

Title: Management of Colorectal cancer in Nigeria in 2016

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Introduction

Colorectal cancer (CRC) is the most common gastrointestinal cancer diagnosed in Nigeria, and is one of the leading causes of cancer deaths worldwide.¹⁻³ Recent trend has shown a rise in the incidence of CRC in Nigeria with a 5-fold increase in incidence from 1979 to 2008.⁴ It is also projected that low-middle income countries (LMICs) will experience a 70% increase in CRC incidence, and a 75% increase in the number of deaths from CRC by the year 2030.⁵ The converse is true in most high income countries where the incidence and mortality from CRC appear to be declining due to the introduction of effective screening programmes which result in early diagnosis.⁶ In addition, the outcome of treatment of both early and advanced cases has improved steadily due to the explosion of robust imaging modalities which enable more precise selection of treatment options and utilization of multi-modality treatment approach.⁷ Hence, it is possible to achieve cure even in metastatic diseases. Similarly, there is better understanding of prognostic, as well as, predictive biomarkers which has significantly enhanced the ability to individualize treatment for each patient.⁸ In resource limited settings like Nigeria however, resources available to screen, diagnose, treat and follow up patients are limited. Cultural perception and acceptability of various treatment modalities also differ.⁹ Hence the need to develop guidelines that will meet up with international standards, and be economically and culturally relevant to the Nigerian context cannot be over emphasized. We are strongly persuaded that when available resources are maximized, it is possible to achieve satisfactory management outcome. The aim of this guideline is to present a framework for the management of CRC in Nigeria bearing in mind the various challenges that clinicians will encounter while managing such patients.

Epidemiology

Currently, there is no population based data on the incidence and prevalence of CRC in Nigeria. According to 2012 Globacan statistic for Nigeria, CRC is the fifth most common cancer trailing behind breast, prostate, cervical and hepatocellular carcinoma, accounting for about 4200 new cases of CRC each year.² About three quarters of these patients died of the disease because over 90% presented as advanced or metastatic diseases. Various institutional reviews have shown progressive increase in the incidence of CRC and precursor lesions such as adenomatous polyps.^{4, 10-12} Worldwide, however, there are 1.36 million cases of CRC which is responsible for 9.7% of the total cancer burden, coming behind lung (1.83 million) and breast cancer (1.67 million).^{2,3}

Risk factors

There are two types of CRC – sporadic and familial. The sporadic form of CRC accounts for almost 70% of cases seen. Risk factors identified with sporadic CRC include increasing age, male sex, previous colonic polyps, previous colorectal cancer, diabetic mellitus, gall stone and environmental factors (eg, increase intake of red meat, high-fat diet, inadequate intake of fibre, obesity, sedentary lifestyle, smoking, and high consumption of alcohol).^{13,14} It is also well recognised that individuals with chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease and other tropical chronic inflammatory conditions such as schistosomiasis, tuberculosis and histoplasmosis) are at increased risk of developing CRC.^{15,16} Previous surgical operations such as cholecystectomy and ureterosigmoidostomy have also been implicated to increase the risk to sporadic CRC.¹³

CRC is perhaps the most familial of all human cancers.¹⁷ About 30% of CRC are associated with an inherited pattern. Of these only about 5-10% have inherited syndromes with known genetic defects.¹⁸ Hereditary CRC syndromes are divided into polyposis syndromes, characterized by the development of multiple colorectal polyps, and non-polyposis syndromes where only few or no polyps occur. Classification and diagnosis are done based

on genetic, pathological and clinical features of each syndrome (Figure 1). Of the hereditary syndromes, the frequencies for inherited syndromes are as follows; the Lynch syndrome, also known as hereditary non-polyposis colorectal cancer, occurs in roughly one in 300 people with colorectal cancer. Familial adenomatous polyposis is much less frequent, and arises in about one in 7000 people affected by colorectal cancer, whereas *MYH*-associated polyposis occurs in about one in 18 000 individuals with colorectal cancer.

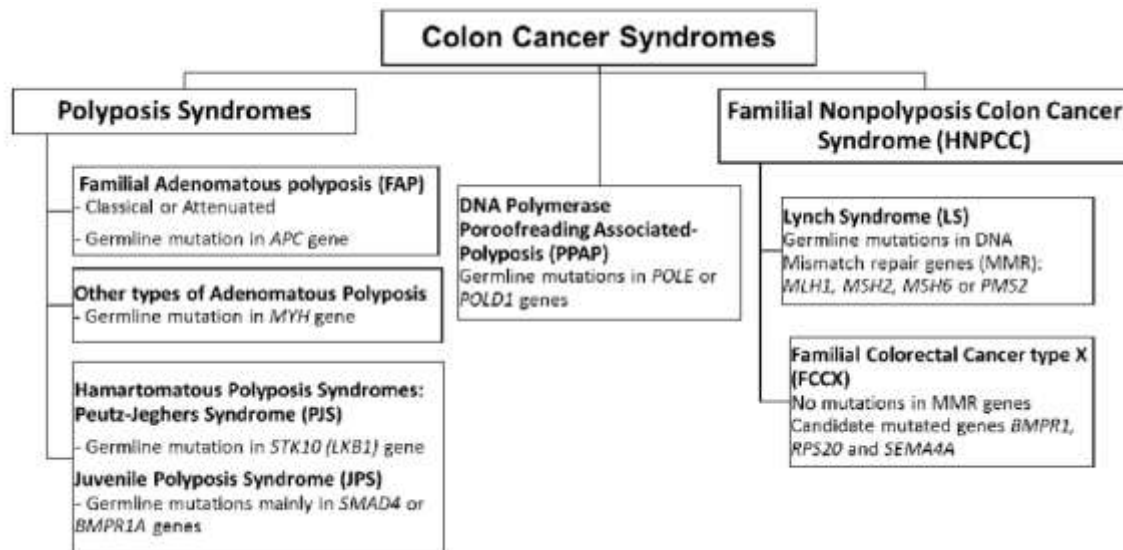


Figure 1: Classification of hereditary CRC (adapted from Lindor et al, 2005)¹⁹

Familial clustering of cases appears to confer increased risk. First-degree relatives of persons with CRC have a 2-3 fold increase in the risk of CRC in comparison with control or population incidence.²⁰ Moreover, the risk increases with the number of relatives with CRC, closeness of relatives to the patient, and with the age of CRC in family members.^{20,21} Individuals with a personal history of colorectal cancer are also at increased risk for subsequent development of cancer. Also, the risk of CRC is increased in persons with a family history of adenomas in close relatives under the age of 60.

Screening for CRC

Colorectal cancer (CRC) is a malignancy with a relatively long preclinical phase (usually about 10 years) which provides a unique opportunity for screening. Screening has been successful in reducing the incidence and mortality of CRC by increasing the proportion diagnosed at an early stage and it also facilitates the removal of pre-neoplastic lesions.²²⁻²⁴ Many developed countries have either established programmatic CRC screening endeavours or use healthcare systems that can facilitate early detection and treatment of CRC. Utilizing the population-based average-risk screening strategy recommended in high income countries (HIC) countries in Nigeria will be very challenging for several reasons. Firstly, early effectiveness data showed that such strategies cannot be financially justified.²⁵ Secondly, health care expenditure in Nigeria is essentially borne through 'out of pocket' expenses. In Nigeria, where about 70% of the population are below poverty line, funding such a program becomes very difficult. Thirdly, low health literacy which leads to patronage of unstandardized alternative medical care including traditional practices and religious (faith) healing may not encourage satisfactory participation in such programme.²⁶ Fourthly, the health care resources available for screening and treatment in Nigeria, like most other African countries, are so limited that such a strategy will easily overwhelm the system. Furthermore, the challenges of following up patients who screen positive, and the uncertainty regarding the

distribution, analysis and reimbursement of tests provided by the government, are greater than in HICs.²⁷ Lastly, there is difficulty in identifying the population to screen. The median age of occurrence of CRC is about 50 years in Nigeria. In view of the fact that it takes about a decade for polyps to become cancerous, the age of starting screening must be earlier in Nigeria compared to countries such as USA.²⁵ Age of screening in most HICs was developed from robust research effort. Unfortunately, no such data is available in Nigeria. Pending the time such data will be generated, **we suggest 40-45 years as the age of commencement of screening for CRC.**

Colorectal cancer screening is complex, as there are multiple options available. It requires considerable patient efforts (Faecal occult blood test slides, colonoscopy preparation, etc.), may require sedation and a health-care partner for some tests (colonoscopy). For a screening program to be successful, multiple events have to occur, beginning with awareness and recommendation from the primary-care physician, patient acceptance, financial coverage, risk stratification, screening test, timely diagnosis, timely treatment, and appropriate follow-up. If any one of these steps is faulty or is not of high quality, the screening will fail. The screening options include tests that can help to detect cancer or precancerous lesions, each with advantages and limitations. These are divided into stool based test (high-sensitivity guaiac Faecal occult blood test (gFOBT), Faecal immunochemical tests (FIT), and faecal DNA test); direct visualization test [sigmoidoscopy, colonoscopy, double-contrast barium enema, computed tomographic colonography (CTC) and Magnetic resonance colonography (MRC)]; and serology [circulating methylated *SEPT 9* DNA (Epi proColon; Epigenomics)]. The advantages and limitation of each of the strategy is shown in table 1.

Bearing in mind the challenges of introducing screening in Nigeria, we suggest screening for three groups of individuals namely: asymptomatic average risk individuals, symptomatic patients (rectal bleeding with change in bowel habit and weight loss) and high risk patients. Figures 2 and 3 show the screening modality. **Our suggestion for the frequency of screening is as follows:**

- (1) biennial screening with FIT (in the absence of FIT we suggest high sensitive gFOBT),
- (2) screening every 10 years with flexible sigmoidoscopy and annual screening with FIT (in the absence of FIT we suggest high sensitive gFOBT),
- (3) screening every 10 years with colonoscopy,
- (4) screening every 5 years with CT colonography,
- (5) FIT-DNA screening every 3 years.

There is urgent need for a feasibility study to assess the impact of the above recommendation on the health system and mortality from CRC in Nigeria.

Screening for genetic mutation and counselling

Genetic mutation analysis is important in some patients with CRC. There is generally no consensus on who should have genetic mutation screening following the occurrence of CRC. The reason for genetic analysis is to detect patients with syndromic CRC who will need risk reduction measures to prevent the occurrence of other cancers. The only measures that guarantee detection of all syndromic CRC is to screen all CRC patients for microsatellite instability (MSI) with immunohistochemistry or Mismatch repair genes (MMR).²⁹ While this is now routine in some cancer centers in developed countries, sustainability of such is difficult in economically challenged countries. Some guidelines recommend MSI screening only for patients with CRC younger than 70 years.³⁰ This measure has been shown to perform better than Revised Bethesda Guidelines for testing CRC for microsatellite instability (MSI)

in terms of missing rate for syndromic CRC (Table 2).³¹ **We recommend that all patients younger than 50 years of age or who are positive based on revised Bethesda guideline should have MSI test performed.** Nevertheless, in 10%–15% of sporadic CRC cases, MSI and loss of expression of MLH1 are due to hypermethylation of the MLH1 gene promoter.^{30,31} These sporadic cases are also frequently associated with the somatic BRAF V600E mutation. Therefore, if loss of MLH1/PMS2 expression is observed, analysis of the methylation of the MLH1 promoter in the tumour or analysis for somatic BRAF V600E mutation should be performed first. If BRAF V600E is negative, the patient should proceed to have mutation analysis Figure 4.³⁰ **We also recommend that facility for MSI and somatic BRAF V600E screening should be available in referral centers for CRC in Nigeria.**

Table 1: Common screening test for colorectal cancer: Its advantages and drawbacks

Test	Advantages	Disadvantages
Sensitive guaiac Faecal occult blood test (gFOBT)	Cheap and can be performed at home; requires few specialized resources; has been shown to reduce mortality	Diet and drug restriction required. Multiple samples needed per test which can make it clumsy. Requires colonoscopy for confirmation when positive. Low sensitivity for adenoma – precancerous lesion
Faecal immunochemical test	Specific for human blood, hence no diet restriction. Also cheap and can be performed at home. Detects precancerous lesions better than gFOBT but not as good as endoscopy	Poor sensitivity for advanced adenomas. Required colonoscopy for confirmation when positive.
Stool DNA	Can detect cancer in stool and can be performed at home. Does not need diet modification	Expensive. Not readily available in Nigeria. Needs confirmation with colonoscopy.
CT colonography	High sensitivity to detect precancerous lesions ≥ 10 mm in diameter; less invasive than colonoscopy. Can detect other incidental lesions in the abdomen.	Radiation exposure. Can miss small lesions. Needs colonoscopy evaluation if positive. Requires bowel preparation
Flexible Sigmoidoscopy	High sensitivity and specificity for left colonic lesion. Expertise can easily be learnt. It is an office-based procedure. Short bowel preparation. Has been shown to reduce mortality. No exposure to radiation.	Needs bowel preparation. Cannot detect proximal lesions
Colonoscopy	High sensitivity and specificity. Precancerous lesions and early cancers can be removed at the same sitting. Has been shown to reduce mortality. No exposure to radiation.	Need bowel preparation. Expensive. Expertise is required. Invasive, with 1–5 serious adverse events per 1000 examinations.
Double contrast barium enema	Not as invasive and relatively more available as colonoscopy	Costly; exposure to radiation; bowel preparation required; least sensitive; positive result needs further confirmatory test.
Serology with circulating methylated <i>SEPT9</i> DNA	None invasive	Low sensitivity, costly, needs further confirmatory tests, limited information on its effectiveness.

Table 2: Revised Bethesda Guidelines for testing colorectal tumours for microsatellite instability (MSI)

Tumors from individuals should be tested for MSI in the following situations:

1. Colorectal cancer diagnosed in a patient who is less than 50 years of age
2. Presence of synchronous, metachronous colorectal or other HNPCC-associated tumors,* regardless of age
3. Colorectal cancer with the MSI-high histology‡ diagnosed in a patient who is less than 60 years of age
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor,* with one of the cancers being diagnosed under age 50 years
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

* HNPCC-related tumors include colorectal, endometrial, gastric, ovarian, pancreatic, ureter/ renal pelvis, biliary tract and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torres syndrome, and carcinoma of the small bowel.

‡Presence of tumor infiltrating lymphocytes, Crohn’s-like lymphocytic reaction, mucinous/signet-ring differentiation or medullary growth pattern.

Umar, A., Boland, C. R., Terdiman, J. P., Syngal, S., de la Chapelle, A., Ruschhoff, J., et al. (2004). Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst*, 96(4), 261–268.

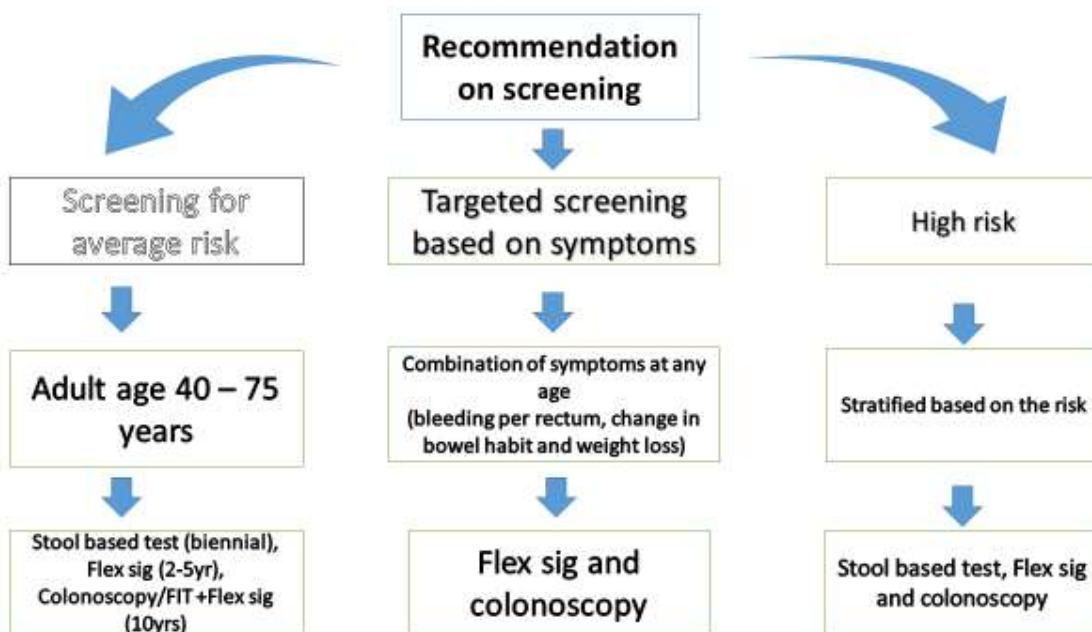


Figure 2: Recommendation for screening strategy for Nigeria

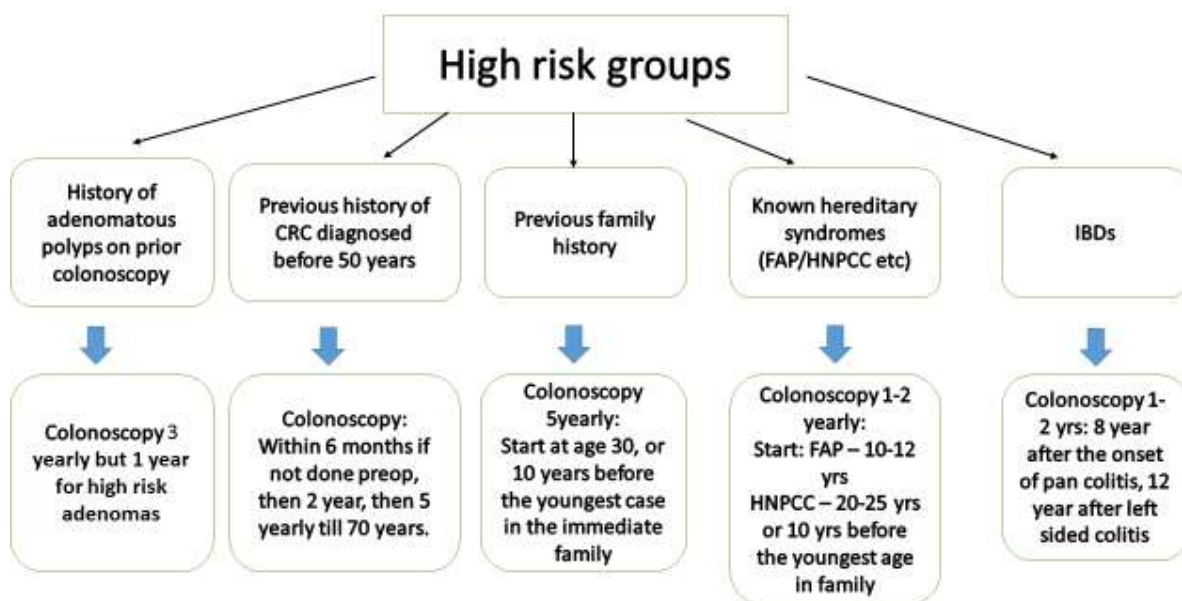


Figure 3: Screening recommendation for high risk group patients

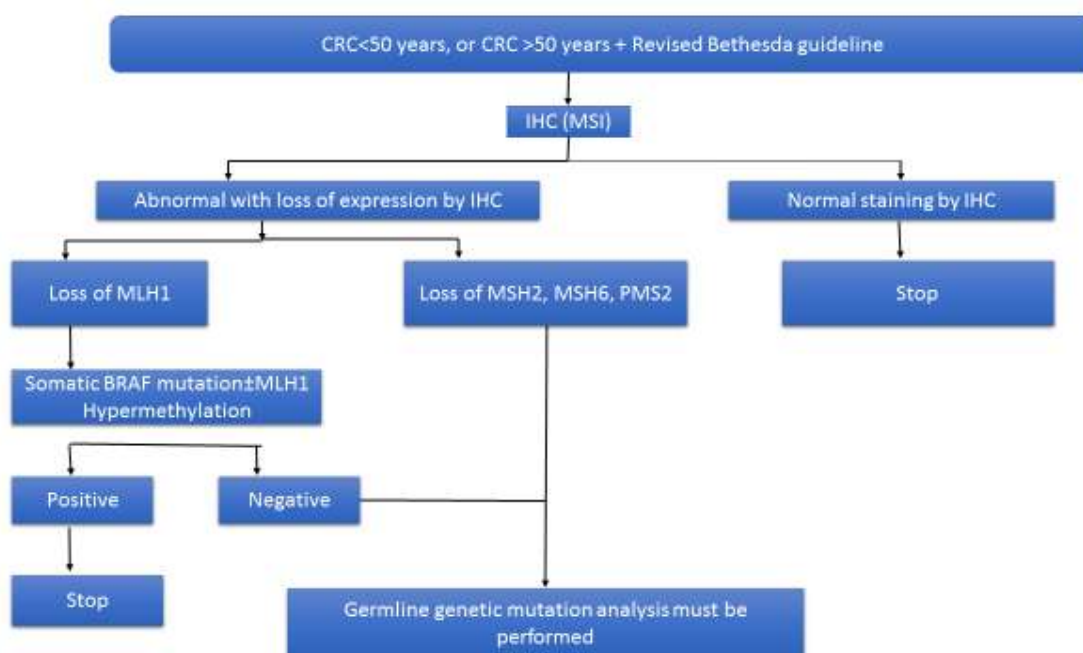


Figure 4: Guideline for genetic mutation analysis (Adapted from ESMO guideline)³³

Prognostic factors

With the idea of personalized medicine in CRC, appropriate treatment strategies should be guided by the prognostic factors identified in each patient.³³ These factors include the specific tumour stage, tumour biology, patient, system-related factors.³³⁻³⁹ The patient-related factors include age (biologic age > 70 years is poor prognostic factor), presence or absence of comorbidities and socioeconomic status. The latter is almost the most important factor in Nigeria as many apparently early diseases end up becoming advanced because the patients cannot afford the cost of treatment. The relevant tumour related factors include the tumour

burden, tumour type, obstruction, perforation or tumour rupture during surgery, tumour lymphocytes infiltration, stage of the cancer, lympho-vascular and perineural infiltration, genetic mutation involved (KRAS and BRAF mutation, SMAD 4 loss, thymidylase synthase positivity greater than 25% in cells, high frequency of microsatellite instability.^{35,36,39-44} Whereas tumour leucocyte infiltration is a good prognostic index, high frequency of genetic mutation influences the choice of chemotherapy and immunotherapy.^{35-37,40} Some biochemical factors may also be used to prognosticate the outcome of CRC. High CEA level > 50µg/L, high alkaline phosphatase >300 U/L, thrombocytosis > 400 X 10⁹/L, leucocytosis >10 X 10⁹/l, high LDL, as well as low albumin and packed cell volume are poor prognostic factors.^{33,45} System related factors is also very important as regionalization of CRC care to high-volume centres and surgeons have significant favourably impact on the outcome of treatment.^{46,47} Similarly, system related delay due to poor referral system often seen in LIC negatively impact outcome. Most patients with CRC who presented at primary health centres are often falsely reassured. **We recommend that patients with rectal bleeding with associated change in bowel habit and weight loss should be referred for CRC screening as soon as possible. This should also include patient with unexplained anaemia**

Most of these predictive factors have been combined to define a prognostic classification score.^{48,49} However, none of these has been validated among Nigerians. **We suggest that research in the validation of prognostic factors in CRC among Nigerians to assess their usefulness be carried out.**

Diagnosis and staging of colorectal cancer

Diagnosis and staging of CRC is made from the combination of clinical, endoscopic and imaging evaluation. Physical examination, family history of CRC, polyps and other cancers, and carcinoembryonic antigen (CEA) should be obtained. **Computerized Tomography (CT) scan of the abdomen is recommended as primary local staging tool to assess growth of the colon tumour into the surrounding structures.** However, pelvic MRI is most desirable for all rectal cancer patients. Endoscopic Ultrasound (EUS) is a useful alternative or an adjunct to pelvic MRI for rectal cancer where this is available. Abdominal ultrasound and full colonoscopy have to be performed either at diagnosis preoperatively or postoperatively in case of obstructing tumours or for other reasons. Colonoscopy is essential to diagnose associated synchronous cancers or adenomatous polyps. Double contrast barium enema performed with fluoroscopy monitoring is a preferred alternative if colonoscopy is not available albeit with low sensitivity. In obstructing tumours, when CT scan cannot be obtained, water soluble enema or at the very least plain abdominal X-ray (supine and erect view - lateral decubitus in patients who cannot stand) should be performed before surgery. This may give idea of the level of obstruction. Minimal requirement for distant staging of colon and rectal cancer is CT of the chest (if not available, X-ray of chest should be obtained bearing in mind its limitation). Fludeoxyglucose Positron Emission Tomography (FDG-PET) scan should not be used routinely for initial staging, but might be used for patients with CT-detected synchronous liver metastases, who are scheduled for curative liver surgery or in the presence of nodes in the common iliac region. FDG-PET is more sensitive than CT to rule out extrahepatic metastases. In the absence of FDG-PET, bone scan and brain imaging should be performed only for patients with related symptoms. Other investigations should be guided by symptoms the patient has at presentation. Minimum blood parameters include blood sugar estimate, complete blood count, electrolyte, urea and creatinine. Liver function tests, serology for hepatitis virus and clotting profile will be essential in case of liver metastasis. The SOGHIN Colorectal guideline adheres to the current TNM staging system of the 7th edition

of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual which is found below.

Primary Tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ: intraepithelial or invasion of lamina propria

T1 Tumour invades submucosa (depending on the extent of invasion of the submucosa, this can be further classified into T1sm 1, 2 or 3)

T2 Tumour invades muscularis propria

T3 Tumour invades through the muscularis propria into pericolorectal tissues

T4a Tumour penetrates to the surface of the visceral peritoneum

T4b Tumour directly invades or is adherent to other organs or structures

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1–3 regional lymph nodes

N1a Metastasis in one regional lymph node

N1b Metastasis in 2–3 regional lymph nodes

N1c Tumour deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis

N2 Metastasis in 4 or more regional lymph nodes

N2a Metastasis in 4–6 regional lymph nodes

N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)

M1b Metastases in more than one organ/site or the peritoneum

STAGE GROUPINGS

Stage	T	N	M	Dukes	MAC
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-T4a	N1/N1c	M0	C	C2
	T2-T3	N2a	M0	C	C1/C2
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	Any T	Any N	M1b	-	-

Rectal cancer

Definition of localization of rectal cancer

The accurate diagnosis of location, local tumour extension, nodal (N) stage, potential circumferential or mesorectal resection margins (CRM/MRF) involvement and extra-mural or venous invasion is essential for defining the treatment strategy.⁵⁰⁻⁵⁴ The primary lesion is identified by digital palpation and/or rigid or flexible endoscopy, with biopsy. The anatomical landmark/reference point for digital examination and rigid endoscopy is the anal verge. Rectal cancers are categorized according to their distal edge measured from the anal verge and are located from anal verge up to 15 cm (< 5cm is low, >5 -10cm is middle, >10-15cm is high; reference point is anal verge) (Figure 5). Definition for low versus mid/high with digital palpation, rigid proctoscopy, pelvic MRI and/or EUS is accurate and more reliable than for flexible endoscopy. MRI confers further advantage in that it is also accurate for determining the length of the tumour, extramural depth, nodal tumour infiltration, safety of plane of dissection, extramural vascular invasion (EMI), and selection of patient for watchful waiting after complete response to preoperative therapy.⁵¹⁻⁵⁴ However, definition of tumour heights with different methods is dependent on the position of the patient during the investigation and the different measurement points, e.g. anal verge for rigid proctoscopy and anorectal junction for MRI.⁵² Definition of tumour location/ heights is important only if it is relevant to the treatment strategy, in particular for low rectal tumours as well as high (separation from colo-sigmoid cancer). In the absence of Pelvic MRI and EUS, multidetector computer tomographic (MDCT) scan should be done before the initiation of treatment. However, the stage-specific management should be based on the best available and affordable staging method before the initiation of treatment.

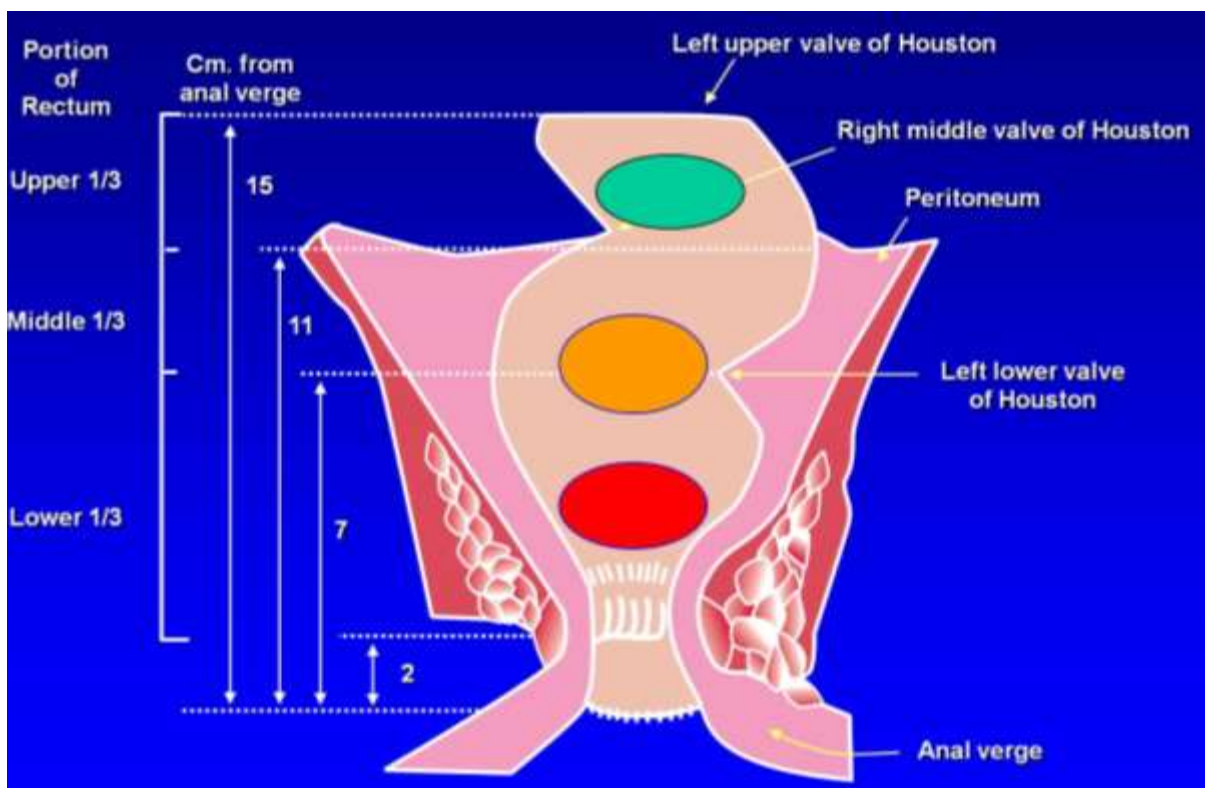


Figure 5: Classification of rectal tumour based on location

Pathology

Basic minimum dataset for reporting colorectal cancer specimen had been published by the Pathology group in SOGHIN.⁵⁵ We appeal that all Pathologists in Nigeria should adopt this guideline as this will be helpful for auditing purposes in Nigeria.

Management Team

Recent results from National cooperative study groups and several European randomized trials indicate that a multimodality treatment approach results in a significantly better outcome than surgery alone. As much as possible, **we recommend that patients with rectal cancer should be staged and treated in centres of excellence in CRC.** In such centres of excellence, treatment should be decided by a multi-disciplinary team (MDT)—before treatment is initiated. The basic minimum for the MDT include Surgical Oncologists with further training in colorectal surgery, Pathologists and Radiologists with interest in abdominal imaging. Where available, Medical Oncologists, Radiation Oncologists, Oncology Nurses, and Stoma therapists should be part of the team. These centres must also audit their figures to determine permanent stoma rates, functional outcomes and local recurrence rates.

In case of an emergency presentation such as intestinal obstruction, a diverting colostomy or colonic stenting and other life saving measures should be offered before referral. Patients with tumour perforation, bleeding and fistula should also have life saving measures before referral. Patients should be classified according to clinical TNM stage, involvement of mesorectal fascia, size, level and localization either as high, middle and low. Other factors, such as clinical nodal stage, vascular and nerve invasion are also relevant.

Treatment standard according to clinical stage and location of the tumour at diagnosis

Patients with tumour above 10cm from anal verge should be generally treated as recto sigmoid cancer. For low and middle rectal cancer stage II and above should have neoadjuvant therapy after resuscitation where necessary. Resuscitation could include palliative resection, stenting or diverting colostomy in case of obstruction, bleeding and fistulation.

Low and middle rectal tumour

Stage 1

For very early stage: cT1 sm1/2 with favourable histology local excision is the best choice. Local excision should go through the muscular layer. There are five technical approaches to local excision: transanal, transcoccygeal, transsphincteric, transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS).⁵⁶⁻⁶⁰ Each approach has advantages and disadvantages. The transcoccygeal approach requires a skin incision and a posterior proctectomy, which may lead to wound infection and the development of rectocutaneous fistula. The transsphincteric route requires complete division of the anal sphincter, which may result in faecal incontinence. As most of the rectal cancers that are candidates for local excision can be excised through the anus, the transsacral and transcoccygeal approaches are rarely used today. Transanal endoscopic microsurgery may be a useful alternative in selected tumours of the upper rectum that cannot be removed by standard transanal techniques if the facilities and expertise are available.

The disadvantage of transanal approach include absence of pathologic staging of nodal involvement and the higher recurrence rate following resection. The higher recurrence rate has been linked to the presence of micrometastasis in the lymph nodes which is undetected by EUS or MRI.^{59,60} Addition of radiotherapy to local surgery has been shown to reduce the risk of recurrence though this has not been shown to be as good as total mesorectal excision

(TME). If the tumour appears to be of higher stage (>pT1sm2) or shows worse prognostic factors (differentiation, venous invasion, perineural invasion), after local excision, the patient should receive TME.³³

For early tumours with unfavourable histology (differentiation, venous invasion, perineural invasion), transabdominal resection, including TME without preoperative treatment is recommended. The two approaches to the transabdominal excision include low anterior resection (LAR) or abdominoperineal resection.

Stage II and Stage III

Except in few cases, for patients with stages II and III rectal cancer, the current standard treatment sequence is as follows: 5 to 6 weeks of chemoradiotherapy (CRT), followed by 6 to 8 weeks of recovery time, followed by surgery (TME), followed by 4 to 6 weeks of postoperative recovery time, followed by initiation of adjuvant chemotherapy (figure 6).⁶¹⁻⁶⁸ It has been shown, that preoperative CRT followed by adjuvant chemotherapy significantly reduces local recurrence rates, has less acute and long-term toxicity and in addition enables a higher rate of sphincter saving surgery by downsizing and thus improves functional outcome in low rectal tumours when compared to postoperative adjuvant CRT.^{69,70} However, distant relapse rate and OS are similar for both approaches. This timeline means that full systemic chemotherapy is not delivered until about 4 months after neoadjuvant CRT is initiated, and such a delay could theoretically allow for the development and dissemination of metastatic disease. With this in mind, some clinical trials have investigated the possibility of giving chemotherapy much earlier and this has suggested another possible sequence as follows: 6 weeks induction chemotherapy (CAPOX/FOLFOX), followed by 5 to 6 weeks of CRT, followed by surgery (TME).⁷¹⁻⁷⁴ Aims of preoperative treatment are reduction of risk of local relapse, improvement of resectability to enable R0-resection in tumour involving the mesorectal fascia or T4 disease, preservation of sphincter function in low located tumours and avoidance of stoma.

Recent evidence has shown that in the absence of radiotherapy, intensive chemotherapy before definitive surgery resulted in improved outcome of treatment.⁷⁵⁻⁷⁹ This recent evidence is important in low income countries where radiotherapy access may be limited. This has been shown to give about 27% pathological complete response.⁷⁸ This measure is the treatment modality of choice when the tumour is located within 10cm from anal verge. This approach is currently being evaluated in a prospective possibly practice changing trial named ALLIANCE PROSPECT trial.⁸⁰

Recently, there is an ongoing debate on what to do for patients that have had complete response following induction chemotherapy and CRT. Watchful waiting has been suggested as a treatment of choice especially when biopsy of the residual ulcer showed no evidence of cancer cell. Some have suggested local resection of the tumour rather than standard TME. Scoring systems have also being developed to determine those that will benefit from organ sparing management.^{81,82} A prospective (OPRA) trial is currently evaluating the possibility of non-operative or organ sparing therapy following complete response to adjuvant therapy.⁸²

Primary surgery can be offered for few stage II/III patients. These include:

- 1) Those that have medical contraindications to CRT;
- 2) Those with T3 disease on MRI or CT with favourable histological features. These patients can be offered short course RT before surgery or adjuvant chemotherapy alone can be considered as adjuvant RT benefit may be very small and clinically not justifiable.

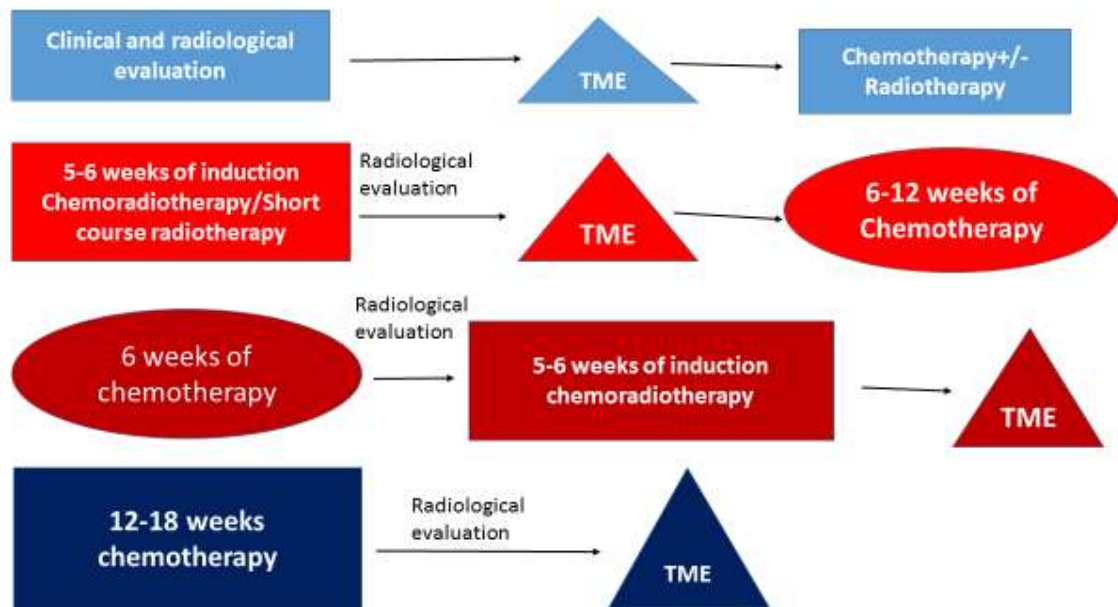


Figure 6: Treatment sequence for stage II and III low and mid rectal cancer

Radiotherapy regimen

Radiotherapy for rectal cancer can either be as short-course radiotherapy with 5×5 Gy followed by immediate surgery or long course radiotherapy with 50.4 Gy in 25–28 fractions, with surgery after a 4–12 weeks break. Short course radiotherapy is given when down staging of tumour is not necessary but rather it is administered to sterilize the margin so as to reduce local recurrence. Nevertheless, the possible acute and chronic toxicity should be borne in mind when this modality is deployed. These include diarrhoea, dysuria, fatigue, skin irritation, haematologic toxicity, rectal urgency and small bowel obstruction. Long course CRT is preferred in locally advanced rectal cancer. A boost up to a total dose of 55.4 Gy can be administered (not mandatory).³³ Brachytherapy or intraoperative radiation is a special form of local boost, but still experimental. Intraoperative radiotherapy is considered for close/positive microscopic margin especially for T4 or recurrent disease. Brachytherapy is considered for macroscopic residual after preoperative chemoradiation and resection.

As regard the simulation and field design, the patient must be in a prone position to reduce the volume of small intestine within the pelvis. The volume to irradiate (clinical target volume), is design to cover the tumour and the entire mesorectum, presacral, internal iliac nodes, external iliac nodes, fossae ischiorectalis, the medial inguinal nodes in case of T4. In whole pelvis treatment(PA), the superior border is at L5-S1, the inferior border is 3cm below the initial tumour volume or inferior obturator foramen and the lateral border is 1.5cm outside pelvic inlet. The posterior border of the lateral field lies behind the bony sacrum in T3 disease whereas the anterior pubic symphysis in T4 (Figure 7).

Preoperative long-course radiotherapy should always be combined with fluoropyrimidine based chemotherapy. Standard preoperative CRT means a dose of 45–50.4 Gy, together with 5-FU given preferably as prolonged continuous infusion or oral 5-FU prodrugs [capecitabine or uracil–tegafur (UFT)]. Other drugs such as oxaliplatin or irinotecan can be added to 5FU based CRT.

Recurrent rectal cancer is often treated the same as T4 disease with combine chemotherapy and radiotherapy followed by surgery and then adjuvant chemotherapy.

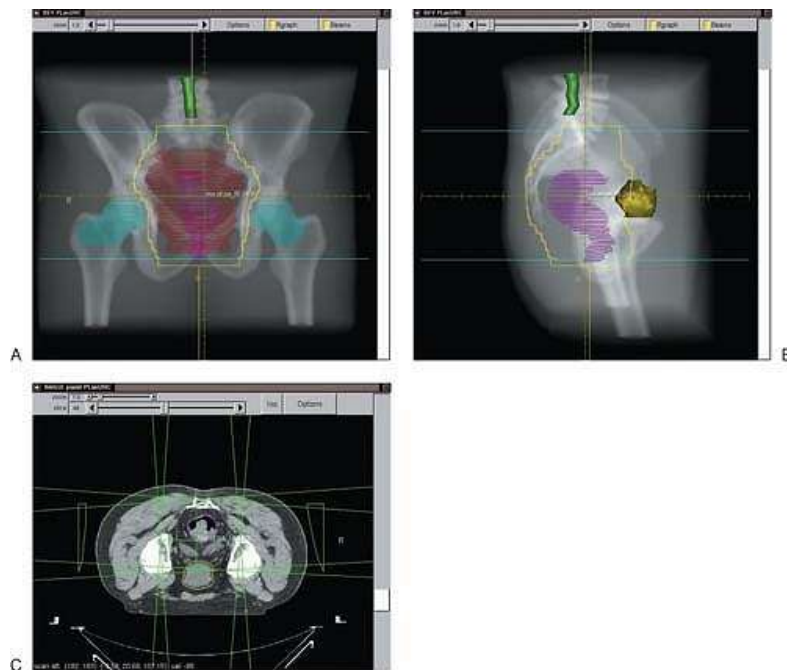


Figure 7: Clinical target volume for patients requiring radiotherapy for rectal cancer (A) Posteroanterior and (B) lateral digitally reconstructed radiograph of the radiation fields for preoperative radiation therapy of a T3N1 rectal adenocarcinoma. The clinical target volume and rectum are outlined. There is a marker at the anal verge to help avoid irradiating the entire anal canal. The field treats the mesorectum and the lymph nodes to the level of the sacral promontory. C: Transverse cut at the middle of the radiation field.

Stage IV – Primary tumour with synchronous metastatic rectal tumour.

Treatment strategy for synchronous oligometastatic rectal cancer should be based on the possibility of achieving R0-resection, either initially or after induction treatment for systemic disease and primary tumour. After 3-6 months of perioperative therapy, patient should be offered surgical ablation for primary and metastatic disease either synchronously or at different time. Metastases that are often amenable to such therapy are to liver, lung and brain.

Type and Quality of Surgery

In low and middle rectal cancer, surgical techniques include LAR and APR depending on location and extent of disease. This can be performed with or without lateral wall dissection. Whenever possible, sphincter preservation should be the aim. The sphincter can generally be preserved, if the tumour can be resected with a 1-2 cm clear distal margin. A protective colostomy or ileostomy should be seriously considered for all low colo-rectal or colo-anal anastomoses. Intestinal stapling devices should be utilized for the surgery. LAR is however possible without the devices if the anastomosis is performed extracorporally. Total mesorectal excision (TME) with appropriate lymphovascular clearance is the standard of care in rectal cancer surgery.⁸⁴ The whole mesorectal fat, including all lymph nodes, should be excised. TME is recommended for patients with all rectal cancers localized in the middle and

lower third of the rectum. Quality control of surgical specimen is crucial and this should be documented by the pathologist. Mesorectal transection for high rectal tumor (>10–15 cm from anal verge) is adequate because of reduced morbidity. Rectum and mesorectum have to be divided 5 cm below tumour.

Abdominoperineal resection (APR) is the preferred surgical approach in case of tumour involvement of the anorectal junction and anal sphincter or as salvage of local failures after local excision with or without prior (chemo) radiotherapy. Basically, four types of APR can be described in relation to the perineal approach and the extent of dissection—conventional synchronous combined APR (figure 8), the intersphincteric APR (figure 9), the extralevator APR (ELAPE) (figure 10), and the ischioanal APR (figure 11)—and the indications are different for these procedures.⁸⁵⁻⁹⁰ Intersphincteric APR is utilized for patients unsuitable for bowel reconstruction because of preoperative history of incontinence or when they have significant comorbidity or high risk of anastomotic leak. This group of patients may also be offered Hartmann's operation as this provide opportunity to monitor for recurrence before the reconstruction is undertaken. ELAPE is indicated in tumour extending less than 1 cm from dentate line (T2–T4 cancer) or tumour with threatening CRM. Ischioanal APE is more preferred for locally advanced cancer infiltrating levator muscles, ischioanal fat, or perianal skin or patients with perforated cancer with abscess or fistula in ischioanal compartment

Adoption of the laparoscopic approach to TME for rectal cancer has been slower because of the difficulty of working in the deep and narrow pelvic space using long, rigid, non-articulated instruments. Three multi-institutional prospective randomized trials have compared open and laparoscopic TME for rectal cancer.⁹²⁻⁹³ The fourth prospective study, the American College of Surgeons Oncology Group ACOSOG-Z6051 (Laparoscopic-Assisted Resection or Open Resection in Treating Patients With Rectal Cancer), conducted in the United States has completed accrual but the results are pending.⁹⁴ The combined experience of these trials indicates that laparoscopic TME results in longer operative time, less blood loss, faster bowel recovery, and shorter hospital stay compared with open TME. Operative mortality and intraoperative and postoperative complications were not different between groups. The proportion of patients having a sphincter saving procedure, a complete mesorectal excision, or a positive CRM was not different between groups, nor was the number of lymph nodes retrieved. However, conversion and positive CRM rates in the laparoscopic arms varied widely. Currently, there is an ongoing clinical trial to examine whether Laparoscopic surgery might reveal equivalent results in terms of function and relapse rate, compared with open surgery in specialized centres. The skill for laparoscopic TME is still very limited in Nigeria. We recommend that where the expertise is available, the approach should be considered.

Robotic platform is also used to perform TME for laparoscopic colorectal resection. The experience accumulated thus far, based on retrospective institutional case series, suggests that a TME performed with the DaVinci platform is equivalent to a laparoscopic TME in terms of completeness of the mesorectal excision, CRM positivity, and short-term oncologic outcomes.^{95,96} Conversion rates appear to be lower compared with laparoscopic TME, but hospital charges are higher.⁹⁶

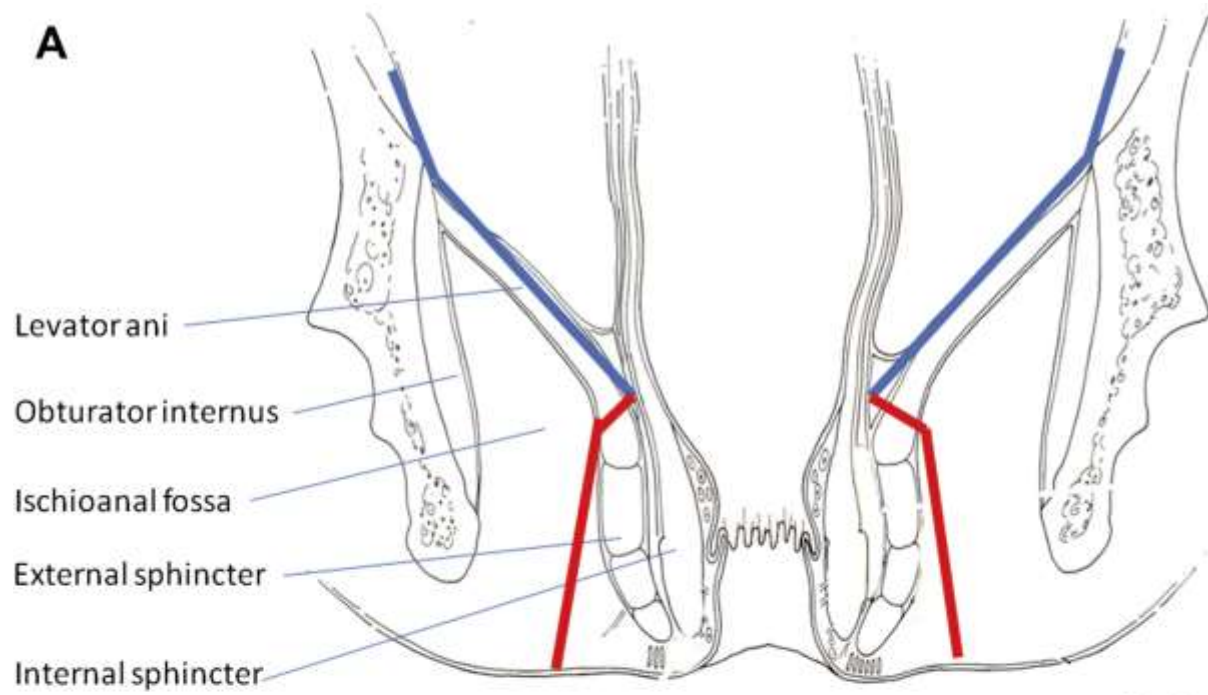


Figure 8: The pelvic dissection in a conventional synchronous combined APE as well as the photograph⁹⁰

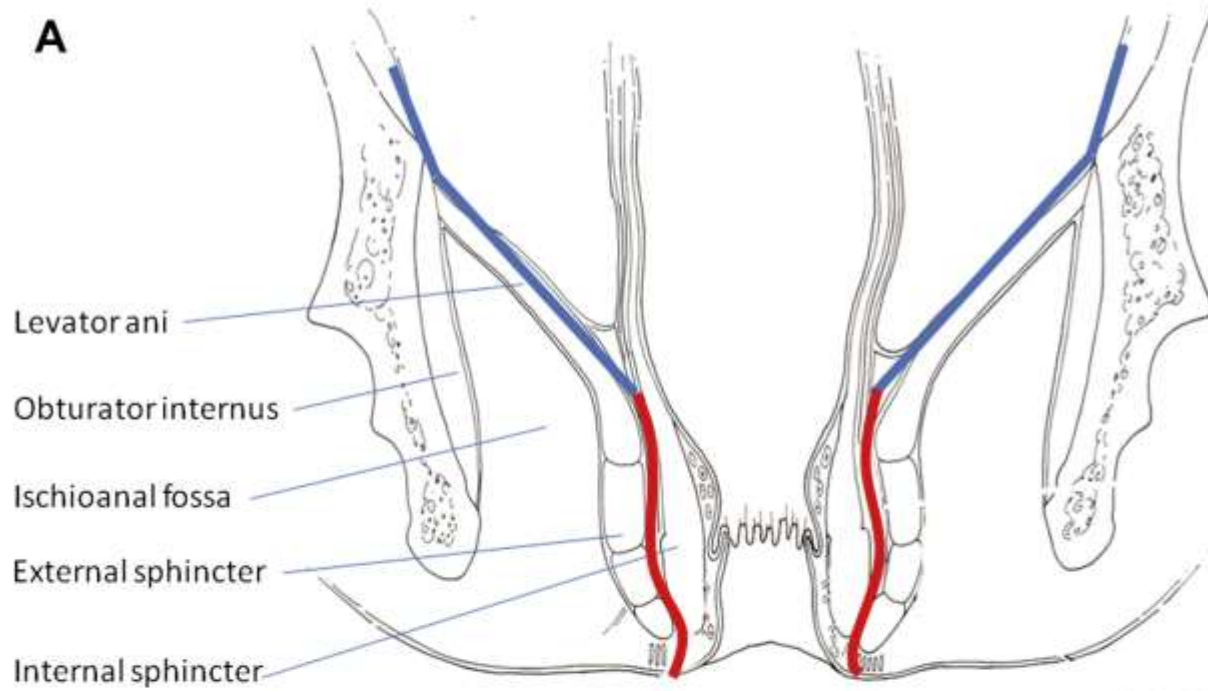


Figure 9: The pelvic dissection in an intersphincteric APE as well as the photograph of the resected specimen⁹⁰

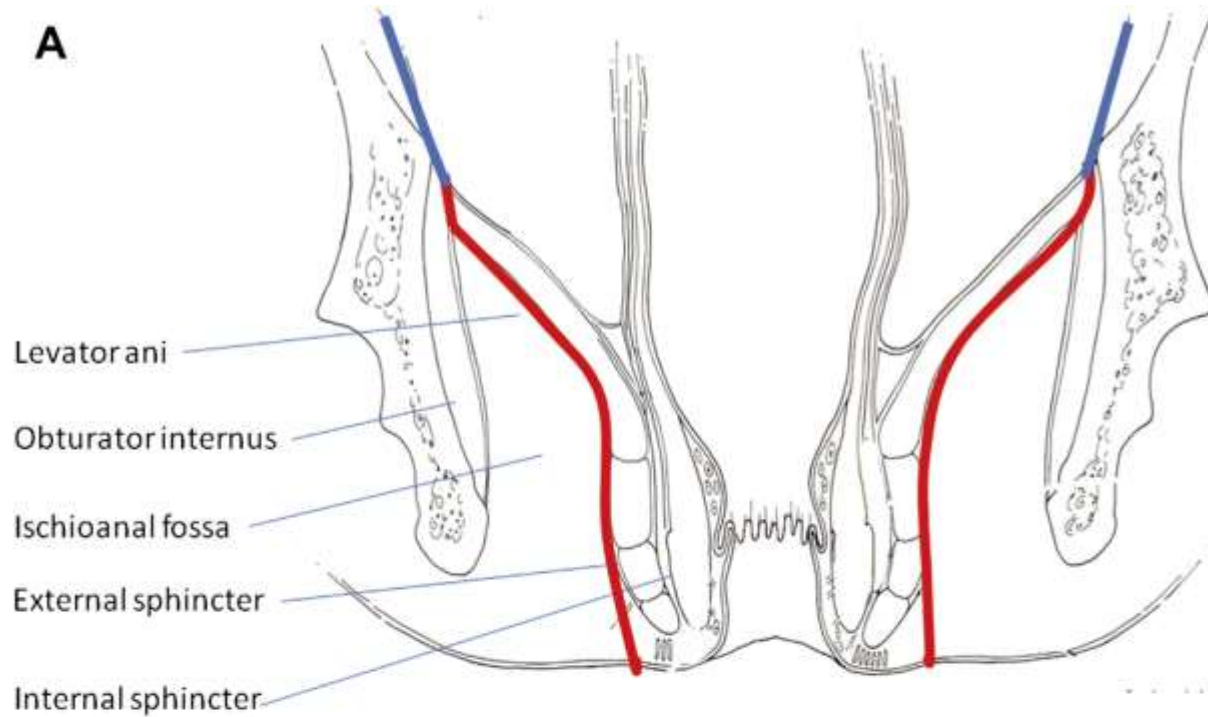


Figure 10: The illustration showing pelvic dissection in an ELAPE as well as the photograph of resected specimen⁹⁰

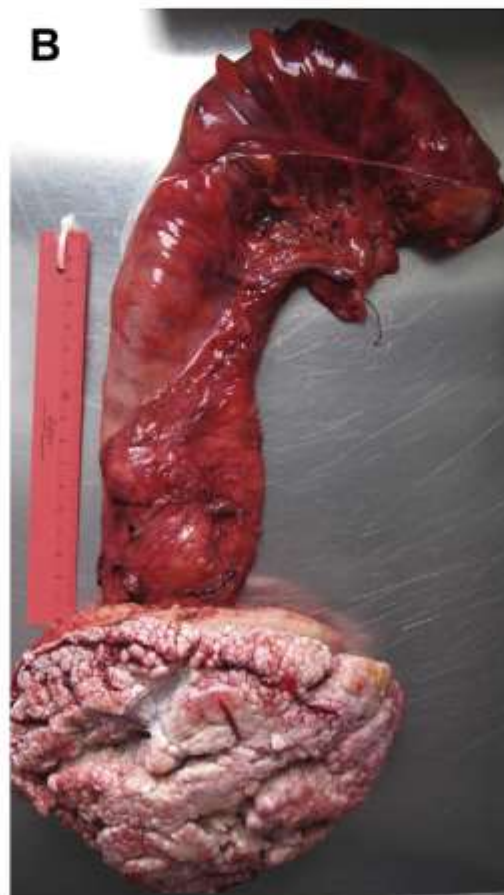
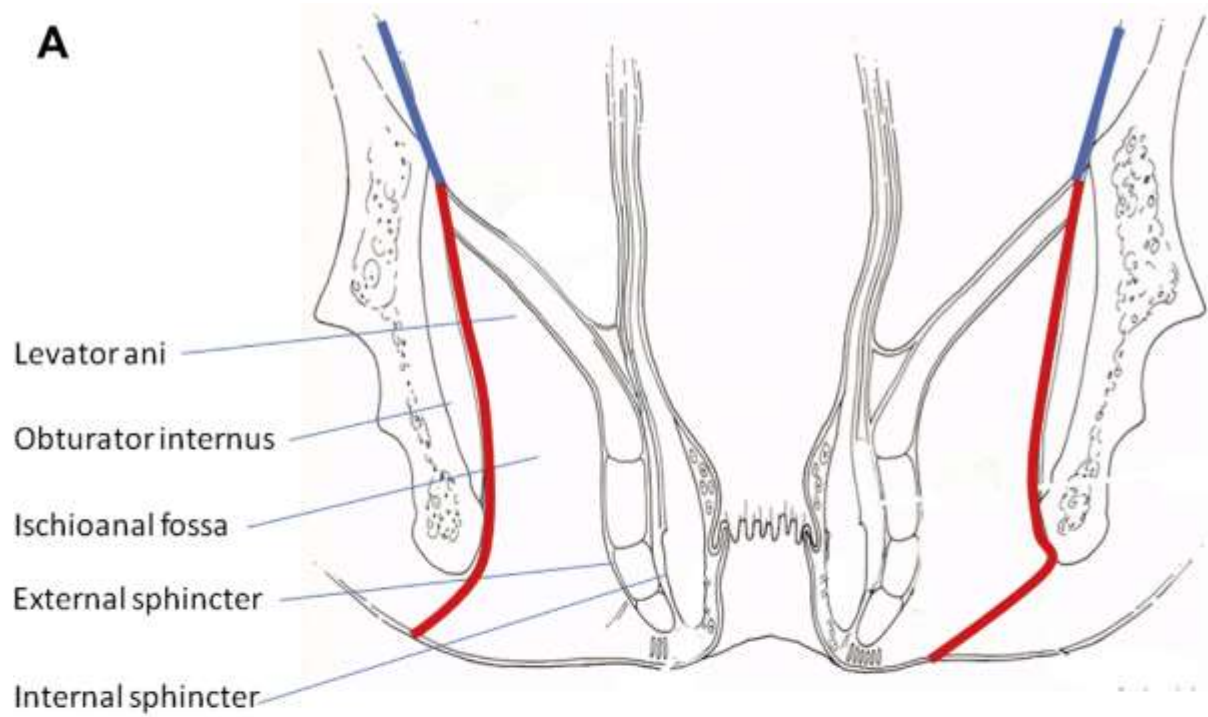


Figure 11: The pelvic dissection in an ischioanal APE and the photograph of the resected specimen⁹⁰

Timing of surgery

The timing of surgery depends on clinical and adjunctive therapy instituted for the patients. After preoperative short-course radiation (5×5 Gy), surgery should be undertaken within 7 days of completion of the therapy. Interval between preoperative long course CRT and surgery should be 4–12 weeks. For elderly (>80 years) or frail patients, surgery should be delayed to 8-12 weeks. CRT or radiation with prolonged interval allow for the tumour to be downsized remarkably. Before surgery is performed, radiological documentation of the down staging is important.

Stoma should be reversed, if feasible, after completion of adjuvant treatment (including radiation) in order to assure timely postoperative therapy. The interval between the last chemotherapy and operation should be at least 5–6 weeks; in case of surgery during adjuvant treatment (e.g. urgent patient request), the interval might be shortened to 3–4 weeks. However, treatment should be resumed after surgery.³³

Colon cancer

Definition of localization of colon cancer

CT of the abdomen is recommended as primary local staging tool to assess growth of the colon tumour into the surrounding structures. Minimal requirements for distant staging are CT of the chest (if not available, X-ray of chest can be performed bearing in mind its limitation) and abdomen, and complete colonoscopy (either pre- or postoperatively). FDG–PET is not recommended for initial staging. Physical examination and medical and family history of CRC, polyps and other cancers should be obtained. CEA should be determined before treatment. Bone scan and brain imaging should be performed only for patients with related symptoms. Colonoscopic evaluation of the colon could be valuable to precisely locate the tumour, which is particularly useful for the surgical approach especially in patients who are candidates for a laparoscopic resection. In the absence of this, virtual colonoscopy or CT colonography can be performed. This could also help to detect other synchronous colonic lesions or polyps if colonoscopy is incomplete (for example in obstructing tumours).

Treatment standard according to clinical stage at diagnosis

Treatment is based on the clinical stage at diagnosis and patient's clinical condition at presentation (obstruction, perforation or bleeding). Unlike rectal cancer, primary treatment in colonic cancer is based on upfront surgery, followed by adjuvant chemotherapy according to the stage. The chemotherapy should start as early as possible 2 – 4 weeks from surgery and latest 8-12 weeks after surgery because timing of commencement of therapy affects outcome. Starting adjuvant chemotherapy after 12 weeks doesn't confer any benefit, so patients should be counselled, and the risk benefit assessment should be done.

For the patients with superficial tumours or malignant polyps, EMR or ESD is preferred. This has been shown to give comparable outcome with surgical resection with reduced morbidity and shorter hospital stay.⁹⁷⁻¹⁰⁰ While EMR is indicated in superficial CRC less than 20mm as well as lateral spreading tumours-granular type (LST-G), ESD is indicated in the following;

- 1) Lesions for which en bloc resection with snare EMR is difficult to apply such as Lateral spreading tumour – non granular type (LST-NG), Lesions showing a VI-type pit pattern, Carcinoma with shallow T1 (SM) invasion, Large depressed-type tumours, Large protruded-type lesions suspected to be carcinoma
- 2) Mucosal tumours with submucosal fibrosis – fibrosis is often due to previous biopsies
- 3) Sporadic localized tumours in conditions of chronic inflammation such as ulcerative colitis

4) Local residual or recurrent early carcinomas after endoscopic resection

For stage 1 tumour that does not qualify for EMR/ESD, as well as stage II and III colonic cancer, primary surgical resection with enbloc lymphadenectomy should be undertaken. The surgical resection can be performed by open or laparoscopic approach. The laparoscopic approach can also be robotic assisted.^{101,102} Bulky tumours, however, are better removed by open surgery. Unfortunately, most of the colonic cancer cases in Nigeria fall into this category making it difficult to develop skilled laparoscopic colorectal surgery. In clinical trials, patients with bulky tumours may benefit from neoadjuvant chemotherapy to induce regression. Other criteria that must be met before laparoscopic surgery include availability of experienced surgeons in both open and laparoscopy colorectal surgery, absence of prohibitive peritoneal adhesions, no locally advanced disease or acute bowel obstruction or perforations.

For patients with stage IV disease, surgical resection is undertaken if it is possible to perform R0 resection of the primary tumour and the metastasis synchronously or at different times. In case of asymptomatic metastatic disease with resectable primary disease, primary surgery should be undertaken as this had been shown to improve survival.¹⁰³⁻¹⁰⁵ This is also the subject of an ongoing randomized control trial tagged CAIRO 4.¹⁰⁶ If the primary tumour cannot be safely removed, induction chemotherapy should be considered before surgery if there is significant response. If chemotherapy alone is utilized, surgery should be delayed for 4 weeks after chemotherapy. As much as possible, prophylactic or palliative resection should be avoided in the absence of acute life threatening presentation such as obstruction, bleeding or perforation. As this has been shown not to improve survival.¹⁰⁷⁻¹⁰⁹ Upfront prophylactic resection of the asymptomatic primary tumour risks surgical complications that may postpone administration of modern chemotherapy, which has been proven to provide not only systemic but also local disease control. Similarly, it has been shown that most patients will never develop symptoms of acute presentation and therefore could be spared an unnecessary operation.

Type and Quality of surgery

The type of surgery performed for colon cancer is based on location of the tumour, mode of presentation, resectability and available resources. For resectable stage II-IV tumours on the right colon they will require right hemicolectomy with ileotransverse colon anastomosis, whereas for tumour on the hepatic flexure or proximal transverse colon will benefit from extended right colectomy with ileocolic anastomosis (Figure 12 & 13). For lesions in the mid transverse colon, transverse colectomy with colo-colonic anastomosis may be done. Lesions on the splenic flexure or distal transverse colon will benefit from extended left colectomy with colo-colonic anastomosis. Some surgeons will perform extended right hemicolectomy for such tumours as well as other transverse colonic tumours. Tumours on the descending colon or proximal part of sigmoid colon will require left hemicolectomy and colo-colonic anastomosis (Figure 14). For lesions in sigmoid colon, sigmoid colectomy with colo-colonic anastomosis is preferred. For tumours on the distal sigmoid colon and rectosigmoid junction, anterior resection should be performed.

For obstructing or perforated tumours, a decision should be taken whether to perform resection and primary anastomosis or resection and diversion. This decision on the appropriate strategy should be individualized. Patients who present late with features of sepsis will better be salvaged with resection and diversion. For the obstructing cases, resectable tumours will benefit from colectomy and primary anastomosis on the right, while lesions on the left colon will benefit from colectomy with or without primary anastomosis

and diversion. Hartmann's operation can be considered for patients with tumour in distal sigmoid or rectosigmoid junction.

For obstructing left non-resectable tumours, the patient will benefit from diversion or stenting. Recent multicentre randomized controlled trial study has shown that self-expandable metallic stent (SEMS) is an effective bridge to surgery in patients with malignant colonic obstruction.¹¹⁰ It has acceptable stoma creation and complication rates. It should also be bored in mind that the procedure is not innocuous, as it may be associated with significant failures and complication. Insertion of SEMS should only be undertaken where in centre with facility and expertise in the insertion of SEMS.¹¹¹ Surgery can be performed as soon as the patient stabilizes or after induction chemotherapy.

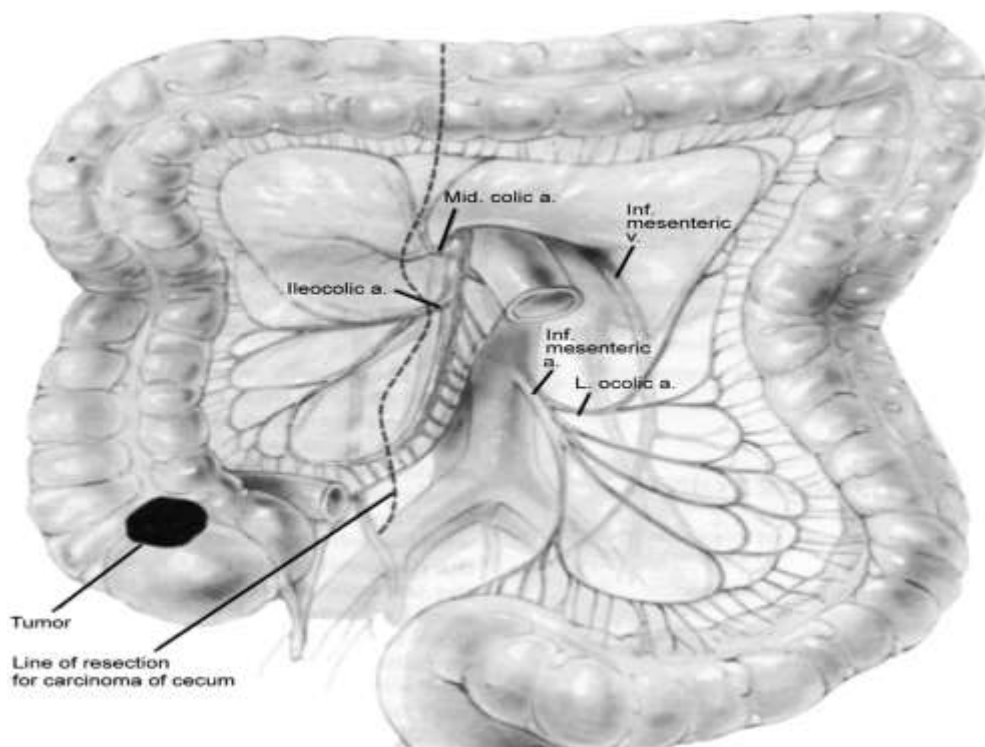


Figure 12: The dissection plane during right hemicolectomy

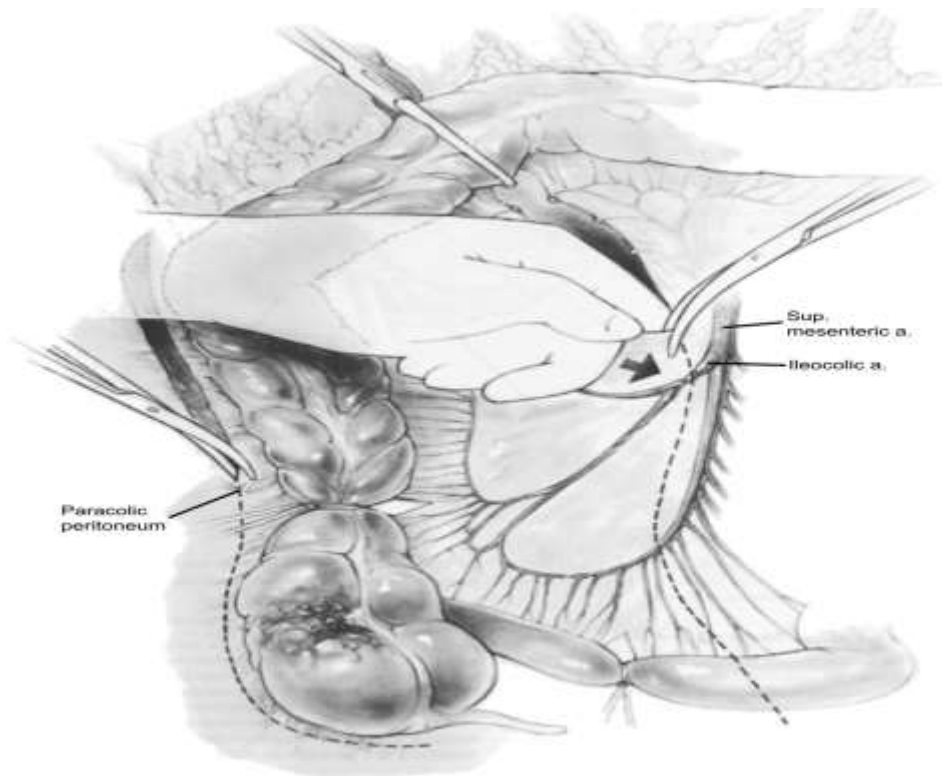


Figure 13: Luminal and vascular control during right hemicolectomy

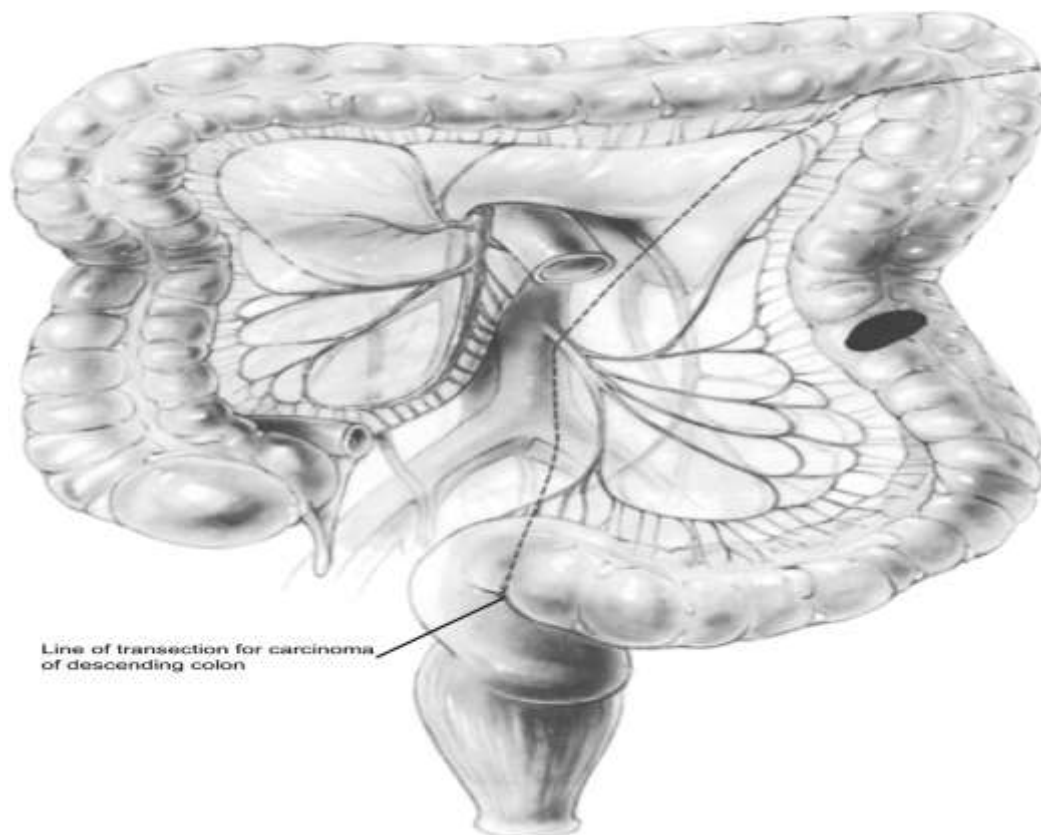


Figure 14: The dissection plane during left hemicolectomy

Principles for Surgery

The principle of colonic resection is wide resection margin with mandatory lymphovascular clearance. The resection should include a segment of colon of at least 5 cm on either side of the tumour, although wider margins are often included because of obligatory ligation of the arterial blood supply. To ensure adequate lymphovascular clearance, the mesocolon should be completely resected and the vascular pedicle should be ligated at the root (Figure 12-14). Lymph nodes at the highest level of ligation should be biopsied and identified for pathological exam. Clinically positive lymph nodes outside the field of resection should also be removed. A minimum of 12 lymph nodes needs to be examined for adequate N staging after surgery.

Enhanced Recovery After Surgery (ERAS)

The ERAS care pathways were first introduced in the mid-1990's and are a more recent addition to the care of patients undergoing colorectal procedures.^{112,113} It encompasses the preoperative, intraoperative and postoperative, as well as post-discharge phases of care.¹¹⁴ The goal is to maximize pre-operative conditioning; optimize recovery after surgery. It is a cost effective approach with significant benefits to the patient, healthcare facilities and the healthcare industry as a whole. The purpose of this pathway is to use current evidence in a streamlined multidisciplinary manner to reduce surgical stress, maintain postoperative physiological function, and enhance mobilization after surgery. This has resulted in reduced rates of morbidity, increase patient satisfaction, faster recovery and shorter length of stay in hospital which allow for greater bed availability in hospital.^{115,116} Figure 15 shows the key component of ERAS pathway. Successful implementation of ERAS pathway can only be achieved when there is a well-motivated and dedicated team. We suggest that every center of excellence in CRC should have institutionalized ERAS dedicated team as well as protocol which should be audited at regular interval.

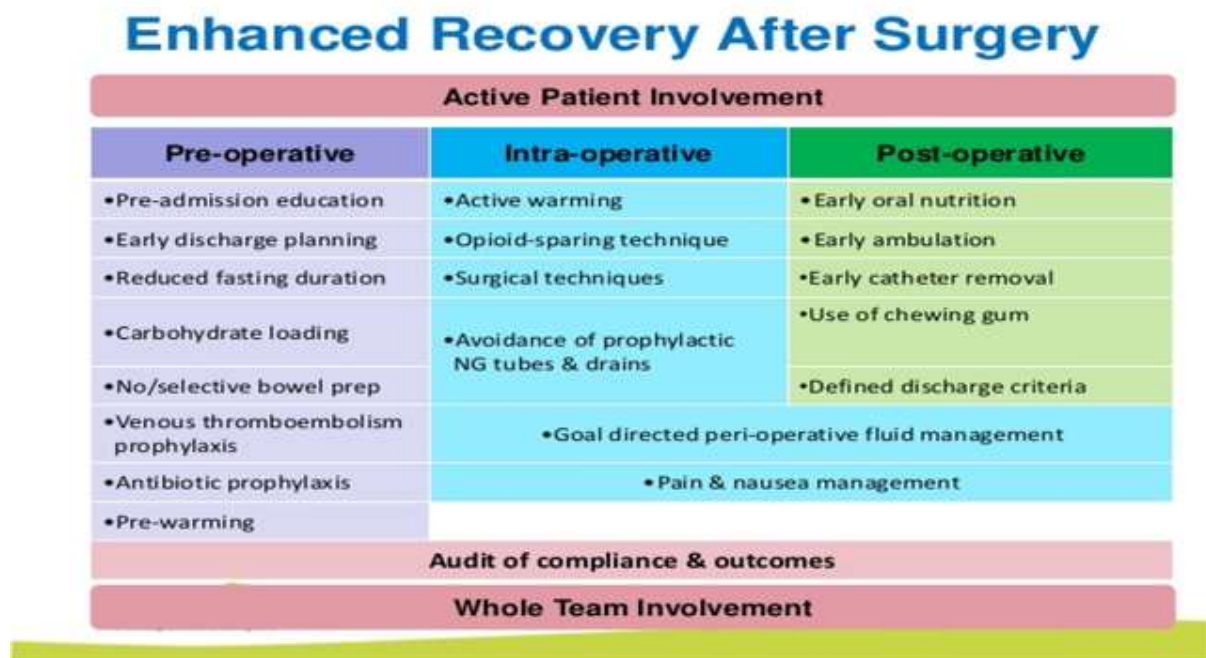


Figure 15: Key elements in ERAS pathways

Systemic therapy

Several factors will affect the choice of chemotherapy in Nigeria. This includes biological age of the patients, co-morbidity, tumour biology, stage of the disease, response rate,

safety/toxicity issues, storage facility, facilities for detection of some tumour markers that will affect choice of drugs, chemotherapy history of the patients, affordability and availability of the agents. Interestingly, virtually all drugs that have been utilized in the treatment of CRC are available in Nigeria. Major limitation is the affordability of the drugs. Some agents are used in adjuvant or neoadjuvant setting. The attending physician has to choose for each patient either single agent therapy, chemodoublet – or chemotriplet. The common first line systemic therapy options include FOLFOX, XELOX, FOLFIRI, XELORI, 5 FU/LV, all with or without monoclonal antibodies. Also Capecitabine or 5FU can be used as single agent.

The antibodies often deployed in CRC include Bevacizumab -VEGF-A inhibitor, Cetuximab – EGFR inhibitors and Panitumumab – EGFR inhibitors. Both VEGF-inhibitors and EGFR antibody therapies should ideally be considered for the treatment of patients with RAS wild-type CRC. Recent evidence revealed, however, that the efficacy benefit of EGFR/VEGF antibody therapies is greater in patients with RAS wild-type/BRAF wild-type tumours than in those with RAS wild-type/BRAF-mutant tumours.¹¹⁷⁻¹²² But no sufficient evidence to exclude RAS wild-type/BRAF-mutant tumours from EGFR antibody therapies however this group may benefit better from VEGF inhibitors. Expanded RAS analyses ideally should be conducted on all patients eligible/being considered for VEGF/EGFR antibody therapy. Other newer agents that can be used as second or third line therapy include Aflibercept – VEGF inhibitors, Regorafenib - dual targeted VEGFR2-TIE2 tyrosine kinase inhibitor, BIBF 1120 - pan VEGFR, PDGF and FGF tyrosine kinase inhibitor and Cediranib - pan VEGFR TK inhibitor, pembrolizumab - immune check point inhibitors.^{8,33} The later clinical benefit can be predicted by the MMR status.⁸

First line chemotherapy can be given in two phases depending on the need of the patients. This includes induction phase and maintenance phase. The induction phase is usually given for 4-6 months. While the maintenance phase can be offered for another 6-12 months. If the tumour progresses on the first line, second line should be introduced for another 5-7 months. In case of progression on the second line therapy, third line therapy can be initiated for about 3 months after few weeks to few months break. If tumour failed to respond to all these, fourth line for few months or best supportive care should be given.

The typical first-line chemotherapy backbone comprises a fluoropyrimidine (intravenous 5-FU or oral Capecitabine) used in various combinations and schedules with irinotecan or oxaliplatin. These can be administered concurrently with VEGF or EGFR inhibitors to achieve induction. Subsequently, therapy could be maintained by the combination of fluoropyrimidine and anti VEGF or EGFR.¹¹⁷

The second line therapy will depend on what is used in the first line. If Irinotecan or Oxaliplatin has not being used in the first line. This should be introduced. Similarly, VEGF inhibitors - Bevacizumab should be introduced. If Bevacizumab had been used, Aflibercept or Ramucirumab can be introduced. These two antibodies are better administered in combination with FOLFIRI.⁸

The third line therapy in RAS wild-type and BRAF wild-type patients not previously treated with EGFR antibodies, should be considered to have cetuximab or panitumumab therapy. Cetuximab and panitumumab are equally active as single agents. The combination of cetuximab with irinotecan is more active than cetuximab alone, in irinotecan refractory patients.⁸ There is no unequivocal evidence to administer the alternative EGFR antibody, if a patient is refractory to one of the EGFR antibodies. Regorafenib should be recommended in

patients pre-treated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies. Trifluridine/tipiracil is recommended for patients pretreated with fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab and in RAS wild-type patients with EGFR antibodies

Supportive therapy

Most of the combination therapies for CRC are emetogenic. Supportive anti-emesis should be prescribed for the patients. Common anti-emesis include 5-HT₃ - receptor antagonist such as Ondasetron, ganisetron, palonosetron, dexamethasone, aprepitant - NK-1 inhibitor, metoclopramide. In most of cases, the aforementioned agents are combined to achieve satisfactory response.

Chemotherapy induced diarrhoea is common following infusion 5FU. Depending on the severity, patient may require hospital admission and fluid resuscitation. Recommended medication include loperamide, octreotide and tinctura opii.

Chronic peripheral sensory neuropathy is cumulative and grade 3 toxicity occurs in 10%–20% of patients receiving oxaliplatin doses of 750–850 mg/m². This gets worse with higher cumulative doses. This neuropathy could be debilitating in some patients. Treatment includes patient reassurance, dose modulation, neuro-modulatory drugs such as calcium and magnesium, acetylcysteine, amifostine, gabapentin, carbamazepine, glutathione, Org 2766, diethyldithiocarbamate or vitamin E. Patients should be adequately warned before the commencement of treatment.

Skin changes are also common in patients taking chemotherapy for CRC. The dermo-toxicity include hyperpigmentation of the skin; hand and foot syndrome which is common in patients taking capecitabine; EGFR-inhibitor-induced skin rashes. Pyridoxine and celecoxib can be given to ameliorate the debilitating effect of hand and foot syndrome. Systemic antibiotics such as tetracycline and doxycycline or topical antibiotic may be given to patients with EGFR inhibitor induced skin rashes.

The risk of febrile neutropenia for oxaliplatin and irinotecan based chemotherapy is <20%, unless additional risk factors as defined. A routine prophylaxis with G-CSF and antibiotics is therefore not indicated, only in patients with high risk of severe infection in case of (prolonged) neutropenia

Chemotherapy and surgical therapy in elderly patients aged 70 years and above

Several factors must be considered before the choice of chemotherapy regime in patients older than 70 years. These include physiologic age, the performance status, comorbid medical conditions, medications, social support, and personal preference. It will be necessary to consider using validated assessment tools to evaluate these characteristics. The common comorbid indices utilized include Karnofsky Performance Status (KPS), and Eastern Cooperative Oncology Group (ECOG) Performance Status, Comprehensive Geriatric Assessment (CGA), Charlson Comorbidity Index (CCI) or National Cancer Institute Combined Index (NCI).¹²³ Available studies have shown that elderly patients benefit from adjuvant chemotherapy.^{123,124} Chemotherapy use, both in the adjuvant and palliative setting, should be offered to older patients and their management should not differ substantially from that of younger patients. Though absolute survival advantage of adding oxaliplatin in this group of patients has been questioned.^{125,126} Recent evidence suggest that selected group of

elderly patients benefit from adding oxaliplatin to the chemotherapy.¹²¹ Combination treatments and targeted therapies are not prohibitive but should be used with critical clinical judgment, with constant and careful monitoring for early detection and treatment of toxicities, along with best supportive care.

Surgery which is the cornerstone of treatment should not be abandoned lightly, as operative outcomes are not considered to be worse in older patients compared with younger patients.³³ Emergency surgery should be avoided when possible and if not, a two-stage procedure or the use of stents should be considered. The less traumatic procedures, like laparoscopic operations, are preferred when feasible. Age should also not be a criterion for exclusion of patients from metastasectomies.

Chemotherapy in stage II disease colon cancer

The use of routine chemotherapy for stage two colon cancer has been questioned in recent clinical trials.¹²⁷⁻¹²⁹ It has been shown that the benefit in some patients with stage II colon cancer is marginal and may not justify the toxicity of the drug. Stage II colon cancer patients must be separated into high and low risk, according to the presence of at least one of the following tumour-related risk factors which include

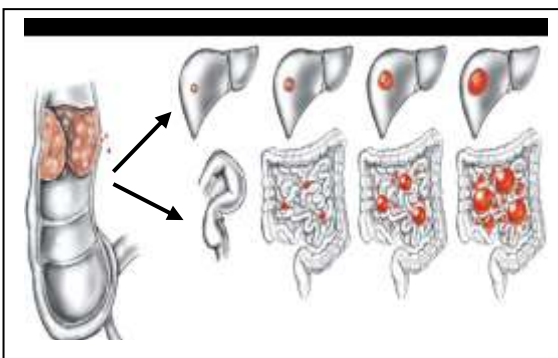
1. Lymph nodes sampling <12,
2. Poorly differentiated tumour,
3. Vascular, lymphatic or perineural invasion,
4. pT4 stage,
5. Clinical presentation with intestinal occlusion or perforation
6. Circulating tumour DNA
7. Oncotype Dx/ColoPrint
8. Presence or absence of MMR/MSI status.

Low risk stage II patients according to this definition should not generally receive adjuvant treatment, although it might be considered in individual patients. High-risk stage II patients may be treated with postoperative chemotherapy with FU with or without oxaliplatin because of a small absolute benefit.

Radiotherapy

There is no clear evidence of survival benefit with use of radiotherapy in colon cancer, but it may be useful in the setting of node-negative disease with close/positive microscopic margin at the primary site where the target can be easily demarcated. The field should include margin around tumour bed based on preoperative imaging and/or surgical clips. The dose is usually 45-50gy in 25-28 fractions

Management of liver metastasis



25-70% of patients with colorectal cancer will present with metastatic disease and approximately 58% will present with metastasis at initial presentation in Nigeria.¹³⁰ Synchronous metastatic liver disease and peritoneum are the most common site seen in Nigeria and are associated with bad prognosis.¹³¹ It has been estimated that about 50% of patients that die of colon cancer have metastasis to the liver at autopsy.¹³¹ Whereas the mechanism of metastasis

to the liver is intraportal, that of the peritoneum is by direct extension. However, with the advent of combination therapy, the outcome has improved. Few patients with metastatic disease can now achieve cure.¹³² Factors that should guide treatment options include site, size and number of metastasis at presentation. The status of the primary tumour is also important. The safety of resection of the metastatic disease should also be considered. Quality imaging – CT scan, will be necessary to make decision on the resectability of the tumour. As a rule, primary chemotherapy should be offered for patients with metastatic disease before surgery. In very few patients with colonic tumour and oligometastasis that is surgical resectable, upfront surgery can be considered. Surgery could also be offered to patients whose resectability status was converted after induction chemotherapy. Prognosis is better if surgery is undertaken after conversion following induction chemotherapy. After induction chemotherapy, assessment of response should be done by 6-8 weeks. If there is significant response, chemotherapy should be continued for 3-4 months to optimize the benefit of chemotherapy. If there is no significant response by 3-4 months, systemic chemotherapy regime could be changed to Hepatic arterial infusion (HAI) or palliative care applied. Hepatic arterial infusion allows delivery of a larger dose of chemotherapy to the tumour without increase in side effects. Two meta-analysis shows survival advantage and increased response rate with use of HAI compared to systemic therapy alone.¹³²⁻¹³⁴ Agents that are used include floxuridine (FUDR), cisplatin, mitomycin C, and doxorubicin. For palliative care, treatment should be tailored to individual situations, patient needs, cumulative toxicity (in particular oxaliplatin) and aggressiveness of the disease.

If surgery is indicated for liver metastasis, such should be performed in a centre with better training of hepatic surgeons and facility for liver resection. These facilities should include vascular sealant, use of “low CVP” anaesthesia, better preoperative and intraoperative imaging modalities, and techniques such as portal vein embolization etc. The ‘technical’ definitions of resectable colorectal cancer liver metastasis (CLM) have evolved over time, with the current consensus proposing that disease should be considered technically resectable as long as complete macroscopic resection is feasible, while maintaining at least a 30% future liver remnant (FLR) or a remnant liver to body weight ratio >0.5 (e.g. >350 g of liver per 70 kg patient). Resectability is not limited by number (e.g. <4), size (>5 cm), and bilobar involvement. Regarding technical aspects, multiple resections can also be performed, provided there is sufficient remnant liver (>30%) and surgery is not too risky because of location. The only universally agreed contraindications for resection now are (1) inability to perform an R0 resection (2) the inability to preserve a remnant liver volume adequate to support life and (3) unresectable primary.¹³⁶ Unfortunately, only very few patients with CLM will have surgical ablation in Nigeria because of sparsity of surgical skill set to perform the procedure. We recommend urgent training of hepatopancreatobiliary (HPB) surgeons who can perform such delicate surgeries. This can be done in partnership with international bodies. Pending availability of such skill set, we recommend that General surgeons with special interest in colorectal surgery should have expanded training in HPB to be able to perform the surgery. It is worth noting that those patients who do not have treatment of CLM develop widespread systemic disease within 3 years of resection of primary tumour irrespective of adjuvant therapy given.¹³¹

Other considerations must include eligibility of the patient for surgery in terms of comorbidity. However, the main determinant of the outcome is—beyond surgery itself—the biology of the disease, which is an essential component of the definition of resectability.^{137,138} Synchronous liver metastasis is a sign of poor prognosis and aggressive disease.¹³⁶

Other ablative therapies that can be used when surgical resection cannot be performed due to patients and tumour related factors, include thermal device such as radiofrequency ablation, cryoablation, microwave ablation and non-thermal therapy such as brachytherapy electroporation, and external body radiotherapy with high-precision RT and percutaneous hepatic instillation.¹³⁹⁻¹⁴² For patients with extensive disease that are non resectable, locoregional therapy such as chemoembolization (transarterial chemoembolization or beads) and/or radioembolisation (selective internal radiation therapy) are other measures that can be offered.^{135,138} Unfortunately, most of these are not available in Nigeria.

Management of peritoneal metastasis

Recent advances have shown that peritoneal metastasis does not preclude cure.¹³² Factors that determine modalities of treatment in CRC with peritoneal metastasis include peritoneal cancer index (PCI), histology of the primary tumour, cytoreduction index which is determined by the amount of small bowel involved, age of the patients, Karnofsky index, comorbidities (cardiovascular, respiratory), carcinomatosis-related complications at the time of surgery (intestinal obstruction, ascites), active infections, previous systemic chemotherapy, chemoresistance, toxicity.¹⁴³⁻¹⁴⁶ The role of staging video laparoscopy as an adjunct to imaging cannot be over emphasized.¹⁴⁴ Options include cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy, cytoreduction plus early postoperative intraperitoneal chemotherapy. Cytoreductive surgery is particularly effective in patients with low-volume peritoneal disease (a PCI <12 is often suggested) and no evidence of systemic disease.¹⁴⁴⁻¹⁴⁶ Bidirectional (IV + IP) intraoperative chemotherapy can also be utilized in selected patients.

Management of lung metastasis

Colorectal cancer is the commonest cancer leading to pulmonary metastasectomy. Synchronous resectable tumour is treated with chemotherapy and resection while unresected tumour is treated with chemotherapy. The prognosis of resectable tumour is 25-35% for 5 years. Resection could be combined or staged. Surgical resection is offered if the primary tumour can be removed completely and if the anatomical resection can be performed while maintaining an adequate pulmonary function. The resection can be video assisted thoracoscopy if the tumour is less than 3cm and is peripherally located. Otherwise open thoracotomy is performed.

For unresectable tumours other forms of ablation can be used which includes stereotactic ablation, radiofrequency ablation or cryoablation. Little is known about their prognosis.

Follow up

After treatment for colorectal cancer, follow-up care is important to help maintain good health, which includes managing any side effects from treatment and watching for long-term side effects. The most important reason for follow-up care, however, is to watch for signs of recurrence. In general, hospital visit and investigation are more frequent within 5 years because 95% of recurrences are found within five years. Patients' follow-up depends on stage, perioperative treatment, whether the cancer is inherited or sporadic, and amenability for resection of recurrent disease.

Regular clinical evaluation of the patients should be done every 3 months post treatment for the first two years and then every 6 months for the next three years. Subsequently, yearly clinical evaluation should be done until the patient is 70 years or 10 years after treatment. During each clinical evaluation, carcinoembryonic antigen (CEA) and rectosigmoidoscopy

should be performed. Computerized tomography (CT) scan of Chest, Abdomen and Pelvic should be performed every year for 5 years. In the absence of this, Abdominal ultrasound and chest X ray can be performed every year. Complete colonoscopy should be recommended within six months of treatment if patients did not have colonoscopy before surgery. If one was done before surgery, colonoscopy should be repeated one year after surgery. Subsequent colonoscopy will be determined by the finding at colonoscopy. If multiple polyps were found, this should be removed. The frequency of colonoscopy should be done every 3 -5 years depending on the presence of adenomatous polyps.

Management of Hereditary CRC

A diagnosis of hereditary CRC influences clinical management of patients with CRC and their family members. A timely identification of individuals at risk for hereditary CRC syndromes offers an opportunity to an early intervention or prevention.¹⁴³⁻¹⁴⁶ The most important step leading to the diagnosis of a hereditary cancer syndrome is the compilation of a thorough family history of cancer. This could be challenging in African setting where there is under reporting of sicknesses. Despite this, a painstaking detailed history of family members and the scenario of the sequence of death of relatives can help to identify the possibility of cancer of all types and sites. Also important is the family member's age at the onset of cancer and any pattern of multiple primary cancers. Referral for genetic counselling should be mandatory for such a family.¹⁴⁸⁻¹⁵² Unfortunately, there is currently sparsity of specialists in this field in Nigeria. We suggest that the attending oncologist or surgical oncologist should fill in the gap by inviting all the first and second degree relatives for a face to face meeting with individual family member and a session may include multiple family members.¹⁵⁰ Each member should have genetic screening performed and the result of tests for mutations should be revealed to the patient on a one-to-one basis. Those with positive mutation should have personalized CRC and extra colonic cancer screening. The option of risk reduction surgical treatment for colonic and extra colonic cancer should be discussed with mutation carriers with no evidence of cancer.

In Nigeria, most of the hereditary CRC are detected after a family member present in the hospital. Only syndromes with distinguishing phenotypes, such as florid colonic adenomas in familial adenomatous polyposis, are more easily diagnosed than hereditary disorders that lack clear phenotypic characteristics. For instance, the attenuated polyposis phenotype of familial adenomatous polyposis is characterized by a paucity of colonic adenomas, and the ones that do occur are primarily in the proximal colon. Often times such index cases present at advanced or metastatic stage precluding curative treatment.¹⁵³ If the cancer is diagnosed early or at precancerous stage, extended colonic resection with ileorectal or ileoanal anastomosis is advocated especially when the patient is young. Segmental colectomy is an option in patients unsuitable for total colectomy if regular postoperative surveillance is conducted.

Though currently only few cases of hereditary CRC have been reported from Nigeria. Most of these cases are those with phenotypic changes.^{153,154} We recommend that a registry be created for such cases.

Chemoprevention

Recently, there is increase focus on the potential use of chemoprevention as a complement to, or instead of, screening in the prevention of CRC.¹⁵⁵ Chemoprevention comprises the use of drugs or natural compounds to prevent the development of benign or malignant tumours.^{155,156} Various systematic reviews have shown that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) [cyclo-oxygenase-2 (COX-2) inhibitors] reduce the risk of

developing colorectal adenomas and cancer.^{157,158} Similarly, calcium and/ or vitamin D, folic acid and some antioxidants such as selenium, vitamin C and E have also been linked to a possible decreased incidence of CRC.¹⁵⁸⁻¹⁶² This has led to the concept of using such agents for the chemoprevention of CRC. While most are yet to be recommended for routine use, due to the fact that some of their side effects outweigh their usefulness, further evidence will be needed to substantiate its use in the clinic,

Challenges in the management of CRC in Nigeria

As mentioned in various sections of the guideline, managing CRC in Nigeria is encumbered with a lot of challenges. Substantial constraints are apparent in prevention, early detection, diagnosis and treatment, and palliation of CRC. Some of the challenges are not peculiar to CRC. This is because the six key building block of good health system according to WHO such as health financing, governance, health workforce, health information, medical products and technologies, and health-service delivery are weak.¹⁶³ However, all these constraints were present as development partners accelerated efforts to respond to HIV, tuberculosis, malaria, and vaccine-preventable diseases.¹⁶⁴ These efforts witness a great level of success. Similar success can be achieved in CRC and other emerging cancers if the following suggestions are deployed:

1. Development of country-based CRC plans which should include how to generate reliable CRC statistics, and to reduce under reporting. This can be achieved by establishing a central coordinating unit made up of all stake holders in cancer management and staff from the Ministry of Health.
2. Develop collaboration and strategy to bridge the educational need which includes technical, epidemiological and public awareness. Educational campaigns regarding cancer prevention, encouraging changes in patterns of lifestyle could thus have a key role in reducing the number of CRC cases.
3. Massive investment of capital in training, infrastructural needs that include basic diagnostic services, surgical and radiotherapy facilities, and expanded palliative care
4. Investment in research into country specific cost effective cancer control model and low cost interventions which should be piloted before scaling up.
5. Develop quality metrics for cancer centers and specialists

Documents reviewed

International Guideline Developers: Scottish Intercollegiate Guidelines Network (SIGN) National Institute for Clinical Excellence (NICE) American Cancer Society (ACS) American Society of Clinical Oncology (ASCO) European Society for Medical Oncology (ESMO) Cancer Society of New Zealand American Society for Therapeutic Radiology and Oncology (ASTRO) National Guidelines Clearinghouse National Comprehensive Cancer Network (NCCN) New Zealand Cancer Control Trust The Cancer Council Australia National Cancer Control Initiative (AUS) The Collaboration for Cancer Outcomes Research and Evaluation (AUS) State Government of Victoria, Australia Peter MacCallum Cancer Centre (Australia) Medical Oncology Group of Australia Cancer UK Cancer Services Collaborative, Avon Somerset and Wiltshire (UK), NHS (UK)

Canadian provincial cancer agencies: Cancer Care Ontario (CCO) clinical practice guidelines, British Columbia Cancer Agency – Cancer management guidelines Alberta Cancer Board – Treatment Guidelines Saskatchewan Cancer Agency – Follow-up Guidelines Cancer Care Manitoba – CCM Home Cancer Care Nova Scotia - Guidelines British Columbia Cancer Agency Nova Scotia Cancer Agency

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