of gastrointestinal bleeding (0.29 to 1.59 per 1000 colonoscopies) and perforations (0.19 to 0.89 per 1000 colonoscopies).<sup>21-22, level II-2</sup>

- A good quality colonoscopy should be practised to ensure effective and safe screening of CRC.

#### d. Colon Capsule Endoscopy

Colon capsule endoscopy (CCE) is used to obtain images of the colon by using video cameras embedded in an ingested capsule. The technique is less invasive but does not allow biopsy or polyp removal.

CCE has a sensitivity of 71% (95% CI 66 to 76) and specificity of 75% (95% CI 66 to 83) for polyps of any size. It is a safe screening modality for CRC with low rate (4.1%) of mild to moderate side effects such as nausea and abdominal pain.<sup>23, level II-2</sup>

#### e. Computed Tomographic Colonography/Virtual Colonoscopy

Computed Tomographic Colonography (CTC) uses multiple thin slice computed tomographic data to construct images of the bowel mucosa in two or three dimensions in detecting polyps.

CTC requires bowel preparation similar to conventional colonoscopy (CC) and during the procedure, air or carbon dioxide is introduced into the rectum via a rubber catheter. No sedation is required and patient is usually able to return to work post procedure.

The sensitivity and specificity of CTC for the detection of adenomas  $\geq 6$  mm are 82.9% (95% CI 74 to 89) and 91.4% (95% CI 84 to 96) respectively. For adenomas  $\geq 10$  mm, the sensitivity and specificity are higher at 87.9% (95% CI 82 to 92) and 97.6% (95% CI 95 to 99) respectively.<sup>24, level II-2</sup>

The drawbacks of CTC include radiation exposure and the need for colonoscopy after the identification of polyps for excision and tissue diagnosis, while smaller lesions need to be followed up by surveillance CTC. Flat adenomas are more likely to be missed by CTC than colonoscopy.<sup>24, level II-2</sup>

#### f. Carcinoembryonic Antigen

There is no recommendation made by the US Preventive Services Task Force, NICE guidelines and SIGN guidelines on the use of serum carcinoembryonic antigen (CEA) test for CRC screening.<sup>25-26; 27, level III</sup> Hence, it should not be relied on as a screening tool.

- Based on a local economic evaluation conducted by MaHTAS, iFOBT followed by colonoscopy shown to be the most cost-effective screening strategy compared with no screening or colonoscopy alone with an estimated incremental cost-effectiveness ratio of RM9,377.65.<sup>28</sup>

### **Recommendation 1**

- Screening of colorectal carcinoma (CRC) should be offered at age of 50 years and continues until age 75 years for average risk population.
- Immunochemical faecal occult blood test (iFOBT) is the preferred method to screen for CRC in average risk population.
- If iFOBT is positive, an early colonoscopy is necessary.
- If iFOBT is negative, yearly test should be performed.

## **2.3 Screening/Surveillance in Moderate and High Risk Groups**

### **2.3.1 Family History**

Family history is a well-established risk factor for CRC. It is affected by first-, second- and third-degree relatives, and might include positive family history from both parents.

#### **a. First-Degree Relatives (FDRs)**

Familial Relative Risk (FRR) of developing CRC increases with greater number of affected FDRs irrespective of second-degree relatives (SDRs) or third-degree relatives (TDRs) as shown in **Table 2**.<sup>29, level III</sup>

**Table 2. Selected FRR Estimates for Probands Considering Only FDR Family History**

No. of affected FDRs	FRR (95% CI)
0	0.89 (0.87 to 0.91)
1	1.91 (1.82 to 2.00)
≥1	2.05 (1.96 to 2.14)
2	3.01 (2.66 to 3.38)
3	4.43 (3.24 to 5.90)
4	7.74 (3.71 to 14.24)
5	19.86 (7.26 to 43.24)

Besides CRC, asymptomatic patients with one FDR of CRC have greater risk of developing pre-cancerous condition i.e. severely dysplastic lesions (OR=2.9, 95% CI 1.0 to 7.8).<sup>30, level III</sup>

Compared with those without family history, the relative risks (RR) for those with family history ( $\geq 1$  affected FDRs) of CRC are:<sup>31, level II-2</sup>

- 1.64 (95% CI 1.26 to 2.14) for 1 affected relative and 2.83 (95% CI 1.33 to 6.02) for  $\geq 2$  affected relatives
- 1.99 (95% CI 1.51 to 2.61) for colon carcinoma but not significant for rectal carcinoma

### b. FRR is affected by FDRs when combined with SDRs and TDRs

Combination of a positive family history of FDRs, SDRs and TDRs significantly increases risk of CRC as shown in **Table 3.**<sup>30, level III</sup>

**Table 3. Selected FRR for Probands with 0 or 1 Affected FDRs and Various Combinations of Affected SDRs and TDRs**

No. of affected FDRs	No. of affected SDRs	No. of affected TDRs	FRR (95% CI)
0	0	0	0.83 (0.81 to 0.86)
0	0	$\geq 3$	1.08 (0.97 to 1.20)
0	1	2	1.33 (1.13 to 1.55)
0	1	$\geq 3$	1.21 (0.98 to 1.48)
0	2	$\geq 3$	1.48 (0.98 to 2.16)
0	$\geq 3$	$\geq 3$	1.02 (0.41 to 2.09)
1	0	0	1.76 (1.63 to 1.89)
1	0	2	1.90 (1.59 to 2.25)
1	0	$\geq 3$	2.10 (1.61 to 2.47)
1	1	0	1.88 (1.59 to 2.20)
1	1	2	2.50 (1.87 to 3.28)
1	1	$\geq 3$	3.28 (2.44 to 4.31)
1	2	0	2.37 (1.58 to 3.43)
1	2	1	1.98 (1.15 to 3.17)
1	2	2	2.70 (1.44 to 4.62)
1	2	$\geq 3$	2.38 (1.19 to 4.26)
1	$\geq 3$	0	2.79 (1.12 to 5.76)
1	$\geq 3$	2	5.32 (2.14 to 10.96)
1	$\geq 3$	$\geq 3$	5.20 (2.24 to 10.24)

Those with positive family history who were diagnosed at younger age have a higher risk of developing CRC with FRR of:

- 4.63 (95% CI 1.43 to 15.0) at age of diagnosis  $<45$  years<sup>31, level II-2</sup>
- 3.31 (95% CI 2.79 to 3.89) at age of diagnosis  $<50$  years<sup>29, level III</sup>

Based on preceding evidences, those with family history of CRC can be categorised by risk stratifications as outlined in **Table 4.**

**Table 4. Risk Categories for Family History with CRC**

Category	Description	Screening recommendation
<b>Category 1 Average risk</b>	No family history and age >50 years	<ul style="list-style-type: none"> <li>• Perform IFOBT (refer to <b>Algorithm A</b>).</li> <li>• Stop screening at age 75.<sup>9, level III</sup></li> </ul>
<b>Category 2 Moderate risk</b>	Family history of CRC either: <ul style="list-style-type: none"> <li>• ≥1 FDR</li> <li>• 1 FDR and &gt;1 SDR</li> <li>• &gt;3 and one of them must be FDR</li> </ul>	<ul style="list-style-type: none"> <li>• FDR with CRC diagnosed at age &lt;60 years, colonoscopy should be performed at age 40 or 10 years younger than affected relative (whichever is younger). If normal, repeat every 3-5 years.</li> <li>• FDR with CRC diagnosed at ≥60 years, colonoscopy should be performed at age 40 years. If normal, repeat every 10 years.</li> <li>• Stop screening at age 75.<sup>9, level III</sup></li> </ul>
<b>Category 3 High risk</b>	Family history of: <ul style="list-style-type: none"> <li>• CRC at age &lt;50 years</li> <li>• FAP</li> <li>• HNPCC (Lynch Syndrome)</li> <li>• Peutz-Jegher Syndrome</li> <li>• Juvenile polyposis</li> <li>• MAP</li> </ul>	<ul style="list-style-type: none"> <li>• For family history of CRC diagnosed at age &lt;50 years, colonoscopy should be performed at age 40 or 10 years younger than affected relative (whichever is younger). If normal, repeat every 3-5 years. Stop screening at age 75.</li> <li>• For hereditary colorectal cancer syndromes, refer to <b>Table 5</b>.</li> </ul>

**Recommendation 2**

- Asymptomatic individuals with positive family history should be screened for colorectal carcinoma.
- Colonoscopy should be performed according to risk category\*.

\*Refer to **Table 4**.

### 2.3.2 Post-Adenomatous Polypectomy

Colonoscopy screening with removal of adenomas is an effective strategy in reducing CRC incidence and mortality.<sup>32, level III</sup> However, periodic surveillance with colonoscopy is necessary to identify recurrent adenomas after polypectomy.

Advanced adenomas are typically defined as adenomas >10 mm, villous components (villous/tubulo-villous), or with high-grade/severe dysplasia. The risk factors associated with recurrence of advanced adenoma are:

- i. number of adenomas (1-2 vs 3) (pooled RR=2.52, 95% CI 1.07 to 5.97)<sup>33</sup>, level I
- ii. size (<1 cm vs ≥1 cm) (pooled RR=1.39, 95% CI 0.86 to 2.26)<sup>33</sup>, level I
- iii. villous histology (pooled RR=1.26, 95% CI 0.95 to 1.66)<sup>33</sup>, level I
- iv. high-grade dysplasia (pooled RR=1.84, 95% CI 1.06 to 3.19)<sup>33</sup>, level I
- v. proximal location (significantly two times higher risk)<sup>34</sup>, level II-2
- vi. male gender with large adenomas (RR=1.81, 95% CI 1.42 to 2.31)<sup>35</sup>, level II-2
- vii. parental history of CRC (RR=2.32, 95% CI 1.77 to 3.04)<sup>35</sup>, level II-2

The risk of recurrent advanced adenoma during surveillance colonoscopy following polypectomy is 2-3 times significantly higher among those with advanced adenoma compared with low risk group.

33, level I; 36, level II-2; 37, level III

Surveillance colonoscopy intervals can be scheduled every 10 years for low risk and every three years for high risk patients after initial clearing. This is because it is estimated that 10% of low risk patients will develop advanced metachronous adenomas after 10 years and 10% of high risk patients will develop it after three years.<sup>35</sup>, level II-2 This is supported by a consensus update by the US Multi-Society Task Force on Colorectal Cancer 2008.<sup>27</sup>, level III

### **Recommendation 3**

- Surveillance colonoscopy should be offered to patients after removal of adenomatous polyps every 10 years for low risk and every three years for high risk patients for colorectal carcinoma.

### **2.3.3 Hereditary Colorectal Cancer Syndromes**

Hereditary colorectal cancer syndromes or defined as genetic susceptibility syndromes includes HNPCC, FAP, MAP, juvenile polyposis and Peutz-Jegher Syndrome. The risk and surveillance strategies are shown in **Table 5**.

### **2.3.4 Inflammatory Bowel Diseases**

The risk of CRC in ulcerative colitis (UC) was found to be 2% at 10 years, 8% at 20 years and 18% at 30 years, irrespective of disease extent.<sup>38</sup>, level II-2 Surveillance colonoscopy is performed annually in UC patients seven to eight years after onset of symptoms.<sup>39</sup>, level III; 40, level II-2

The risk of cancer in colonic Crohn's disease is similar to that in UC. Patients with colonic Crohn's disease should therefore be offered entry into a similar surveillance programme to those with UC.<sup>40</sup>, level II-2

**Table 5. Hereditary Colorectal Cancer Syndromes Risk and Surveillance of CRC**

High risk condition	Risk (preferably life time risk)	Initial screening age	Surveillance procedures	Surveillance interval
<b>Familial Adenomatous Polyps (FAP)</b>	Risk increased by 2.4 times for every 10 years 41, level III	FAP gene carriers: 10-14 years old 42-44, level III  Attenuated FAP: 18-20 years old 42-44, level III	Initial screening by sigmoidoscopy. Once adenoma detected, colonoscopy has to be performed.  In attenuated FAP, colonoscopy is recommended 42-44, level III	Colonoscopy interval of 1-2 yearly until surgery is performed 42-44, level III In FDR without identified APC mutation, 2-yearly interval until age 40. After age 40, intervals may be longer (i.e. 3-5 years) and surveillance may discontinue at age 50 <sup>44, level III</sup>
<b>Lynch syndrome/ Hereditary non-polyposis colorectal cancer (HNPCC)</b>	Lifetime cumulative risk to develop CRC is 78% 45, level III	20-25 years old or 5 years before the earliest age of cancer diagnosed in the family 42-43, level III; 46, level II-2; 47, level III	Colonoscopy 42-43, level III; 46, level II-2; 47, level III	1-2 yearly 42-43, level III; 47-48, level III
<b>Peutz-Jeghers Syndrome</b>	Cumulative risk: 39% <sup>49, level III</sup>	8 years old 49, level III	Colonoscopy 49, level III	If polyps are found, examination is repeated every 3 years. If no polyp, repeat at age 18 years and then every 3 years thereafter 49, level III
<b>Juvenile Polyposis</b>	Cumulative risk: 38% <sup>47, level III</sup>	15 years old or earlier if symptoms occur especially rectal bleeding 47, level III; 50, level III	Colonoscopy 47, level III	2-yearly 50, level III
<b>MUTYH-Associated Polyposis (MAP)</b>	Cumulative risk: 63% at age 60 years <sup>51, level II-2</sup>	18-20 years old 51, level II-2	Colonoscopy 51, level II-2	1-2 yearly 51, level II-2

**Recommendation 4**

- All hereditary colorectal cancer syndromes should be referred and managed by colorectal surgeons.
- Surveillance of moderate and high risk group populations for hereditary colorectal cancer syndromes should be based on the risk conditions\*.

\*Refer to **Table 5** and subchapter on Inflammatory Bowel Diseases.

### **2.3.5 Other Risk Factors**

Smoking attributes to 16% greater risk of developing CRC compared with those who had never smoke. The risk of developing CRC is higher if the duration of smoking is more than 25 years (RR=1.23, 95% CI 1.07 to 1.41).<sup>52, level II-2</sup>

Diabetes mellitus is one of the common chronic diseases in general population. Besides its own vascular complications, diabetic individuals have an increased risk of CRC with RR of 1.27 (95% CI 1.21 to 1.34).<sup>53, level II-2</sup>

In relation to body mass index, there is a significant positive association between overweight or obese and CRC among males.<sup>54-55, level II-2</sup>

Alcohol consumption greater than 30 gram/day (g/d) is positively associated with risk for CRC (RR=1.23, 95% CI 1.07 to 1.12).<sup>56, level II-2</sup>

Meat consumption has received a growing interest in its association with CRC. A systematic review on Caucasian population showed that increased intake of 100 g/d red meat (OR=1.17, 95% CI 1.05 to 1.31) and 25 g/d of processed meat (OR=1.49, 95% CI 1.22 to 1.81) were risk factors for CRC.<sup>57, level II-2</sup> However, a systematic review on Japanese population showed no association between CRC and high intake of red meat or high intake of processed meat. The amount of red meat was not quantified.<sup>58, level II-2</sup> SIGN recommends to keep consumption of red meat to less than 500 g (18 ounces) per week and avoid processed meat.<sup>25</sup> Thus, further evidence is needed before a specific advice can be given to general population.

- It is advisable to avoid processed meat and minimise red meat consumption as it may be a risk factor for CRC based on current but limited evidence.

## 2.4 Genetic Counselling and Testing

In the range of 65-75%, CRC are sporadic in nature. Familial CRC contributes to 25-30% whereas hereditary colorectal cancer syndromes only constitute between 5-8% of all CRCs. Familial CRC is defined as having one or more relatives diagnosed with CRC and is related to a combination of genetic and environmental factors.

The hereditary colorectal cancer syndromes are attributed to highly penetrant genes and associated with life-time CRC risk that may approach 70-90%, whereas familial CRC is associated with a two-threefold increase in the individual's risk of CRC compared to general population.<sup>59, level III</sup>

Family history and appropriate genetic testing can provide estimates of cancer risk that inform appropriate cancer screening, surveillance and/or preventative interventions. Molecular tumour screening, prediction models and clinical selection strategies such as Amsterdam Criteria (to find a mutation in one of the MMR genes) and Bethesda Guidelines (to find microsatellite instability in a tumour) are modalities to identify patients with Lynch syndrome.<sup>60, level I</sup>

There are limitations in sensitivity and specificity in using Amsterdam Criteria and Bethesda Guidelines in identification of patients with Lynch syndrome.<sup>60, level I</sup> Prediction models for the identification of Lynch syndrome have been developed to quantify an individual's risk of carrying a mismatch repair gene mutation and help clinicians decide for whom further risk assessment and genetic testing is necessary. MMRPredict, MMRPro and PREMM1,2,6 models all provide a quantitative assessment of the risk of being a MMR gene mutation carrier and have superior performance over existing clinical guidelines. These models are yet to be used locally.<sup>61, level III</sup>

All individuals whose family history is suggestive of a hereditary colorectal cancer syndrome should be referred to a clinical genetics service for genetic counselling, genetic risk assessment and consideration of genetic testing to clarify the risk.<sup>25</sup>

Targeting genetic services for patients with a strong family history of cancer rather than screening the entire population proved to be cost-effective. Predictive or pre-symptomatic testing and identification of cancer-predisposing mutations in carriers have shown that surveillance, prophylactic and chemoprevention techniques extend survival and are cost-effective.<sup>62, level I</sup>

- Refer patients with any of the following to a clinical genetics service for further genetic risk evaluation/assessment for hereditary colorectal cancer syndromes:<sup>25; 63, level III</sup>
  - Personal history of CRC before age 50
  - Personal history of CRC and endometrial cancer at any age
  - Personal history of CRC and ovarian cancer at any age
  - Personal history of CRC and stomach, small bowel, biliary or urinary tract cancer at any age
  - Personal history of CRC and two first-degree relatives with history of colorectal, endometrial, or ovarian cancer at any age
  - Family history of inherited syndromes such as Lynch, FAP or familial diffuse gastric cancer
  - Personal history of 10 or more adenomatous polyps
  - Personal history of multiple primary colon cancers at any age
  - Cumulative >5 proximal serrated polyps, at least two >10 mm
  - Cumulative >20 serrated polyps
  - ≥2 juvenile or Peutz-Jeghers polyps

#### **Recommendation 5**

- All individuals whose family history is suggestive of a hereditary colorectal cancer syndrome\* should be referred to a clinical genetics service for genetic risk assessment, where accessible.

\* Refer to yellow box on hereditary colorectal cancer syndromes.

### **3. PRIMARY CARE AND REFERRAL**

In Malaysia, CRC screening is done mainly in primary care. Most of the patients with symptomatic CRC often present at later stages of the disease. In an attempt to improve early detection of CRC, various efforts have been done to establish CRC screening programme in primary care setting.

Therefore, one of the objectives of this CPG is to assist Family Medicine Specialists and other primary care providers in providing structured screening and referral programme according to the symptoms and risk stratification (refer to **Algorithm A** and **B**).

## 4. DIAGNOSTIC AND RADIOLOGICAL INVESTIGATIONS FOR STAGING

### 4.1 Diagnostic Investigations

#### a. Colonoscopy

Complete endoscopic colonoscopy is required in all suspected CRC cases in order to detect synchronous lesion and obtain biopsy specimen.

#### b. Barium Enema

Barium enema (BE) is the established radiological method to investigate patients with symptoms suggestive of CRC or large polyps in clinical practice although its utilisation is declining.

Recent advent of virtual colonoscopy (VC) has shown to have a higher sensitivity than BE and patients prefer VC to BE. Detection rate of CRC or large polyps is significantly higher with VC than BE group (RR=1.31, 95% CI 1.01 to 1.68). The rate is higher in large polyps ( $p=0.0098$ ).<sup>64, level I</sup>

#### c. Computed Tomographic Colonography/Virtual Colonoscopy

An evidence showed that CTC or VC is effective and safe in identifying carcinoma and polyps >10 mm when compared with CC with high sensitivity and specificity.<sup>65, level II-2</sup>

However, a more recent and larger evidence showed that CTC required additional colonic investigation compared with colonoscopy (RR=3.65, 95% CI 2.87 to 4.65). Almost half of the referrals after CTC were for small (<10 mm) polyps or clinical uncertainty. Detection rates of CRC or large polyps were 11% for both procedures. CTC missed 1 of 29 CRC and colonoscopy missed none (of 55). Serious adverse events were rare.<sup>66, level I</sup>

Advantages for CTC over CC are the ability to evaluate the whole colon, particularly in the presence of a stenosing lesion, detect and stage CRC, and identify incidental pathology which may have a bearing upon management.

- CTC is an alternative modality in diagnosing CRC in symptomatic patients at high risk of the disease.
- Radiation exposure from CTC is approximately 20% lower than the typical dose for double-contrast BE.
- CTC is a more sensitive test than BE. It can be the preferred radiological test for patients with symptoms suggestive of CRC.

#### d. Carcinoembryonic Antigen

CEA is a glycoprotein present in normal mucosal cells and elevated amount of CEA is associated with adenocarcinoma, especially in CRC. Therefore, it has a role as a tumour marker. However, normal level of CEA does not indicate absence of CRC.

- The use of CEA is exclusively confined for monitoring and follow-up. It is performed pre-operatively in patients with CRC for baseline investigation and surveillance.

### 4.2 Radiological Investigations for Staging

Although practice varies between treatment centres, evidence suggests that the best method for diagnosing CRC or polyps is direct visualisation of bowel mucosa by CC followed by histopathological examination (HPE).

#### a. Computed Tomography

Computed tomography (CT) is routinely used and remains the mainstay technique for primary staging and disease surveillance in patients with CRC. It is used for identification of the location and size of the lesion, demonstration of local extension, and detection of distant metastases or complications such as perforation, obstruction or pericolic abscess formation.<sup>67, level III</sup>

Although CT shows only 75% accuracy in identifying both T1 and T2 carcinoma, it has poor agreement between pre-operative CT staging with the histopathology for individual T stages ( $\kappa=0.208$ ).<sup>67, level III</sup>

For T3 or more, the accuracy is higher at 86%. The accuracy for N stage has been reported as high as 80%. Overall, CT scan has a sensitivity of 70.2% and specificity of 79.2% for T- and N-staging when compared with histopathology staging.<sup>67, level III</sup>

- CT accuracy in identifying CRC and nodal metastases depends on the stages of the tumour. It is not the best modality for the assessment of early CRC.
- Radiological staging for CRC must include contrasted CT thorax.
- Radiological report must include pertinent findings for patient's optimal management including TNM classification.

## b. Magnetic Resonance Imaging

The optimal management of rectal carcinoma requires detailed pre-operative planning that includes the assessment of the relation of tumour to the mesorectal fascia. Normal anatomy of rectum on magnetic resonance imaging (MRI) is as shown in **Appendix 3**. The presence or absence of tumour within 1 mm of the surgical circumferential resection margins (CRM) of the excised surgical specimen strongly influences outcome and is an independent predictor of survival and local recurrence.<sup>68, level III</sup>

High resolution MRI consistently shows the mesorectal fascia. It could predict tumour at the potential CRM with an accuracy of 94% (95% CI 91 to 96) if the tumour is within 1 mm of the mesorectal fascia on the scan. Thus, pre-operatively, MRI accurately predicts whether the surgical resection margins will be clear or affected by tumour. It is also feasible, reproducible and reliable for pre-operative staging.<sup>68, level III</sup> MRI also provides an accurate assessment of cancer local spread pre-operatively.

- MRI staging provides an accurate assessment of rectal carcinoma local spread pre-operatively.
- MRI is the best modality in assessing the relation of the rectal carcinoma with the potential CRM. MRI predicts whether the surgical resection margins will be clear or affected by the carcinoma.

## MRI in Colorectal Carcinoma with Liver Metastasis

Accurate assessment of the size, location and segmental distribution of liver metastases is critical for selection of patients to undergo radical surgery or minimally invasive therapy such as radiofrequency ablation (RFA), cryoablation, chemoembolisation or radioembolisation. Although practice varies between treatment centres, the best methods for detection of liver metastases from CRC are CT and MRI. MRI can be used for characterisation of focal liver lesions. For small metastases to the liver, MRI with hepatocyte-specific contrast medium will facilitate detection because of the high contrast between the avidly enhancing normal liver parenchyma and the non-enhancing metastases in the hepatocellular phase of contrast uptake.<sup>69, level II-2</sup>

In performing the study, combined reading of images from both techniques i.e. diffusion-weighted MRI (DW-MRI) with hepatocyte-specific MR contrast medium such as gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI significantly improve the accuracy of colorectal liver metastasis detection compared with parenchymal phase Gd-EOB-DTPA-enhanced

imaging or DW-MRI images alone. Combining DW-MRI with Gd-EOB-DTPA-enhanced imaging set significantly improves the identification of liver metastases (AUC=0.96, 0.97) compared with reading of the Gd-EOB-DTPA image set (AUC=0.86, 0.89) or the DW-MRI image set alone ( $p<0.016$ ) (AUC=0.93, 0.92).<sup>69, level II-2</sup>

- In MRI study, combined reading of DW-MRI images with hepatocyte-specific contrast medium in the hepatocellular phase images are highly suggested in detecting liver metastasis.

### c. Endorectal Ultrasound

Two meta-analyses showed that endorectal ultrasound is comparable to MRI in rectal carcinoma on:

- T-staging (sensitivity of 0.88 vs 0.89, specificity of 0.79 vs 0.76)<sup>70, level I</sup>
- N-staging (sensitivity of 0.63 vs 0.76, specificity of 0.80 vs 0.77)<sup>71, level I</sup>

Endorectal ultrasound has high accuracy (pooled sensitivity of 0.97 and specificity of 0.96) in assessing early rectal carcinoma and may be used with MRI in identifying patients who may benefit from endoscopic resection.<sup>72, level II-2</sup>

However, endorectal ultrasound use is limited to non-stenosing tumours and its accuracy is significantly reduced in T- and N-staging among patients who have had neoadjuvant chemotherapy and radiotherapy (RT). Thus, MRI of pelvis is still the preferred choice of staging investigation of rectal carcinoma.<sup>70-71, level I</sup>

### d. $^{18}\text{F}$ -fluorodeoxyglucose Positron Emission Tomography CT

For detection of extrahepatic metastases and local recurrence of CRC, CT and  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography CT (FDG PET-CT) are commonly used. FDG PET-CT is more accurate in T4 disease, distant metastases and recurrence when compared with CT alone.<sup>73, level II-2</sup>

PET-CT should not be used routinely for initial staging and surveillance. It can be used in conjunction with liver MRI and contrast-enhanced CT of the thorax, abdomen and pelvis in patients with high risk of metastases.<sup>74, level III</sup>

- Contrast-enhanced FDG PET-CT is preferred as it will provide more detailed information as compared with uncontrasted FDG PET-CT study.
- FDG PET-CT has a role in the evaluation of recurrent CRC with elevated CEA and often with equivocal/negative CT.

- In utilising an imaging modality with ionising radiation, the indication must be justified in which benefits from the diagnostic information obtained outweigh the risks associated with radiation.
- Basic radiation safety principle “As Low as Reasonably Achievable” to minimise radiation doses and employ “reasonable methods” to patients must be adhered to at all times. This helps to prevent unnecessary exposure and overexposure.

#### **Recommendation 6**

- Computed tomography scan should be used for staging and surveillance of colorectal carcinoma.
- Magnetic resonance imaging is the modality of choice in diagnosing and staging of rectal carcinoma.

### **4.3 Histopathological Examination**

HPE of the resected colorectal specimen is essential for patient's management, including the estimation of post-operative outcome and the rationale for adjuvant therapy.

#### **a. Important Pathological Parameters**

Royal College of Pathologists Minimum Pathology Dataset identifies significant prognostic factors for 5-year survival in surgically resected CRC as follows:<sup>75, level III</sup>

- local invasion
- total number of lymph nodes retrieved
- nodal stage (number of lymph nodes involved by cancer)
- extramural vascular invasion
- peritoneal involvement
- tumour perforation
- distance of invasion beyond the muscularis propria
- CRM involvement and distance to this margin (for rectal carcinoma)

The World Health Organisation (WHO) Classification of CRC has been widely used because of its consistency and uniformity in pathologic reporting of colorectal histologic tumour type (refer to **Appendix 4**).<sup>76, level III</sup>

Most CRC are adenocarcinoma. Some other histologic subtypes such as signet-ring and mucin-producing carcinoma have significantly poor prognostic features.<sup>77-78, level III</sup>

Patients with >12 nodes retrieved have significantly higher survival rate compared with those lower nodal yield (53.0% vs 45.4%; p<0.01).<sup>75, level III</sup>

Evaluation for Lynch syndrome may include tumour screening for mismatch repair (MMR) deficiency. MMR-deficient (or microsatellite instability-high) carcinoma frequently demonstrates mucinous differentiation or medullary features in the form of a solid architecture with prominent tumour-infiltrating lymphocytes. MMR status can be readily evaluated by immunohistochemistry (IHC). However, given the resource implications of implementing this, it is not considered a core data item for reporting CRC resection specimen.<sup>77, level III</sup>

Tumour differentiation is important for prognosis.<sup>77, level III</sup> The prognostic validity of grade is highly significant, showing a better survival for the well-differentiated carcinomas compared with poorly differentiated type.<sup>79, level III</sup>

In a systematic review, perineural invasion remained an independent prognostic factor for five-year disease-free survival (DFS), five-year overall survival (OS) and five-year cancer-specific survival.<sup>118, level I</sup>

Prognostic factors for local recurrence in rectal carcinoma are:

- location below the peritoneal reflection and completeness of the plane of mesorectal excision<sup>77, level III</sup>
- histologic grade of regression after pre-operative therapy<sup>77, level III</sup>
- CRM<sup>77, level III</sup>
- distal resection margin (DRM) (Hazard ratio (HR) for 5-year local recurrence in DRM ≤10 mm=2.33, 95% CI 1.28 to 4.25)<sup>80, level III</sup>

- Histopathological reports of CRC should include core histological data, which are:<sup>75, level III; 77, level III</sup>

**i. Macroscopic core items**

- Nature of specimen and type of operation
- Site of tumour
- Maximum tumour diameter
- Distance to nearer longitudinal resection margin
- Relation of tumour to the peritoneal reflection (rectal tumours only)
- Grade of plane(s) of surgical excision (total mesorectal excision (TME) for anterior resection and abdominoperineal resection (APR) specimens)

**ii. Microscopic core items**

- Histological tumour type
- Histological differentiation
- Maximum extent of local invasion (pT stage) and maximum distance of extramural spread
- Grade of tumour regression following pre-operative (neoadjuvant) therapy
- Resection margins (longitudinal and circumferential margins)
- Lymph nodes status (number present, number involved, highest lymph node status)
- Venous invasion
- Perineural invasion

Clinical pathological stage is the most significant independent prognostic factor in CRC either classified according to the Astler and Coller system (with stage D proposed by Turnbull) or pTNM.<sup>79, level III</sup>

CRC staging according to TNM is widely used internationally (refer to **Appendix 4**). Major changes between the 5<sup>th</sup> and 7<sup>th</sup> editions are in the definitions of lymph node involvement. Such changes destabilise historical staging data and longitudinal analyses. For these reasons, the criteria used in the 5<sup>th</sup> edition of TNM are retained for colorectal reporting.<sup>77, level III</sup> In local setting, the pathology report include both the 5<sup>th</sup> and 7<sup>th</sup> editions of TNM staging, as well as Dukes' staging.

**b. Reporting**

Complete and accurate histopathology reports are fundamental in providing quality cancer care. A randomised controlled trial (RCT) showed that the use of pre-defined forms led to a 24.5% (95% CI 11.0 to 38.0) increase in complete reporting of a minimum required data for patient management.<sup>81, level I</sup>

National electronic template reporting improves the inclusion of important key parameters for CRC resection specimen compared with reporting by checklists, locally developed electronic templates or free text ( $p<0.05$ ).<sup>82</sup>, level III

In view of the importance of high quality reporting of CRC resection specimen, Pathology Service of MoH has developed a standardised histopathology reporting proforma for this purpose (refer to **Appendix 5**).

#### **Recommendation 7**

- In colorectal carcinoma,
  - reporting of resection surgical specimens should contain core macroscopic and microscopic histological items\*
  - standardised histopathology reporting proforma incorporating tumor-node-metastasis (TNM) staging system should be used
  - a minimum of 12 lymph nodes should be aimed for proper histopathological examination

\*Refer to yellow box on histopathological report of CRC.

## 5. SURGICAL MANAGEMENT

- The mainstay of treatment for CRC is surgical resection, which offers the best curative outcome. Chemotherapy and RT are used to downstage, as adjuvant therapy and for palliative purposes. The treatments for colon and rectal carcinoma are outlined in **Algorithm C** and **Algorithm D**.

### 5.1 Pre-Operative Preparation

Pre-operative preparation is important to reduce peri-operative morbidity and mortality.

#### a. Antibiotic Prophylaxis

In a Cochrane systematic review, antibiotic prophylaxis reduced wound infections in colorectal surgery by 66% (RR=0.34, 95% CI 0.28 to 0.41). Combination of aerobic and anaerobic bacteria coverage showed better outcomes compared with the use of aerobic or anaerobic antibiotics alone. There was no difference in terms of duration of antibiotic prophylaxis.<sup>83, level I</sup>

#### b. Venous Thromboembolism (VTE) Prophylaxis

Colorectal surgery has a high risk of post-operative thromboembolic complications. Heparin significantly prevented deep vein thrombosis and/or pulmonary embolism (OR=0.32, 95% CI 0.02 to 0.53). There was no difference between unfractionated heparin and low molecular weight heparin in the outcomes (OR=1.01, 95% CI 0.67 to 1.52).<sup>84, level I</sup>

Combined prophylactic modalities (intermittent pneumatic compression and anticoagulants) reduced the incidence of VTE significantly by 61% to 84% when compared with single method.<sup>85, level I</sup>

#### c. Bowel Preparation

A Cochrane systematic review of 15 trials showed no significant difference between mechanical bowel preparation and no bowel preparation in terms of:<sup>86, level I</sup>

- anastomotic leakage
- wound infection
- peritonitis
- re-operation
- mortality

In another sub-analysis on rectal surgery, there was no difference between mechanical bowel preparation and rectal enema for the above outcomes.<sup>86, level I</sup>

Even though there was no difference in post-operative complications between mechanical bowel preparation and no bowel preparation, consensus among RC and DG agreed that bowel preparation prior to rectal carcinoma surgery resulted in lesser morbidity.

#### **Recommendation 8**

- Patients undergoing colorectal carcinoma surgery should have:
  - antibiotic prophylaxis
  - venous thromboembolism prophylaxis
- Mechanical bowel preparation:
  - should be performed in rectal carcinoma surgery
  - may be performed in colon carcinoma surgery

## **5.2 Techniques in Colorectal Surgery**

Surgery in CRC involves en-bloc removal of the cancer with clear margins and its associated regional lymphatic drainage. The aim is to achieve complete resection (R0) of the cancer.

### **a. Colon Carcinoma**

A thorough surgical exploration of the abdomen should be performed at the time of resection. This is to exclude any possible synchronous lesion, assess the extent of primary disease and if there are any distant metastases and to exclude any other coexisting pathology.

The extent of bowel resection for colon carcinoma depends on the site of the primary lesion, blood supply and lymphatics to the affected segment. Complete mesocolic excision and flush ligation of the colonic vessels has demonstrated reduced risk of local recurrence (6.5% vs 3.6%) and improved five-year survival rate (89.1% vs 82.1%) compared with earlier techniques.<sup>87, level II-2</sup>

Total number of lymph nodes evaluated at the time of resection has been associated with survival.<sup>88, level I</sup> It is recommended that at least 12 lymph nodes to be evaluated to assign N0 stage.<sup>89</sup> Thus, surgery performed should ensure at least 12 lymph nodes are harvested.

Synchronous colon carcinoma can be treated by two separate resections or subtotal colectomy.<sup>88, level I</sup>

### **b. Rectal Carcinoma**

Survival in rectal cancer improves and complication rates decrease when credentialed surgeons are involved in the care of CRC patients. The surgeons are more likely to perform restorative procedures, leading to fewer permanent ostomies.<sup>90, level I</sup>

Treatment of rectal carcinoma is based on clinical disease stage. Patients with early stage disease are treated with primary surgery. Treatment of locally advanced disease requires a multidisciplinary approach which includes neoadjuvant RT or concurrent chemoradiotherapy (CCRT) followed by surgery.<sup>90, level I</sup>

For cancer of the upper rectum, the mesorectal excision should extend 5 cm below the distal edge of the cancer, whereas a TME is required for cancer of the middle and lower rectum.<sup>90, level I</sup>

A positive CRM is an independent predictor of local recurrence and decreased survival. Thus, it is critical to obtain an adequate CRM for local control.<sup>90, level I</sup>

In most rectal carcinoma, resection of 2 cm distal mural margin is adequate when combined with a TME. For cancers located at or below the mesorectal margin, 1 cm distal mural margin is acceptable.<sup>90, level I</sup>

A meta-analysis showed that defunctioning stoma decreased clinical anastomotic leak rate and re-operation rate in rectal carcinoma ( $p<0.001$ ).<sup>91, level I</sup> Thus, it should be considered after low anterior resection.

Loop ileostomy is preferred over loop colostomy because of the ease in reversal although the former is associated with an increased incidence of high stoma output and dehydration.<sup>90, level I</sup>

Currently there is no strong evidence to support the practice of rectal washout before an anastomosis in preventing local recurrence in rectal carcinoma.<sup>92, level II-1</sup> However, it may be performed as it is relatively risk-free and does not prolong the operative time.

In low rectal carcinoma, cylindrical APR reduced the rate of CRM involvement ( $p<0.013$ ) and intra-operative perforations ( $p<0.0255$ ) compared with traditional APR.<sup>93, level III</sup> This may help to reduce local recurrence of the cancer.

Choice of procedure would depend largely upon the surgeon's preference and expertise. Options include - TEO (transanal endoscopic operation), TEMS (transanal endoscopic microsurgery), TAMIS (transanal minimally invasive surgery). Locally advanced rectal cancers with involvement of adjacent pelvic organs may require a multidisciplinary approach with a multivisceral resection such as pelvic exenteration.

### c. Laparoscopic Surgery in Colorectal Carcinoma

The same surgical principles applied in both open surgical resection and laparoscopy. Two Cochrane systematic reviews showed no significant difference in operative mortality or recurrence at primary site between laparoscopic and open colorectal resection.<sup>94-95, level I</sup>

Significant short-term benefits from laparoscopic procedures compared with conventional colorectal surgery were:<sup>95-96, level I</sup>

- lesser blood loss
- shorter post-operative hospital stay
- lower post-operative ileus rate
- lower post-operative wound infections

- Resection margins of CRC specimens must be tagged for orientation.

#### **Recommendation 9**

- A thorough surgical exploration should be performed at the time of resection in colorectal carcinoma.
- Low rectal surgery should be performed by surgeons credentialed in the management of rectal carcinoma.
- Total mesorectal excision should be performed for middle and low rectal carcinoma.
- If abdominoperineal resection (APR) is required, it should be performed as cylindrical APR.

## **5.3 Surgical Treatment of Metastatic Colorectal Carcinoma**

### a. Liver Metastases

Treatment options for liver metastasis consist of hepatectomy, systemic chemotherapy, hepatic arterial infusion therapy and thermal coagulation therapy. Liver resection comprises of systematic and non-systematic (non-anatomical) resection.<sup>97, level III</sup>

A Cochrane systematic review on resection of colorectal liver metastases (CRLMs) showed insufficient high level evidence to support the effectiveness or otherwise of a single approach, either surgical or non-surgical, for the management of the condition.<sup>98, level I</sup> Liver resection however has been the mainstay of treatment of resectable colorectal liver metastases. Treatment should be individualised and guided by a team approach.

Criteria for liver resection are listed below:<sup>97, level III; 99-100, level III</sup>

- i. The patient is fit for surgery. Overall health status, organ/liver function, and concomitant non-malignant disease must be assessed.

- ii. The primary cancer has been controlled or can be controlled.
- iii. There are no extrahepatic metastases or they can be controlled.
- iv. The metastatic liver cancer can be completely resected.
  - Resectability includes the expectation that a margin-negative resection (R0) of  $\geq 1$  mm can be achieved.<sup>99-100, level III</sup>
- v. The function of the remaining liver will be adequate. This includes:
  - the anticipated ability to preserve two contiguous segments
  - the anticipated ability to preserve adequate vascular inflow, outflow and biliary drainage
  - the anticipated ability to preserve adequate future liver remnant volume (25% in normal liver and 35-40% in pre-treated liver with chemotherapy, or pre-existing liver damage)<sup>101, level III</sup>

RFA has been shown to have a role in the treatment of unresectable metastases, sometimes in conjunction with the surgical removal of resectable metastases.<sup>99, level III</sup> However, a Cochrane systematic review showed insufficient evidence on the effectiveness of RFA alone as a curative treatment of CRLMs.<sup>102, level I</sup>

Selective internal radiation therapy (SIRT) has limited evidence to demonstrate improvement in clinical response rates, longer median time to liver progression and OS when used in combination with first-, second- or third-line chemotherapy as well as salvage treatment. Selection of patients should be based on a strict criteria.<sup>103, level I</sup>

### **b. Pulmonary Metastases**

A systematic review of observational studies showed that resection of colorectal pulmonary metastases can be performed safely with a low mortality rate in selected patients. Overall five-year survival rate of patients with resection of colorectal pulmonary metastases ranged between 41% and 56%.<sup>104, level III</sup>

The following conditions should be considered for potentially curative resection of pulmonary colorectal metastases:<sup>97, level III; 104, level III</sup>

- technically resectable pulmonary metastases
- patient is fit for surgery
- primary cancer has been controlled or can be controlled
- no extrathoracic metastases detected with the exception of resectable hepatic lesions
- remaining lung function is adequate for good quality of life

### **c. Hepatopulmonary Metastases**

CRC patients presenting with simultaneous hepatic and pulmonary metastases without extrahepatic and extra-pulmonary disease should be offered curative resection if physiologically capable, and the primary

cancer is controlled. The median survival is 54.2 months with a five-year survival rate of 43%.<sup>97, level III; 105, level III</sup>

#### **Recommendation 10**

- Treatment for metastatic colorectal carcinoma should be individualised and guided by a multidisciplinary approach.

### **5.4 Cancer-Related Emergencies**

CRC complications such as bleeding, perforation and obstruction are serious and potentially life-threatening conditions. The aims of treatment for these conditions are to prevent sepsis and/or shock, to achieve the best possible cancer control and to allow initiation of appropriate adjuvant or systemic treatment.<sup>88, level I</sup>

#### **a. Bleeding**

Surgical resection to stop bleeding from localised colon carcinoma should follow the same principles as in elective resection. Chronic blood loss is more common than acute massive lower gastrointestinal bleeding in this condition. Selective embolisation may play a role in controlling acute bleeding, but surgical resection is the definitive treatment. Pre-operative or intra-operative efforts should be made to localise the site of bleeding. If the bleeding site cannot be determined but a colonic cancer is suspected, a subtotal colectomy may be considered.<sup>88, level I</sup>

#### **b. Perforation**

The overall prognosis of colon perforation due to a colon carcinoma is worse than perforation from other causes due to its association with advanced cancer or sepsis. If perforation occurs:<sup>88, level I</sup>

- proximal to an obstructing cancer, resection of the cancer should be performed whenever possible, in addition to resection of the perforated segment
- at the cancer site but contained by adjacent structures, resection should ideally incorporate the adjacent structures en-bloc

Primary anastomosis (with/without proximal diversion) may be considered in patients with minimal contamination, healthy tissue quality and clinical stability.<sup>88, level I</sup>

#### **c. Obstruction**

The management of patients with an obstructing cancer should be individualised but may include a definitive surgical resection. Options for treatment of obstructing cancer depend on the site of obstruction and presence of proximal colonic distention. It is either:<sup>88, level I</sup>

- resection with/without anastomosis (e.g. right hemicolectomy, Hartmann's procedure, etc.)
- resection of the distended bowel (e.g. subtotal/total colectomy)
- temporary relief of obstruction (e.g. stoma or stenting)

Hartmann's procedure offers no survival benefit compared to segmental colonic resection with primary anastomosis. It should be considered in patients with high surgical risks.<sup>106, level III</sup>

Colonic stenting can be considered for those who are not fit for immediate resection or in those with advanced disease. In a Cochrane systematic review, colonic stenting in malignant colorectal obstruction had no advantage over emergency surgery.<sup>107, level I</sup>

The prognosis among patients with obstructing cancers may be worse than among those without obstruction because of the inherently more advanced nature of their disease. However, this does not preclude the potential for curative resection.

## 6. CHEMOTHERAPY AND RADIOTHERAPY

While surgery remained the primary treatment for CRC, the roles of chemotherapy and RT are mainly as neoadjuvant, adjuvant and palliative options. The treatments for colon and rectal carcinoma are outlined in **Algorithm C** and **Algorithm D**.

### 6.1 Colon Carcinoma

#### a. Stage I and II Colon Carcinoma

In colon carcinoma without lymph node involvement (stage I and II), the prognosis is good with surgical intervention alone. Stage II colon carcinoma patients have a relatively favourable prognosis. However, some patients with high risk stage II disease have a relapse rate approaching that of stage III colon carcinoma patients.<sup>108, level I</sup>

In a Cochrane systematic review of adjuvant therapy for completely resected stage II colon carcinoma, there was no improvement in OS (RRR=0.96, 95% CI 0.88 to 1.05). However, the DFS in patients who received adjuvant therapy was significantly better than without adjuvant therapy (RRR=0.83, 95% CI 0.75 to 0.92). Most trials included in the review used the combination of fluorouracil (5-FU) plus folinic acid, with or without levamisole.<sup>108, level I</sup>

Prognostic indicators correlated with high risk for subsequent failure in stage II colon carcinoma include obstruction, poorly differentiated tumour, perforation, venous invasion, inadequate lymph node sampling (<12) or T4 disease. The benefit of adjuvant systemic chemotherapy in patients with high risk features is not well established. The co-morbidities and likelihood of tolerating adjuvant systemic chemotherapy should be considered as well.<sup>108, level I</sup> Patients should be counselled carefully on the risk of chemotherapy vs a potential small benefit of treatment.

The addition of oxaliplatin to 5-FU based chemotherapy also failed to show benefit of adjuvant chemotherapy for stage II patients. In the MOSAIC trial (Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer), six months of 5-FU/leucovorin (LV) was compared with six months of 5-FU/LV with oxaliplatin (FOLFOX regimen). There was no statistically significant improvement in five-year DFS and six-year OS in stage II colon carcinoma. In an exploratory analysis, the probabilities of DFS at five years and OS at six years in high-risk stage II patients were also not statistically significant but there was a trend toward improved DFS at five years in this group of patients treated with FOLFOX4 compared with 5-FU/LV. Thus, the role of adjuvant therapy for stage II colon carcinoma remains controversial.<sup>109, level I</sup>

Similar results from another trial demonstrated an overall benefit in DFS (HR=0.8, 95% CI 0.69 to 0.93) for the addition of oxaliplatin to 5-FU/LV but failed to demonstrate a significant difference in the stage II subset.<sup>110, level I</sup> In both trials above that used oxaliplatin, the relative positive effect of adjuvant treatment on DFS was similar for stage II and III patients, as denoted by comparable HRs for the subgroups.

- High risk features for stage II colon carcinoma are presence of any of the following:
  - obstruction
  - perforation
  - T4 disease
  - poorly differentiated tumour
  - lymphovascular invasion
  - inadequate lymph node sampling (<12)

### **b. Stage III Colon Carcinoma**

For stage III disease, the recurrence rate can exceed 50% and adjuvant chemotherapy may have a role to reduce the risk of recurrence.

The role of 5-FU based chemotherapy in stage III colon carcinoma is well established in improving OS. Several 5-FU regimens are available either as infusion or bolus regimes, with different side effect profile but similar efficacy.

QUASAR was a large trial of adjuvant chemotherapy for CRC using a standard adjuvant cytotoxic chemotherapy regimen, 5-FU and folinic acid with or without levamisole, in either a once-weekly or five-day course at four-weekly intervals. Both schedules were for six months duration. There was no difference in recurrence rates and survival at three years as well as mortality rate between the weekly and four-weekly schedules. However, four-weekly schedule had higher toxicity with more frequent diarrhoea, stomatitis and neutropaenia ( $p<0.001$ ).<sup>111, level I</sup>

The combination of 5-FU and oxaliplatin improved OS even further. In MOSAIC trial, FOLFOX4 was more effective than 5-FU/LV in six-year OS ( $p=0.023$ ) and five-year DFS ( $p=0.005$ ) among stage III colon carcinoma patients. However, there were more grade 3 side effects in the oxaliplatin group including neutropaenia and sensory neuropathy.<sup>109, level I</sup>

Oral chemotherapy using capecitabine have been shown to be equivalent to 5-FU with a favourable side effect profile. In a large RCT comparing oral capecitabine with bolus 5-FU/LV as adjuvant treatment for resected stage III colon carcinoma over a period of 24 weeks, the

DFS was equivalent between capecitabine and 5-FU/LV. Capecitabine improved relapse-free survival ( $p=0.04$ ) and was associated with significantly fewer adverse events compared with 5-FU/LV ( $p<0.001$ ).<sup>112, level I</sup>

In a Cochrane systematic review of adjuvant chemotherapy, there was no significant difference in relapse-free survival and OS between shorter (three to six months) and longer (nine to 12 months) duration chemotherapy. This finding confirmed that adjuvant chemotherapy for CRC should not last for more than six months. Prolonged duration would result in lower benefit-to-risk ratio.<sup>113, level I</sup>

#### **Recommendation 11**

- Adjuvant chemotherapy may be considered for stage II colon carcinoma with high risk features. Patient should be carefully selected and counselled.
- Fluorouracil/leucovorin (5-FU/LV) with oxaliplatin should be given in stage III colon carcinoma.

## **6.2 Rectal Carcinoma**

Adjuvant treatment for low risk rectal cancer (T1-T2 N0) is not indicated unless surgical margin is compromised. Locoregional recurrence after resection of rectal carcinoma is difficult to treat and associated with severe debilitating symptoms. Local recurrence rates were reported to be as high as 50% for patients with T3-T4 and/or node positive rectal carcinoma before the advent of standard CCRT and TME.<sup>114-116, level III</sup>

RT to pelvis with or without chemotherapy plays an important role in the management of rectal carcinoma. It may be given as short or long course schedule.

TME has led to improvements in morbidity and survival in rectal carcinoma. Dutch Colorectal Cancer Group investigated the value of pre-operative short course RT of 25 Gy in five fractions in combination with TME in rectal carcinoma. The 10-year cumulative incidence of local recurrence was 5% in RT and TME group compared with 11% in the TME alone group ( $p<0.0001$ ). However, there was no difference in OS. For patients with TNM stage III cancer with negative CRM, the 10-year survival was 50% in the pre-operative RT group vs 40% in the surgery alone group ( $p=0.032$ ).<sup>117, level I</sup>

- A short course pre-operative RT is a treatment option for rectal carcinoma.

A large, landmark Swedish Rectal Cancer Trial also showed that when compared with surgery alone, the addition of a short course of pelvic radiation (25 Gy in five fractions) pre-operatively resulted in a significant reduction in local recurrence rate (11% vs 27%) and improvement in OS (58% vs 48%) at five-year follow-up in rectal carcinoma.<sup>119</sup>, level I

The timing of adjuvant therapy pre- or post-operatively was addressed in a large German RCT on stage II to III rectal carcinoma. Patients were given either pre-operative CCRT 50.4 Gy with concurrent 5-FU, TME and four cycles of adjuvant 5-FU chemotherapy, or the same schedule of CCRT used post-operatively except for the delivery of a boost of 5.4 Gy. The surgery was scheduled six weeks after completion of CCRT. The benefits of pre-operative CCRT were:

- decrease in local failure (6% vs 13%; p=0.006)
- higher sphincter preservation (39% vs 19%) although not significant
- lower grade 3 or 4 acute toxicity (27% vs 40%; p=0.001) and lower long-term toxicity (14% vs 24%; p=0.01)

However, there was no significant improvement in OS between the two arms.<sup>120</sup>, level I

The role of adjuvant chemotherapy in rectal cancer is not well established. In two large RCTs on resectable rectal cancer T3 or T4, adjuvant chemotherapy after pre-operative CCRT/RT and TME surgery alone did not improve DFS and OS.<sup>121-122</sup>, level I

Pre-operative CCRT (45 Gy + bolus 5-FU/LV) increases pathological complete response (*p*CR) compared with pre-operative RT alone (11.4% vs 3.6%; p<0.05) in addition to receiving four cycles of 5-FU/LV adjuvant chemotherapy. CCRT has lower five-year incidence of local recurrence (8.1% vs 16.5%; p<0.05) but higher grade 3 or 4 acute toxicity (14.6% vs 2.7%; p<0.05). There is no difference in sphincter preservation and five-year OS.<sup>123</sup>, level I In a systematic review of 10 RCTs, tumour shrinkage after pre-operative RT or CCRT did not result in a statistically significant higher anterior resection with sphincter preservation rate.<sup>124</sup>, level I

- Pre-operative chemoradiotherapy resulted in lower incidence of local recurrence compared with RT alone.
- Long course CCRT may be given pre- or post-operatively.
- Neoadjuvant CCRT has become the preferred option.
- Multidisciplinary approach and CRM assessment prior to deciding therapy is important.

T4 cancer with deep local invasion into adjacent structures requires a more extensive surgical resection at the expense of major morbidity.

Pre-operative RT results in good clinical response and may allow potentially curative resection.<sup>125-126, level III</sup>

The European Society for Medical Oncology guidelines 2017 recommend post-operative CCRT if pre-operative CCRT not given in selected patients. Refer to **Appendix 7 on Potential Indications for Post-operative CCRT if Pre-operative CCRT Not Given.**

- High risk features for stage II rectal carcinoma are presence of any of the following:<sup>26; 75, level III; 77, level III</sup>
  - obstruction
  - perforation
  - T4 disease
  - positive CRM
  - poorly differentiated tumour
  - lymphovascular invasion
  - inadequate lymph node sampling (<12)
  - incomplete mesorectum

#### **Recommendation 12**

- Neoadjuvant chemoradiotherapy should be offered to T3-T4 or node positive rectal carcinoma.

### **6.3 Metastatic or Locally Advanced Colorectal Carcinoma**

Stage IV CRC accounts for a third of total CRC cases in Malaysia.<sup>1, level III</sup> The optimal treatment strategy for metastatic colorectal carcinoma (mCRC) involves a multidisciplinary team approach. Management centres around palliation and control of symptoms, lengthening progression-free survival (PFS) and OS. Patients with good performance status, marrow reserve and organ functions have a potential for benefits from chemotherapy. Patients with poor performance status and significant co-morbidities should be considered for supportive care only.<sup>127, level III</sup>

Palliative chemotherapy to mCRC patients is effective in prolonging time to disease progression (TTP) at 12 months (RR=0.86, 95% CI 0.77 to 0.96) and OS at 18 months (RR=0.88, 95% CI 0.82 to 0.96).<sup>128, level I</sup>

5-FU/LV is used clinically since 1957 and is the standard cytostatic agents in CRC. A two-weekly regime which combines 5-FU/LV bolus and infusion has longer PFS ( $p=0.001$ ) and lower grade 3 and 4 toxicity ( $p=0.0004$ ) compared with five-days 5-FU/LV bolus. However, there is no significant difference in OS.<sup>129, level I</sup>

The use of combination regime as first-line chemotherapy improves response rate and TTP compared with 5-FU/LV alone. A two-weekly regime 5-FU/LV bolus and infusion (46 hours) plus irinotecan (FOLFIRI) regime has a response rate of 49% ( $p=0.001$ ) and an improvement of 3.3 months in OS compared with 5-FU/LV alone ( $p=0.031$ ).<sup>130, level I</sup> In comparison, a two-weekly regime 5-FU/LV bolus and infusion (day one and two) plus oxaliplatin (FOLFOX4) regime has a 50.7% response rate ( $p=0.0001$ ) but with no survival benefit.<sup>131, level I</sup> Generally, additional grade 3 and 4 toxicity are more significantly frequent in the combination regimes.<sup>130-131, level I</sup>

There is no statistical difference in PFS and OS between FOLFOX6 and FOLFIRI as first-line chemotherapy in mCRC. However, their toxicity profiles are different. Grade 3 sensory neurotoxicity, grade 3 or 4 neutropaenia and thrombocytopenia are significantly more frequent with FOLFOX6 while grade 3 or 4 febrile neutropaenia, nausea, vomiting, mucositis and fatigue are significantly more frequent with FOLFIRI. More patients have serious adverse events with FOLFIRI than with FOLFOX6 (14% vs 5%,  $p=0.03$ ).<sup>132, level I</sup>

In a large RCT on CRC patients with potentially resectable liver metastases, peri-operative chemotherapy with FOLFOX4 (six cycles before and six cycles after surgery) improved PFS of resected patients (HR=0.73, 95% CI 0.55 to 0.97) compared with surgery alone.<sup>133, level I</sup>

Capecitabine, an oral fluoropyrimidine carbamate, results in superior response rate, equivalent TTP and OS compared with intravenous 5-FU/LV.<sup>134, level I</sup> It also has significantly improved safety profile and conveniently used as first-line treatment for mCRC.<sup>136, level I</sup> Therefore, capecitabine offers an alternative to 5-FU/LV. However, compliance towards medication is an important factor to obtain the similar results.

- In potentially resectable liver metastasis, peri-operative chemotherapy with FOLFOX (six cycles before and six cycles after surgery) improves PFS.

### a. Targeted Therapy

Monoclonal antibodies against vascular endothelial growth factor (bevacizumab) and against epidermal growth factor receptor (EGFR) (cetuximab) have been used in combination with chemotherapy for mCRC.

Adding bevacizumab to FOLFIRI compared with FOLFIRI alone resulted in a significant difference in median PFS (10.6 months vs 6.2 months) and OS (20.3 months vs 15.6 months).<sup>137, level I</sup> The survival advantage was not evident when bevacizumab was combined with

oxaliplatin-based chemotherapy. Bevacizumab plus oxaliplatin-based chemotherapy as first-line treatment in mCRC resulted in modest improvement of PFS compared with chemotherapy alone (9.4 months vs 8 months,  $p=0.0023$ ). There was no significant difference in OS.<sup>135, level I</sup>

KRAS is a protein which involved in cell signalling pathways that control cell growth, cell maturation, and cell death. The natural, unchanged form of the gene is also called the wild-type KRAS. Patients with wild-type KRAS are likely to response to anti-EGFR therapy. In wild-type KRAS mCRC patients, cetuximab plus FOLFIRI and FOLFIRI alone showed significant difference in median PFS of 9.9 months and 8.7 months respectively. However, there was no difference in median OS.<sup>138, level I</sup>

A HTA report in 2007 concluded that the use of bevacizumab in first-line setting and cetuximab in second-line setting mCRC was not cost-effective.<sup>139, level I</sup> This is supported by an economic evaluation published in USA whereby bevacizumab in addition to chemotherapy was not cost-effective in both the first- and second-line treatment in mCRC.<sup>140, level I</sup>

### b. Palliative Pelvic Radiotherapy

Palliative pelvic RT for symptomatic rectal carcinoma appears to provide relief for a variety of pelvic symptoms. A systematic review has shown that palliative RT has 75% pooled overall symptom response rate among 1084 cases and positive responses were reported for pain (78%), bleeding and discharge (81%), mass effect (71%) and other pelvic symptoms (72%).<sup>141 level I</sup>

#### Recommendation 13

- Palliative chemotherapy may be considered in metastatic colorectal carcinoma.
  - Combination chemotherapy is the preferred regime.
  - Oral chemotherapy may be considered as an alternative.

## 7. FOLLOW-UP AND SURVEILLANCE

Surveillance should be guided by presumed risk of recurrence and functional status of the patient (important within the first two to four years). Any new, persistent or worsening symptoms warrant the consideration of a recurrence.

- Follow-up strategies in post-surgery and/or adjuvant treatment are:<sup>142, level III</sup>
  - i. History, physical examination and CEA levels every three to six months for five years.
  - ii. Surveillance colonoscopy at year one and every three to five years thereafter, dictated by the findings of the previous investigation.
    - If a colonoscopy has not been performed before diagnosis, it should be done after completion of adjuvant therapy (before one year).
  - iii. CT scan of thorax, abdomen and pelvis is performed annually for three years. For high-risk patients, it is reasonable to consider imaging every six to 12 months for the first three years.

In a cohort study on stage III colon carcinoma, patients treated with surgery and adjuvant chemotherapy, and survived without recurrence six months after treatments, those who continued to engage in at least 18-metabolic equivalent task-hours per week of activity (equivalent of walking  $\geq 6$  hours per week at an average pace) had significant improvement in DFS compared with inactive patients at a median follow-up of 3.8 years.<sup>143, level II-2</sup>

Survivors of CRC should be encouraged to:<sup>144, level III</sup>

- maintain an ideal body weight throughout life
  - adopt a physically active lifestyle
  - consume a healthy diet
  - limit alcohol consumption and quit smoking
- 
- CRC survivors are encouraged to maintain an ideal body weight, participate in regular physical activity and consume a well-balanced diet.

## 8. PREVENTION OF COLORECTAL CARCINOMA IN GENERAL POPULATION

Acetylsalicylic acid (ASA) such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) may have protective effect against CRC mainly due to reduction in prostaglandin production and induction of apoptosis.

Aspirin had mixed results in prevention of CRC in general population. It was not significant in primary prevention<sup>145, level I</sup> but significant in secondary prevention with a reduction of 23 to 28% risk of CRC.<sup>145-146, level I</sup> There was no difference in adverse events including serious ones between the treatment and control groups.<sup>145, level I</sup>

In a systematic review of observational studies, CRC incidence was reduced with non-aspirin NSAIDs. However, the review also reported an increased risk of peptic ulceration and gastrointestinal haemorrhage with non-ASA NSAIDs use.<sup>147, level I</sup>

Even though aspirin and NSAIDs have shown some benefits in the prevention of CRC, long-term safety profiles are warranted before any recommendation can be made on their use.

There was no significant benefit from daily consumption of calcium, flavanoids or increased dietary fiber in prevention of CRC in general population.<sup>148-150, level I</sup>

## 9. IMPLEMENTING THE GUIDELINES

Implementation of CPG is important as it helps in providing quality healthcare services based on best available evidence applied to local scenario and expertise. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

### 9.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:

1. availability of CPG to healthcare providers (hardcopies and softcopies)
2. conferences and updates on management of CRC involving professional societies or bodies (Malaysian Society of Colorectal Surgeons, Malaysian Society of Gastroenterology & Hepatology, Malaysian Oncological Society)
3. public awareness CRC campaign such as World Digestive Day, etc.

Limiting factors in the CPG implementation include:

1. limited awareness and knowledge in management of CRC among healthcare providers
2. different levels of CRC care due to expertise, facilities and financial constraints

### 9.2 Potential Resource Implications

To implement the CPG, there must be strong commitments to:

1. ensure widespread distribution of CPG to healthcare providers via printed copies and online accessibility
2. reinforce training of healthcare providers via regular seminars and workshops
3. involve multidisciplinary team at all levels of health care
4. improve the diagnostic and therapeutic facilities
5. train more experts in the field of CRC
6. strengthen the cancer registry

To assist in the implementation of the CPG, the following is proposed as the clinical audit indicator for quality management:

$$\text{Percentage of patients with positive iFOBT or with symptoms of CRC undergoing urgent colonoscopy within 2 weeks} = \frac{\text{Number of patients with positive iFOBT or with symptoms of CRC undergoing urgent colonoscopy within 2 weeks in a period}}{\text{Total number of patients with positive iFOBT or with symptoms of CRC referred for urgent colonoscopy in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module.

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**Appendix 1****EXAMPLE OF SEARCH STRATEGY**

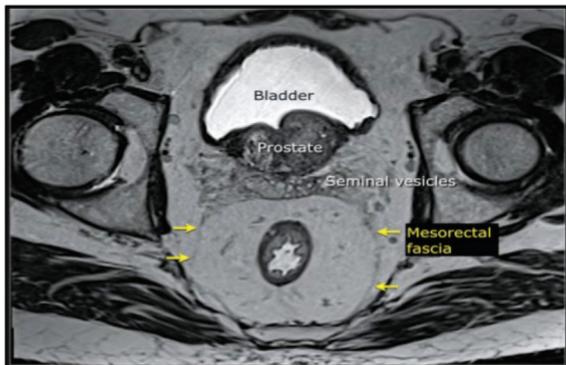
1. COLORECTAL CANCER/
2. (colorectal or colon\* or rect\*) adj1 (carcinoma\* or tumo?r\* or cancer\* or neoplasm\*).tw.
3. 1 or 2
4. MASS SCREENING/
5. (screen\* adj1 mass).tw.
6. screen\*.tw.
7. EARLY DETECTION OF CANCER/
8. (cancer adj2 (early detection or early diagnosis)).tw.
9. (cancer adj1 (screening or screening test\*)).tw.
10. ((early detection or early diagnosis) adj2 cancer).tw.
11. (test\* adj2 cancer screening).tw.
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. OCCULT BLOOD/
14. (occult adj1 blood).tw.
15. ((Stool or f?ecal or f?eces) adj1 test\*).tw.
16. GUAIAC/
17. Guaiac.tw.
18. IMMUNOLOGIC TESTS/
19. (diagnos\* adj1 immunologic\*).tw.
20. immunodiagnos\*.tw.
21. (test\* adj1 immunologic\*).tw.
22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 3 and 12 and 22
24. limit 23 to (English language and humans and "all adult (19 plus years)" and last 20 years)

**Appendix 2****CLINICAL QUESTIONS**

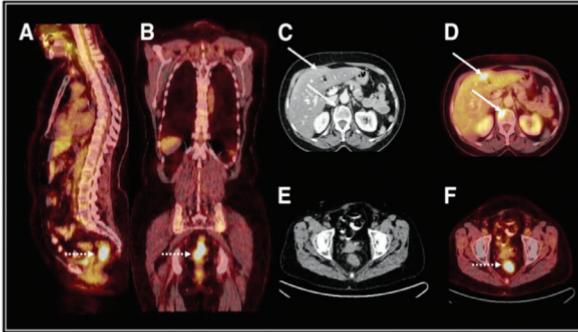
1. What is the appropriate age to start screening for CRC in healthy/general population?
2. What is the appropriate interval for screening for CRC in healthy/general population?
3. What are the effective and safe screening modalities for CRC in general population and risk group?
4. Who are at risk of developing CRC and what are the effective surveillance methods for moderate and high risk groups?
5. Who should be offered genetic counselling and/or genetic testing in CRC?
6. What are the safe and effective imaging techniques in diagnosing and staging investigations for CRC?
7. Does inclusion of pathological parameters in histopathological report important in determining the prognosis of CRC?
8. Does template proforma increase the rate of inclusion of minimum criteria needed to ensure completeness of the CRC resection specimen reporting?
9. What are the effective and safe pre-operative preparations of patients with CRC?
10. What are the safe and effective surgical techniques in CRC?
11. What are the safe and effective neoadjuvant/adjuvant chemoradiotherapy in rectal and colon cancer and its indications?
12. What are the safe and effective chemotherapy in CRC?
13. What are the safe and effective measures to prevent CRC in general population?
14. What is the optimum strategy for follow up of CRC patients?

## Appendix 3

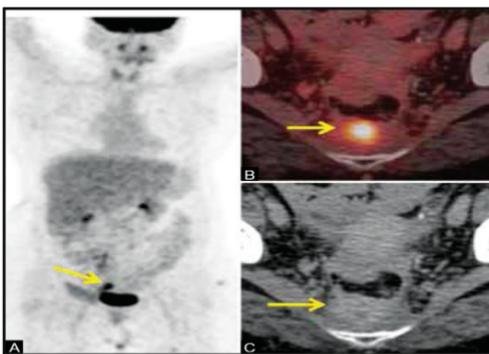
## RADIOLOGICAL IMAGES OF COLORECTAL CARCINOMA



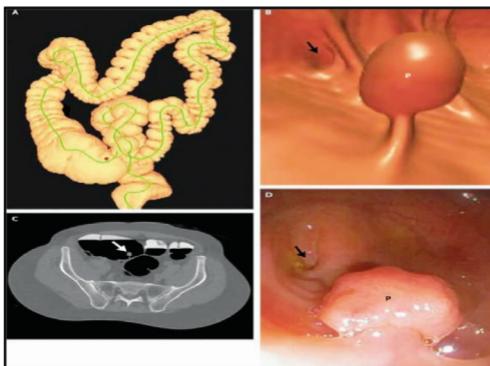
**Figure 1.** Normal anatomy of rectum on MRI. The mesorectal fat has high signal intensity on both T1- and T2-weighted images. The mesorectal fat is surrounded by the mesorectal fascia, which is seen as a fine line of low signal intensity (arrows). High resolution T2-images are needed to clearly identify the mesorectal fat. (*Source:* Rectal Cancer - MR staging 2.0, available at <http://www.radiologyassistant.nl/en/p56195b237699d/rectal-cancer-mr-staging-20.html>)



**Figure 2.** At initial diagnosis of CRC, sagittal (A) and coronal (B) PET/CT images indicate increased metabolic activity of malignant primary (arrows); transaxial CT (C) and PET/CT (D) images indicate synchronous bone and liver metastases (arrows), leading to change from curative resection to systemic chemotherapy; and transaxial CT (E) and PET/CT (F) images at another level indicate primary tumour. (*Source:* Buck AK, Herrmann K, Stargardt T, et al. Economic evaluation of PET and PET/CT in oncology: evidence and methodologic approaches. *J Nucl Med Technol.* 2010;38(1):6-17)



**Figure 3.** A case of carcinoma rectum post APR, nine months post-surgery with increasing CEA. (A) MIP image of the PET scan shows a hypermetabolic focus in the pelvis (arrow) (B) Fused PET/CT image shows FDG-avid pre-sacral mass (arrow) suspicious for recurrent disease (C) CT image shows a pre-sacral mass. Indeterminate whether it is benign fibrosis or disease recurrence. Biopsy confirmed recurrence of adenocarcinoma. (**Source:** Agrawal A, Rangarajan V. Appropriateness criteria of FDG PET/CT in oncology. Indian J Radiol Imaging. 2015;25(2):88.)



**Figure 4.** Solitary 16 mm pedunculated caecal polyp in a 55-year-old man at average risk for colorectal neoplasia. Panel A shows a schematic map of the air-filled colon generated from the computed tomographic (CT) scan obtained with the patient in the prone position. The green line is the center line that is automatically generated for virtual navigation; the red dot is a “bookmark” indicating the location of the polyp within the caecum. Panel B, a 3D view from the endoluminal “fly-through” generated from the same CT scan, shows the caecal polyp (P) and the appendiceal orifice (arrow) in the background. This display was used for the primary detection of polyps. Panel C is an axial, two-dimensional CT image obtained with the patient in the prone position; it shows the polyp (arrow) on a stalk within the air-filled caecum. The residual luminal fluid is opacified by oral contrast agent, which enables the software program to “cleanse” the 3D image. This 2D display was used for the confirmation of suspected findings on the 3D view. Panel D is a digital photograph from optical colonoscopy performed immediately after CT virtual colonoscopy; it shows the caecal polyp (P) and the appendiceal orifice (arrow). Histologic examination revealed that the polyp was adenomatous. (**Source:** Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. N Engl J Med. 2003;349(23):2191-200)

**Appendix 4**

**WHO CLASSIFICATION OF COLORECTAL CARCINOMA 2010 AND  
TNM CLASSIFICATION OF TUMOURS OF THE  
COLON AND RECTUM (7<sup>TH</sup> EDITION)**

WHO Classification of Colorectal Carcinoma 2010 <sup>72</sup>					
<ul style="list-style-type: none"> <li>• <b>Adenocarcinoma</b> <ul style="list-style-type: none"> <li>◦ Cribiform comedo-type adenocarcinoma</li> <li>◦ Medullary carcinoma</li> <li>◦ Micropapillary carcinoma</li> <li>◦ Mucinous adenocarcinoma</li> <li>◦ Serrated adenocarcinoma</li> <li>◦ Signet ring cell carcinoma</li> </ul> </li> <li>• <b>Adenosquamous carcinoma</b></li> <li>• <b>Spindle cell carcinoma</b></li> <li>• <b>Squamous cell carcinoma</b></li> <li>• <b>Undifferentiated carcinoma</b></li> </ul>					
<b>TNM Classification of Tumours of the Colon and Rectum (7<sup>th</sup> Edition)</b>					
<b>T - Primary tumour</b>		<b>M - Distant metastasis</b>			
TX	Primary tumour cannot be assessed	M0	No distant metastasis		
T0	No evidence of primary tumour	M1	Distant metastasis		
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria	M1a	Metastasis confined to one organ		
T1	Tumour invades submucosa	M1b	Metastasis in more than one organ or the peritoneum		
T2	Tumour invades muscularis propria				
T3	Tumour invades subserosa or into non-peritonealized pericolic or perirectal tissues				
T4	Tumour perforates visceral peritoneum and/or directly invades other organs or structures				
T4a	Tumour perforates visceral peritoneum				
T4b	Tumour directly invades other organ or structures				
<b>N - Regional lymph nodes</b>					
NX	Regional lymph nodes cannot be assessed	<b>Stage Grouping</b>			
N0	No regional lymph-node metastasis	Stage	T	N	M
N1	Metastasis in 1 to 3 regional lymph nodes	Stage 0	Tis	N0	M0
N1a	Metastasis in 1 regional lymph node	Stage I	T1, T2	N0	M0
N1b	Metastasis in 2 to 3 regional lymph nodes	Stage II	T3, T4	N0	M0
N1c	Tumour deposit (s), i.e. satellites, in the subserosa, or in non-peritonealized pericolic or perirectal soft tissue without regional lymph-node metastasis	Stage IIA	T3	N0	M0
N2	Metastasis in 4 or more regional lymph nodes	Stage IIB	T4a	N0	M0
N2a	Metastasis in 4 to 6 regional lymph nodes	Stage IIC	T4b	N0	M0
N2b	Metastasis in 7 or more regional lymph nodes	Stage III	Any T	N1, N2	M0
		Stage IIIA	T1, T2	N1	M0
			T1	N2a	M0
		Stage IIIB	T3, T4a	N1	M0
			T2, T3	N2a	M0
			T1, T2	N2b	M0
		Stage IIIC	T4a	N2a	M0
			T3, T4a	N2b	M0
			T4b	N1, N2	M0
		Stage IVA	Any T	Any N	M1a
		Stage IVB	Any T	Any N	M1b

**Source:** Edge SB, Compton CC. The American Joint Committee on Cancer: the 7<sup>th</sup> edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471-4.

**Appendix 5****HISTOPATHOLOGY PROFORMA FOR COLORECTAL CARCINOMA**

 <b>PERKHIDMATAN PATOLOGI</b> <b>HOSPITAL _____</b> <b>COLORECTAL CANCER HISTOPATHOLOGY WORKSHEET</b>	
<b>Name:</b>	<b>HPE No:</b>
Specimen container labelled as:	
<b>1. GROSS DESCRIPTION</b>	
1.1 Type of specimen:	
<input type="checkbox"/> Total colectomy <input type="checkbox"/> Subtotal colectomy <input type="checkbox"/> Right hemicolectomy <input type="checkbox"/> Anterior resection (AR) <input type="checkbox"/> Left hemicolectomy <input type="checkbox"/> Hartman's procedure <input type="checkbox"/> Sigmoid colectomy <input type="checkbox"/> Abdominoperineal excision (APE) <input type="checkbox"/> Other (specify): .....	
1.2 Bowel length:	
1.3 Site of tumour: <input type="checkbox"/> Caecum <input type="checkbox"/> Asc. colon <input type="checkbox"/> Hepatic flexure <input type="checkbox"/> Transv. colon <input type="checkbox"/> Splenic flexure <input type="checkbox"/> Desc. colon <input type="checkbox"/> Sigmoid colon <input type="checkbox"/> Rectosigmoid <input type="checkbox"/> Rectum	
Other comment(s):	
1.4 Maximum tumour diameter:	
1.5 Gross subtype (optional): <input type="checkbox"/> Fungating <input type="checkbox"/> Ulcerative <input type="checkbox"/> Infiltrative <input type="checkbox"/> Ulcero-fungating	
1.6 Margins: - Tumour to proximal / nearer (if untagged) longitudinal margin: ..... mm. - Tumour to distal / opposite (if untagged) longitudinal margin: ..... mm.	
1.7 Tumour perforation (pT4): <input type="checkbox"/> No <input type="checkbox"/> Yes	
1.8 For rectal tumour:	
<ul style="list-style-type: none"> <li>• Relation to peritoneal reflection:  <input type="checkbox"/> above      <input type="checkbox"/> astride      <input type="checkbox"/> below</li> <li>• Plane of surgical excision (Total mesorectal excision (TME) for AR and APE):  <input type="checkbox"/> Mesorectal fascia (Complete)      <input type="checkbox"/> Intramesorectal (Partially Complete)      <input type="checkbox"/> Muscularis propria (Incomplete)</li> <li>• Distance from dentate line (APE specimens): ..... mm</li> <li>• Plane of resection of the sphincters (APE specimens):  <input type="checkbox"/> Extralevator      <input type="checkbox"/> Sphincteric      <input type="checkbox"/> Intrasphincteric</li> </ul>	
1.9 Polyps: <input type="checkbox"/> No <input type="checkbox"/> Yes (specify number, site, sessile or pedunculated)	
1.10 No. of lymph nodes retrieved: ..... (..... mm to ..... mm in diameter).	
1.11 Additional comments:	
1.12 Tissue sampling:	
Grossed by:	

**2. HISTOLOGY****2.1 Microscopic description:**2.2 Type:  Adenocarcinoma (NOS/usual-type);  well-  mod-  poorly-differentiated Other (specify e.g. mucinous): \_\_\_\_\_**2.3 Additional features (optional/non-core data items):**

- |  |                                    |   |
|--|------------------------------------|---|
| • Lymphatic invasion                     | <input type="checkbox"/> No        | <input type="checkbox"/> Yes                  |
| • Perineural invasion                    | <input type="checkbox"/> No        | <input type="checkbox"/> Yes                  |
| • Leading edge of tumour                 | <input type="checkbox"/> Expansile | <input type="checkbox"/> Infiltrative         |
| • Extracellular mucin (>10% but <50%)*   | <input type="checkbox"/> No        | <input type="checkbox"/> Yes                  |
| • Intratumoural lymphocytic infiltrate** | <input type="checkbox"/> None      | <input type="checkbox"/> Yes: (Mild / Marked) |
| • Peritumoural lymphoid aggregates***    | <input type="checkbox"/> None      | <input type="checkbox"/> Yes: (Mild / Marked) |

Note (guide for pathologist; not included in final report):

\*Not applicable if tumour is mucinous carcinoma

\*\*Tumour-infiltrating lymphocytes: Mild: 3-15/h.p.f (40x)

Marked: &gt;15/h.p.f (40x)

\*\*\*Peritumoural lymphoid aggregates: Mild: Occasional lymphoid aggregates

Marked: ≥ 2 aggregates with germinal centers per tissue section

**2.4 Local invasion (TNM 7th edition)**

- Submucosa (pT1)  
 Muscularis propria (pT2)  
 Beyond muscularis propria (pT3)  
 Tumour penetrates the visceral peritoneal surface (pT4a)  
 Tumour directly invades or is adherent to other organs/structures (pT4b)

**2.5 Maximum distance of spread beyond muscularis propria (NA if intramural tumour): ..... mm****2.6 Response to pre-operative (neoadjuvant) therapy:**

- Not applicable (pre-op therapy not given/not known to be given)  
 No viable tumour cells (fibrosis or mucus lakes only)  
(Entire tumour site and/or scarred area had been submitted for histology)  
 Single cells or scattered small groups of cancer cells  
 Residual cancer outgrown by fibrosis  
 Minimal or no regression (extensive residual tumour)

**2.7 Tumour involvement of margins:**

- |   |                                       |                              |                             |                              |
|---|---------------------------------------|------------------------------|-----------------------------|------------------------------|
| • Proximal doughnut                     | <input type="checkbox"/> No           | <input type="checkbox"/> Yes | <input type="checkbox"/> NA | <input type="checkbox"/> NS  |
| • Distal doughnut                       | <input type="checkbox"/> No           | <input type="checkbox"/> Yes | <input type="checkbox"/> NA | <input type="checkbox"/> NS  |
| • Proximal / Nearer longitudinal margin | <input type="checkbox"/> No (.....mm) |                              |                             | <input type="checkbox"/> Yes |
| • Distal / Opposite longitudinal margin | <input type="checkbox"/> No (.....mm) |                              |                             | <input type="checkbox"/> Yes |
| • Circumferential margin                | <input type="checkbox"/> No (.....mm) |                              |                             | <input type="checkbox"/> Yes |

Note: Circumferential margin of ≤ 1 mm is considered involved

NS – Not submitted by pathologist

## 2.8 Metastatic spread:

No. of lymph nodes identified: .....

- No. of involved lymph nodes: ..... (pN .....)  
[pN1a: 1 node; pN1b: 2-3 nodes; pN2a: 4-6 nodes; pN2b: 7+ nodes involved]
- Highest node involved:  No  Yes (Dukes C2)
- Tumour deposits  No  Yes (No: .....)  
[pN1c: Tumour deposits in subserosa/mesentery/periolic/perirectal tissues without nodal metastasis]
- Biopsy-confirmed distant metastasis  NA  No  Yes - Site(s)  
[pM1a: Single site; pM1b: Multiple sites or peritoneal surface]

## 2.9 Deepest level of venous invasion:

 None  Submucosal  Intramural  Extramural

## 2.10 Separate abnormalities:

 No Yes : - Polyps (types(s), number, size) / polyposis (specify type) / UC / CD/ Diverticulosis  
- Synchronous carcinoma (separate proforma for each carcinoma)

## 2.11 Complete resection (by &gt;1 mm) at all surgical margins:

 Yes (R0) No (R1 - microscopic margin involvement) No (R2 - macroscopic margin involvement)2.12 TNM (7<sup>th</sup> Edition 2009): pT..... pN..... pM.....  
OR yPT..... ypN..... ypM.....

Note: 1. pMX does not exist  
 2. pM0 does not exist (except at autopsy)  
 3. pM1: Distant metastasis proven microscopically (if suspected metastatic site is negative on biopsy, then it becomes cM0 and NOT pM0)

## For Malaysian National Cancer Patient Registry - Colorectal Cancer:

- TNM (5<sup>th</sup> Edition): pT..... pN..... pM.....  
 OR yPT..... ypN..... ypM.....

## 2.13 Modified Dukes stage:

- A (Growth limited to wall/muscularis propria, nodes negative)
- B (Growth beyond muscularis propria, nodes negative)
- C1 (Nodes positive, highest node negative)
- C2 (Highest node positive)
- D (Histology-proven distant metastasis)
- NA (No tumour or no lymph nodes identified)

## 2.14 Mismatch repair (MMR) immunohistochemistry (if applicable/available)

 Not performed Performed:

- |                                 |                                 |                                    |   |
|---------------------------------|---------------------------------|------------------------------------|---|
| <input type="checkbox"/> MLH 1: | <input type="checkbox"/> Normal | <input type="checkbox"/> Equivocal | <input type="checkbox"/> Loss of protein expression |
| <input type="checkbox"/> MLH 2: | <input type="checkbox"/> Normal | <input type="checkbox"/> Equivocal | <input type="checkbox"/> Loss of protein expression |
| <input type="checkbox"/> MLH 6: | <input type="checkbox"/> Normal | <input type="checkbox"/> Equivocal | <input type="checkbox"/> Loss of protein expression |
| <input type="checkbox"/> PMS 2: | <input type="checkbox"/> Normal | <input type="checkbox"/> Equivocal | <input type="checkbox"/> Loss of protein expression |

## 3. DIAGNOSTIC SUMMARY

(Tumour type, differentiation, staging, margins and if present, venous invasion)

**Appendix 6****CHEMOTHERAPY DRUGS AND COMMON/IMPORTANT SIDE EFFECTS**

Medication	Common and important side effects	Comments
Capecitabine	<ul style="list-style-type: none"> <li>Diarrhoea, nausea, vomiting, mucositis, abdominal pain</li> <li>Hand-foot syndrome</li> <li>Fatigue/weakness</li> <li>Hyperbilirubinaemia</li> <li>Cardiotoxicity - uncommon but can be fatal</li> </ul>	<ul style="list-style-type: none"> <li>Use cautiously in patients with history of heart disease</li> <li>Dose reduction is required in patients with moderate renal dysfunction</li> <li>Monitor for hand-foot syndrome</li> </ul>
Fluorouracil (5-FU)	<ul style="list-style-type: none"> <li>Gastrointestinal (diarrhoea, stomatitis, oesophagitis, heart burn)</li> <li>Blood (anaemia, thrombocytopaenia, neutropaenia)</li> <li>Cardiovascular (angina pectoris, myocardial infarction, arrhythmia, acute pulmonary oedema)</li> <li>Dermatological (alopecia, dermatitis, hand-foot syndrome)</li> <li>Gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain, anorexia, mucositis)</li> <li>Blood (anaemia, thrombocytopaenia, neutropaenia)</li> <li>Fatigue/weakness</li> </ul>	<ul style="list-style-type: none"> <li>Prophylactic anti-emetics and corticosteroids should be given</li> <li>Use cautiously in patients with history of heart disease</li> <li>Monitor for hand-foot syndrome</li> </ul>
Irinotecan	<ul style="list-style-type: none"> <li>Gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain, anorexia, mucositis)</li> <li>Blood (anaemia, thrombocytopaenia, neutropaenia)</li> <li>Fatigue/weakness</li> </ul>	<ul style="list-style-type: none"> <li>Prophylactic anti-emetics for moderate emetic risk should be given</li> <li>In early onset diarrhoea and cholinergic symptoms, subcutaneous atropine can be used (prophylactic atropine is required in subsequent cycles)</li> </ul>
Leucovorin (LV)/calcium folinate/folinic acid	<ul style="list-style-type: none"> <li>Allergic reaction, rash, pruritis, erythema, urticaria, nausea, vomiting, pyrexia</li> </ul>	
Oxaliplatin	<ul style="list-style-type: none"> <li>Gastrointestinal (nausea, vomiting, mucositis, diarrhoea, hiccup)</li> <li>Blood (anaemia, thrombocytopaenia, neutropaenia)</li> <li>Peripheral sensory neuropathy</li> <li>Pharyngolaryngeal dysesthesia (difficulty in breathing or swallowing seen shortly after drug infusion)</li> <li>Liver increase in transaminases, alkaline phosphatase</li> <li>Allergic reaction</li> </ul>	<ul style="list-style-type: none"> <li>Prophylactic anti-emetics for moderate emetic risk should be given</li> <li>Allergic reactions: Monitor for development of rash, urticaria, erythema, pruritis, bronchospasm and hypotension</li> <li>Neuropathy: Reduce the dose or discontinue if necessary</li> </ul>

**Sources:**

- Xeloda® (capecitabine) [package insert]. South San Francisco, CA: Hoffman-La Roche, Inc; 2015.
- Micromedex Solutions, Truven Health Analytics Inc. MIMS Gateway Service Portal (Available at <http://www.mimsgateway.com/Malaysia/Online.as>)
- Camptosar® (irinotecan) [package insert]. New York, NY: Pfizer Inc; 2014.
- Eloxatin® (oxaliplatin) [package insert]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2011.
- Ministry of Health & Ministry of Higher Education Malaysia. Systemic Therapy Protocol. Putrajaya: MoH & MoHE; 2016
- Hand-foot syndrome=the palms of the hands and soles of the feet become dry, red, numb, tingling, with/without swelling, blistering, moist desquamation or pain

**Appendix 7****POTENTIAL INDICATIONS FOR POST-OPERATIVE CCRT IF PRE-OPERATIVE CCRT NOT GIVEN**

<b>Sufficient and necessary</b>	<ul style="list-style-type: none"> <li>• CRM ≤1 mm</li> <li>• pT4b</li> <li>• pN2 extracapsular spread close to MRF</li> <li>• Extranodal deposits (N1c)</li> <li>• pN2 if poor mesorectal quality/defects</li> </ul>
<b>Sufficient</b>	<ul style="list-style-type: none"> <li>• pN2 low tumours within 4 cm of anal verge (risk of involved LPLN)</li> <li>• Extensive extramural vascular invasion/perineural invasion close to MRF</li> </ul>
<b>Borderline sufficient</b>	<ul style="list-style-type: none"> <li>• pN2 low tumours within 4 cm of anal verge (risk of involved LPLN)</li> <li>• CRM 1-2 mm</li> <li>• Circumferential obstructing tumours</li> </ul>
<b>Insufficient and unnecessary</b>	<ul style="list-style-type: none"> <li>• pT1/pT2</li> <li>• pT3</li> <li>• CRM &gt;2 mm</li> <li>• pT4a above peritoneal reflection</li> <li>• pN1</li> <li>• If good quality smooth intact mesorectum</li> </ul>

CRM=circumferential resection margin; LPLN=lateral pelvic lymph node; MRF=mesorectal fascia

**Source:** Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl\_4):iv22-iv40.

**LIST OF ABBREVIATIONS**

APR	abdominoperineal resection
ASA	acetylsalicylic acid
AUC	area under the curve
BE	barium enema
CEA	carcinoembryonic antigen
CC	conventional colonoscopy
CCE	colon capsule endoscopy
CCRT	concurrent chemoradiotherapy
CI	confidence interval
CPG	clinical practice guidelines
CRC	colorectal carcinoma
CRM	circumferential resection margins
CRLMs	colorectal liver metastases
CT	computed tomography
CTC	computed tomographic colonoscopy
DFS	disease-free survival
DG	Development Group
DRM	distal resection margin
EGFR	epidermal growth factor receptor
FAP	familial adenomatous polyposis
FDG PET/CT	<sup>18</sup> F-fluorodeoxyglucose Positron Emission Tomography CT
FDR	first-degree relatives
FRR	family relative risk
Gd-EOB-DTPA	gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid
Gy	gray
HNPCC	hereditary non-polyposis colorectal cancer
HPE	histopathological examination
HR	hazard ratio
HTA	health technology assessment
IBD	inflammatory bowel disease
iFOBT/IFOBT	immunofaecal occult blood test
IHC	immunohistochemistry
LV	leucovorin
MaHTAS	Malaysian Health Technology Assessment Section
MAP	MUTYH-associated polyposis
mCRC	metastatic colorectal carcinoma
MoH	Ministry of Health
MMR	mismatch repair
MRI	magnetic resonance imaging
NSAIDs	non-steroidal anti-inflammatory drugs
NICE	National Institute for Health and Clinical Excellence
OR	odds ratio
OS	overall survival
PFS	progression-free survival
RC	Review Committee
RCT	randomised controlled trial
RFA	radiofrequency ablation
RR	relative risk
RRR	relative risk ratio
RT	radiotherapy

SDR	second-degree relatives
SIGN	Scottish Intercollegiate Guidelines Network
TDR	third-degree relatives
TME	total mesorectal excision
TNM	Tumour-Node-Metastasis
UC	ulcerative colitis
VC	virtual colonoscopy
vs	versus
VTE	venous thromboembolism
WHO	World Health Organization
5-FU	fluorouracil

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**MALAYSIAN HEALTH TECHNOLOGY  
ASSESSMENT SECTION**  
Medical Development Division  
Ministry of Health Malaysia  
Level 4, Block E1, Precinct 1  
62590 Putrajaya, Malaysia

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