Colorectal Cancer

Olusegun Alatise *MBChB, FWACS*
O Lawal *MBBS, FWACS, FMCS*
A Adesunkanmi *MBBS, FWACS, FICS,FMCS*
Augustine Agbakwuru *MBBS, FWACS, FICS, FMCS*
***A Adisa**, *MBChB*
Anthony Arigbabu, *FWACS, FACS*
D Akinola , *FWACS, FACS*
Department of Surgery, Obafemi Awolowo University, Ile-Ife, Nigeria
**Senior Registrar, General Surgery Unit, OAUTHC, Ile-Ife*

INTRODUCTION

Colorectal Cancer (CRC) is a cancer that develops in the colon and the rectum. CRC represent a major public health problem accounting for over one million cases of new cancers and about half a million death worldwide[1]. It is the third most common malignant disease after lung and breast cancer and the second leading cause of cancer related death in United States and Canada[2]. The lifetime risk of developing CRC is 1 in 17, affecting men and women alike in almost equal proportion[3].

Although national or regional figures for CRC is not available, the incidence of CRC was believe to be low in sub-saharan African and Indian, however, some studies have shown a rising incidence in major Urban centres. CRC has emerged as the most common gastrointestinal tumours in Nigeria. The low incidence is used to be thought to be due to low intake of fatty food, reduced incidence of premalignant conditions and reduce life expectancy among the blacks[4]. However, recent data among African American shows CRC incidence and mortality rate are highest with incidence about 15 higher in African American men and women than white men and women, while mortality rate in African American are about 40% higher than in whites[5].

PREDISPOSING FACTORS

CRC could be sporadic or hereditary. Most cases of CRC are sporadic accounting for about 80% while the remaining are hereditary[6]. In the sporadic colorectal cancer, the risk factors implicated include older age, male sex, previous cholecystectomy, ureterocolic anastomosis and hormonal factors: nulliparity, late age at first pregnancy and early menopause. Other factors identified in sporadic CRC include, Diet rich in meat and fat, diet poor in folate and calcium, sedentary lifestyle, obesity, diabetic mellitus, smoking, previous irradiation, high alcohol intake and asbestos exposure. Previous history of CRC especially before age 60 predisposes the individual to develop metachronous tumour. Similarly, people who had one or more adenomatous polyps have an increased risk for CRC. This risk is particularly high if the polyps is a villous adenoma, sessile, multiple, or if the base of the polyps is greater than 2cm. The presence of chronic inflammatory bowel disease of significant duration (8-10years) and involving the entire bowel have an increase risk of developing CRC[5,7]

The hereditary CRC develop in the setting of defined hereditary cancer syndromes. The two main forms are hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis coli ~~(APC) gene~~[8]. Various hamartomatous polyposis syndromes are also associated with an increased risk of CRC, such as Peutz-Jeghers syndrome, Juvenile Polyposis syndrome, Cronkite - Canada syndrome, and Cowden syndrome[8, 9]. FAP is an autosomal dominant disease. In about 80% of affected individual, a germ line mutation can be identified in the adenomatous polyoposis coli (APC) gene located at chromosome 5q21[8, 9].A subset of people with FAP and attenuated FAP has bi allelic mutations of the MYH gene[10]. FAP patients can develop more than 100 colorectal adenomas (50% of patients by age 15years, 95% by age 35years); if left untreated, colorectal cancer arises in almost all patients by age 40years[11].

HNPCC is also an autosomal dominant disorder caused by germline mutations of mismatch repair genes. Tumours that arise in the setting of HNPCC typically have a molecular characteristic called microsatellite instability which helps in making the diagnosis. This instability is defined as frequent mutations in microsatellites, which are short repeated DNA sequences[12]. The penetrance of CRC in HNPCC is 70 85%. On the average, affected patients develop CRC by age 44years, tumours tend to be right sided, and have classical histological pattern which include presence of tumour infiltration, Crohn's like lymphocyte reaction, mucinous signet ring differentiation or medullary growth pattern[8,9]. Diagnosis of HNPCC is difficult because no typical phenotype features, therefore clinical criteria defining HNPCC were developed known as Amsterdam I and II criteria. (Table I).

Table 1
Bethesda guidelines
_ Colorectal cancer diagnosed in patient who is younger than 50 years

_ Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours, irrespective of age
_ Colorectal cancer with the MSI-H† histology‡ diagnosed in a patient who is younger than 60 years
_ Colorectal cancer diagnosed in one or more first degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under the age 50 years.
_ CRC diagnosed in two or more first or second degree relatives with HNPCC-related tumours, irrespective of age

Amsterdam I and II criteria

_ One individual diagnosed with colorectal cancer (or extracolonic HNPCC-associated tumours) before age 50 years
_ Two affected generations
_ Three affected relatives, one a first-degree relative of the other two
_ FAP should be excluded
_ Tumours should be verified by pathological examination.

PATHOGENESIS

Over the past two decades, intense research effort has focused on elucidating the genetic defects and molecular abnormalities associated with development of colorectal adenoma and carcinoma. Colorectal carcinogenesis is a stepwise process, through a (nonlinear) series of genetic alterations, which at a cellular level is characterized by changes from normal mucosa through early and advanced adenomas to invasive carcinoma[13]. This is referred to as the adenoma-carcinoma sequence (Figure 1). Within this model, some observed changes may be effects rather than causes of the neoplastic transformation[14].

Traditionally, colorectal carcinogenesis is explained by two pathways, the gatekeeper and the caretaker pathway[15]. The gatekeeper pathway is responsible for about 85% of sporadic colorectal cancers; and is the mechanism of carcinogenesis in patients with FAP. Gatekeepers are genes that regulate growth. One of the key steps of this pathway is mutation of the tumour suppressor gene APC. Many other tumour suppressor genes (e.g. DCC, DPC4/Smad 4, p53. nm32) and oncogenes (e.g. K-ras, c-myc, c-neu, c-erb-2, c-src) are also involved[16].

The caretaker pathway is characterized by mutations or epigenetic changes of genes that maintain genetic stability (e.g. mismatch repair genes)[8]. HNPCC is the hereditary form of this pathway; about 15% of sporadic colorectal cancers are also thought to be caused by this mechanism. Besides oncogenes and tumour suppressor genes in the gatekeeper pathway, further tumour suppressor genes such as TGF□RII, IGF2R, and BAX are mutated in the pathway[8,17].

In fact, the two pathways might not be completely separated since the Apc gene can act as a caretaker, mismatch repair genes, and can affect cell proliferation[18]. Additional pathways could exist e.g. the serrated pathway as well as distinct pathways for carcinogenesis of flat and depressed colorectal neoplasms and carcinogenesis in inflammatory bowel disease[18-19]. Epigenetic mechanisms such as change in DNA methylation, loss of imprinting, and histone acetylation, as well as modifier genes, such as the cyclooxygenase 2 gene and the peroxisome proliferators activating receptor gene also seem to be involved in the genesis of CRC[17,20]. Other genes, such as those for tyrosine phosphatases, activin type 2 receptor, phosphatidylinositol 3 kinases, and hCDC4 might also contribute to colorectal carcinogenesis[21].

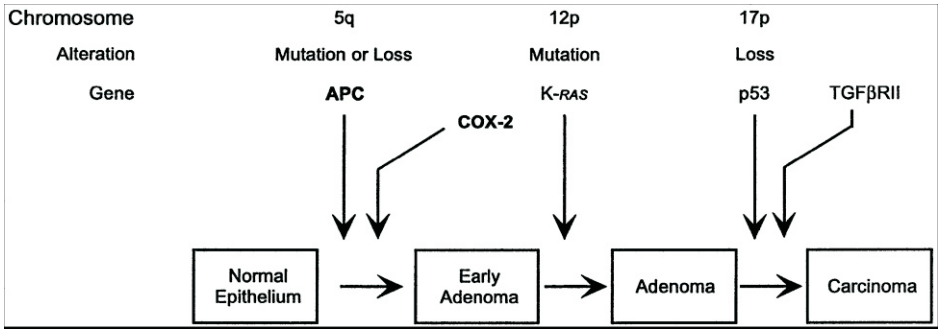
PATHOLOGY

Four macroscopic type of CRC have been described. These include proliferative or cauliflower type, malignant ulcer type, annular otherwise called the scirrhous or string stricture type and tubular or infiltrative type. The annular and tubular types are more common in the left colon and they tend to cause obstructive symptoms while the cauliflower and malignant ulcer tend to occur more on the right colon presenting with abdominal mass and anemia.

Over 80% of CRC are adenocarcinoma, while the rest being colloid or anaplastic carcinoma.DISTRIBUTION OF CRC

The prefer site CRC is the rectum and sigmoid colon accounting for over 60% of the tumour, follow by the

Figure 1



ascending colon 18%, transverse colon 9% and descending colon 5%[22].

SPREAD AND STAGING

Carcinoma of the colon and rectum spreads by direct infiltration through the bowel wall and then to adjacent organs, lymphatic, blood stream to the liver, lungs, adrenals, kidneys, bones and the brain, and transperitoneal spread to the ovaries. Various modality of staging classification are available. This includes the Dukes' Staging, Astler Coller Modification of Dukes' staging and TNM staging system (Table 2).

Table 2: **TNM staging system for colorectal cancer and published survival rates for different stages**[23]

Tprimary tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1 Tumour invades submucosa
T2 Tumour invades muscularis propria
T3 Tumour invades through the muscularis propria into subserosa
or into non-peritonealised pericolic or perirectal tissues
T4 Tumour directly invades other organs or structures and/or
perforates visceral peritoneum

Nregional lymph nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

Mdistant metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage	T	N	M	5-year survival
Stage I	T1, T2	N0	M0	80-95%
Stage IIA	T3	N0	M0	72-75%
Stage IIB	T4	N0	M0	65-66%
Stage IIIA	T1, T2	N1	M0	55-60%
Stage IIIB	T3, T4	N1	M0	35-42%
Stage IIIC	Any T	N2	M0	25-27%
Stage IV	Any T	Any N	M1	0-7%

CLINICAL PRESENTATION

Symptoms of colon and rectal cancers are nonspecific and generally develop when the cancer is locally advanced. The classic symptoms are change in bowel habits and rectal bleeding. The change in bowel habit could be change in the frequency diarrhea, constipation or alternating constipation with diarrhea, or change in caliber of stool/and consistency of stool. Tumours on the right side of the colon present with abdominal mass, weight loss, dyspepsia because of gastrocolic reflex, features of anaemia from necrosis and bleeding. Tumour on the left side of the colon present with passage of mucoid bloody stool, constipation and borborymi. Rectal tumour present with tenesmus and when it spread to involve the anal canal, it presents with anal pain, anal protrusion and incontinence of feaces. Patients may also have features of metastasis which include bone pain from bone metastasis, jaundice from liver metastasis, cough, dyspnoea and chest pain from lung metastasis, features of renal failure from obstruction of ureter by the mass or metastasis to the kidney. Few patients with CRC may present as an emergency due acute on chronic obstruction, perforation with peritonitis, paracolic abscess and acute lower gastrointestinal bleeding.[7]

INVESTIGATION

The aims of investigating the patients with CRC is to confirm the diagnoses, stage the tumour and to ancillary investigation necessary to prepare patient for surgery.

Colonoscopy is the gold standard for diagnosis of colorectal cancer; in addition to physical examination, abdominal ultrasound and chest radiography which are routinely done. Biopsy for histopathology will be taken when the lesion is identified on colonoscopy. Colonoscopy also offers opportunity to identify the presence of synchronous tumour. Barium enema is a good alternative to colonoscopy where the facility is not available. Abdominal ultrasonography can detect the presence of ascites and liver metastasis. Chest radiography will demonstrate the presence of cannon ball metastasis.

Better imaging of rectal cancer is important for planning of treatment. Local staging can be done by endorectal ultrasound, CT, or MRI[24]. Where the facility is available, high resolution MRI is a promising tool for depiction of important anatomical structures such as the mesorectal fascia[25]. Position emission tomography is valuable for detection of recurrent colorectal cancer, but has little role on staging of primary cancer.

Other ancillary investigation necessary for surgery will include complete blood count, electrolyte and urea, urinalysis and grouping and cross-matching. If patient has anaemia or electrolyte derangement, this must be corrected before surgery. Tumour markers which can help in diagnosing, screening, monitoring for recurrence, can also be assay for most tumour. Tumour markers useful in CRC are neither tumour or organ specific. They include carcino-embryomic antigen (CEA), CA 19-9 and CA 29-5.

TREATMENT

Multidisciplinary approach in the management of these patients is highly rewarding. The disciplines involved include General surgeon/Colorectal surgeon, Oncologist, Pathologist, Nursing and Psychologist. Surgery offered better outcome for the patients. The surgery offered can be for curative or palliative purposes. With excellent technique and selection of patients, excellent results can be obtained by surgery alone without radiotherapy even in lymph node positive patients[26]. The aim of curative surgery is to ensure primary resection, luminal and lympho-vascular control using the no-tourch technique popularized by Turnbull[22]. The type of surgery will depend on the stage of the disease and the site of the colon affected. Resectable tumours of the caecum and ascending colon will benefit from right hemicolectomy. The tumours of the hepatic flexure will benefit from extended right hemicolectomy, while patient with tumour in the transverse colon should have transverse colectomy. Tumours at the splenic flexure will benefit from extended left hemicolectomy, and the tumours on the descending colon should have left hemicolectomy. Tumours in the sigmoid colon will benefit from sigmoid colectomy. Anterior resection is done for patient with tumour in the distal part of sigmoid colon or upper part of rectum beyond 10cm from anal verge. Low anterior resection which is a form of sphincter saving surgery is reserved for patient with rectal tumour between 6cm to 10cm from anal verge. Below this level abdominal perineal resection will be the treatment of choice with terminal colostomy.

The concept of sphincter saving surgery aimed at reducing the morbidity associated with terminal colostomy was brought about by the finding that CRM rarely metastasis beyond 1-2cm from the macroscopic site of the tomour inferiorly[27]. Whether quality of life after sphincter saving preservation for very low tumours is better than abdomino-perineal resection is still debatable[28]. Options for reconstruction after low anterior resection include straight anastomosis, side to end anastomosis, colonic J-pouch and transverse coloplasty pouch[29-31]. The later 3 options give a better functional outcome. The reconstructions are better done using staplers.

Local rectal tumours restricted to the mucosa and submucosa can be removed by transanal endoscopic microsurgery (TEM)[32]. TEM is design for mobile, exophytic and well differentiated tomours with no lymphovascular invasion, located around 3-18cm from the dentate line. These tumours are seen in places where screening programme for CRC is well developed. Another procedure for local tumours is the posterior resection such as the transphincteric (Mason) and the transsacral (Kraske) procedure.

Metastasis to the liver and lung does not prelude curable surgery, in that this can be resected at the same siting or later. Unresectable tumours will benefit from diverting colostomy for left colonic tumours or ileotransverse anastomosis for right colonic tumours. These palliative procedures can be reverse for definitive surgery if patients' responses to adjuvant treatment at the second look surgery. Moreover, these palliative surgeries will help to relieve malignant bowel obstruction. Other modalities that can be used for patients with bowel obstruction especially when the patient cannot withstand colostomy include the use of stent, cryosurgery, laser and hyperthermia.

Other adjunctive therapies in the management of patient with CRC include chemotherapy, radiotherapy, or chemoradiotherapy[33-35]. The chemotherapeutic agent of choice for CRC is 5 fluorouracil ,which is usually combine with leucovorin. This can be given as loading dose, continuous infusion, or sequential treatment. Recently, two agents have been added with superior response in patient with CRC. These agents are Irinotecan a tropoisomerase inhibitor and oxaliplatin a third generation platinum derived chemotherapeutic agent. Combination of 5FU, leucovorin and oxaliplatin (FOLFOX) regime has been found to improve survival in patient with metastatic tumour from 6months to 14 16months[35].

Laboratory studies have identified molecular sites in tumour tissue that may serve as specific targets for treatment. The goal of such a therapeutic strategy is the interruption of cellular pathways essential for tumour growth, survival and metastasis and potentially, a reduction in toxic effects associated with less specific cytotoxic chemotherapies. Currently, two promising classes of targeted compounds have been introduced into the clinical management of advanced CRC: epidermal growth factor receptor antagonist Cetuximab and angiogenesis inhibitors Bevacizumab. Combination of Bevacizumab and FOLFOX regime has improved response of patient with metastasis tumour to over 20 months[35].

Response to the chemotherapeutic agents depends on concentration of some markers[36]. For fluorouracil based chemotherapy, intratumoral thymidylase synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase as well as microsatellite instability status can be used. Intratumoral concentration of tropoisomerase I seem to allow response prediction for Irinotecan.

PROGNOSIS

Prognosis factors can be divided into three main groups: patient, treatment and tumour related factors. Patient related factors that affect outcome include the age, presence of comorbidity and availability of fund for treatment especially in less developed countries where health insurance are not yet developed.

Outcome of patients with CRC depends on treatment. The so-called volume/outcome relation

postulates that a higher caseload and specialization results in improved outcome. Most studies show that a higher caseload and specialization are associated with better outcome. Quality of surgery and pathological work up can be assessed by the number of removed lymph nodes. Patients with more such nodes have better prognosis in most studies, which relates to a more precise staging of the patients as well as to potential therapeutic benefits of more thorough lymphadenectomy. The status of the resection margin after surgery is another important treatment related factor which in turn depends on competence of the surgeon.

The tumour related prognosis factors include the tumour grade and tumour stage. The higher the grade and stage the worst the prognosis. Some molecular marker has also detected which potentially affect prognosis. This include tumour suppressor genes and oncogenes (k-ras, c-mye, p53, DCC, smad 4, nm 23), apoptosis and cell suicide related gene (bcl 2, BAX), growth factors and growth factor receptor genes (TGF, TGF, HER 2/neu, EGRR), mismatch repair genes (MSH 2, MLH 1) and proliferation indices (ki 67, Mib 1, proliferation cell nuclear antigen) to mention but few. None of this molecular marker is of any value in clinical practice.

FOLLOW - UP

The objectives of follow up after curative resection of CRC are improvement of survival, psychological support, quality control of medical care. Colonoscopy is recommended every 3 5years to detect metachronuous CRC. Also measurement of carcinoembronic antigen (CEA) every 3 6months for up to 5years has been found to be most useful. Some has suggested regular liver and chest imaging and surveillance CT scan in combination with CEA.

SCREENING AND PREVENTION

Screening is effective in reducing mortality from colorectal cancer. Screening procedures include fecal occult blood tests, flexible sigmoidoscopy, double contrast barium enema, and colonoscopy. One of these options should be offered to asymptomatic people aged 50year or older. The ideal screening method is till controversial, with no test unequivocally better than another. Risk, costs and effectiveness need to be taken into account when discussing different options. Total colonoscopy certainty has the advantage of allowing assessment of the entire colon with the possibility of simultaneous biopsy or polypectony. These advantages have to be balance against the higher cost, risks, and inconvenience to the patients.

Recent techniques introduced into screening of patient include magnification endoscopy and chromoendoscopy increase the sensitivity of colonoscopy. Confocal laser endomiscroscopy allows invivo histology during colonoscopy with a diagnostic yield similar to conventional histology after biopsy. Other new screening modalities such as virtual colonoscopy MRI colonography, molecular stool test, and serum proteonmics are promising but are not yet ready for routine clinical use.

The most important and cheapest form of prevention of CRC is a change lifestyle. Observational studies indicate that tobacco avoidance, physical activity and weight control can reduce risk. The use of dietary interventions (e.g. increase in fibre, fruits and vegetables and reduction in fat and alcohol) offer some benefits in reducing the risk. Studies has shown a significant risk reduction for CRC for several drugs such as Aspirin, non steroidal anti-inflammatory drugs, COX 2 inhibitors, calcium, antioxidants like selenium, retinoic acid, polyamine inhibitors, polyphenials and dithiolthiones.

Surgical prevention is established for FAP and ulcerative colitis, and restorative proctocolectomy with ileoanal J-pouch is the recommended procedure for most patients.RECENT ADVANCES

Recently, several important surgical questions relevant to the management of CRC were resolved. Of probably most importance is the widespread acceptance of the technique called total mesorectal excision (TME) that was popularized by Cecil et al[37] for resection of rectal cancers. The sharp dissection of the entire intact vascular, lymphatic, and fatty tissues surrounding the rectum rather than the former technique of blunt dissection has decreased the local recurrence rate from as high as 50% in some cases to less than 10%.

CRC can be safely treated laparoscopically. term oncological results are similar to the conventional approach. Similarly, most of the traditional methods in colorectal surgery such as urinary catheters, drains, nasogastric tubes, preoperative bowel preparation, postoperative fasting, and intraoperative fluid excess can be safely omitted in what is called Fast Track Surgery (FTS). FTS reduces hospital stay, perioperative morbidity and cost[21].

The concept of sentinel lymph node mapping has been introduced into the management of patient with CRC. This concept aims to enable the pathologist to analyze more meticulously one or few lymph nodes habouring the highest risk of metastic disease. The practice of sentinel lymph node mapping is yet to be routine in clinical practice.

FUTURE TRENDS

The molecular genesis of CRC and therapies focusing on specific molecular targets attract the most attention and promise major advances. Individualized treatment according to genetic tumour profiles might become possible. Moreover, we should not forget that better screening and prevention programmes could serve many lives: public education should therefore be a top

priority. Prediction of an individual risk of CRC with individualized screening and prevention could become reality in the nearest future.

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