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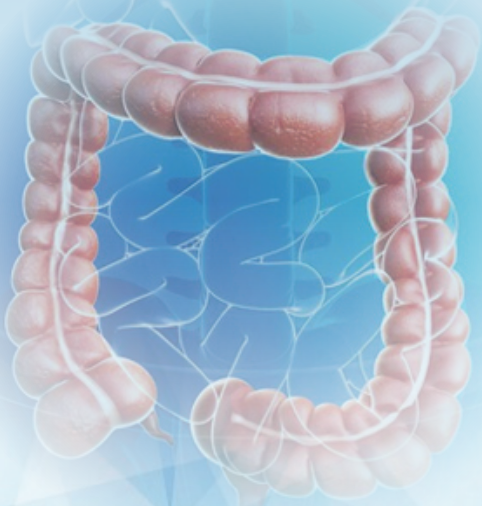

COLORECTAL CANCER HANDBOOK

VISION

The Philippine Society of Gastroenterology envisions itself as the leading organization of world-class gastroenterologists imbued with the highest level of moral and ethical values, committed to the advancement of the science and practice of Gastroenterology through research, education, and service to the Filipino people and the global community.

MISSION

The Society shall endeavor to:

1. Develop highly competent gastroenterologists through comprehensive training and CME programs. - EDUCATION

2. Produce and publish quality researches that will improve diagnosis, treatment and prevention of digestive diseases. – RESEARCH

3. Undertake advocacy programs to promote the health care needs of the communities. – ADVOCACY

4. Safeguard the interest and welfare of its members, and assist the national government in formulating health policies.

FOREWORD

This Handbook on Colorectal Cancer, made by the Civic Action Committee of the Philippine Society of Gastroenterology, is intended for use as a practical guide to general physicians, internists and gastroenterologists. It is a humble contribution to our advocacy on colon cancer awareness.

Disclaimer: Data on colon cancer contained in this handbook obtained from textbooks, journals, and international/local guidelines should not replace most up-to-date information.

The Philippine Society of Gastroenterology released for dissemination this Colorectal Cancer Handbook in January 2019.

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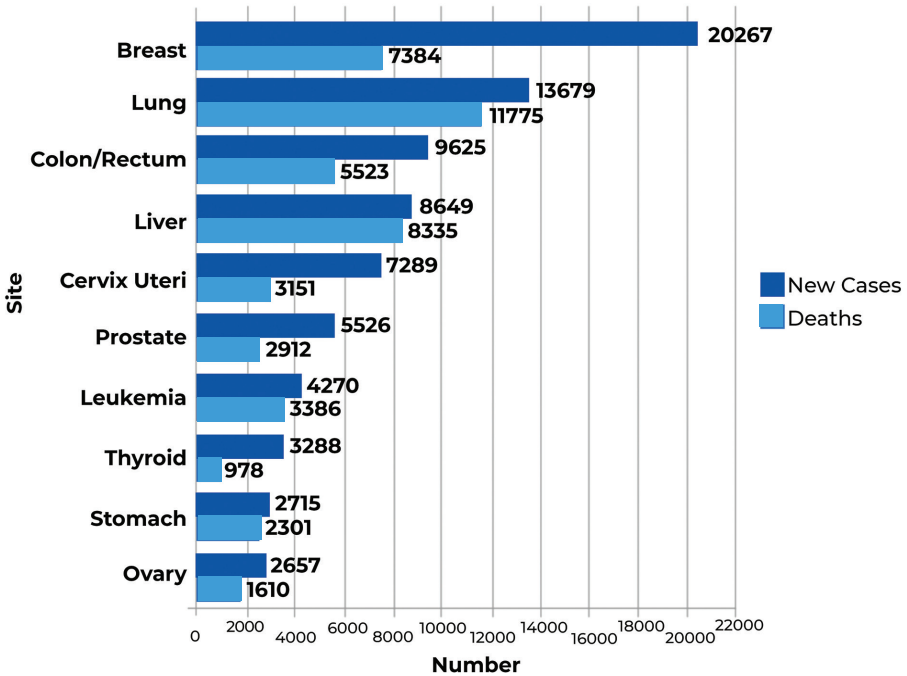
I Epidemiology

Incidence and Mortality

Cancer caused 8.8 million deaths worldwide in 2015 with Colorectal Cancer (CRC) ranking as the third most common cause of cancer deaths.[1] In the Philippines, CRC was also noted to be the third most common cancer in 2015 with 9625 new cases noted in both sexes and an estimated 5523 deaths in both sexes as shown in figure 1.[2]

Figure 1: Number of New Cases for 10 Most Common Cancers in 2015, Both Sexes, and Corresponding Number of New Deaths



Source: 2015 Philippine Cancer Facts and Estimates, www.philcancer.org.ph[2]

Risk Factors

KEY NOTES

- There are modifiable and non-modifiable risk factors for CRC.
- Ninety percent of patients diagnosed with the disease are 50 years and older.
- A previous history of CRC predisposes an individual to develop another carcinoma (metachronous carcinoma) which may occur within 5 to 7 years from the initial lesion.
- Adenomatous polyps are precursor lesions. Within a span of 10-15 years, an adenomatous polyp can progress to CRC. A previous history of adenomatous polyp increases the risk for CRC development.
- Individuals with first degree relatives who had CRC have 2-3x increased risk to develop the disease especially if it occurred at a young age or more than one relative had the disease.
- Five percent of patients with CRC can be attributed to the presence of a genetic syndrome. The 2 most common inherited conditions are: Lynch Syndrome (Hereditary Non-Polyposis Colon Cancer) and Familial Adenomatous Polyposis (FAP).
- Inflammatory Bowel Disease (IBD) is an important risk factor for the development of the disease . The longer the duration of illness and the anatomical extensiveness increase the risk to develop CRC.
- Abdominal radiation exposure of more than 30Gy for childhood malignancy increases adult risk for CRC.
- There are modifiable environmental and dietary risk factors for CRC. Some of these may increase the risk to develop CRC and others may provide some protective benefits against CRC.

There are several risk factors that can predispose patients to develop colorectal carcinoma.

Table 1: Risk Factors for Colorectal Cancer

NON-MODIFIABLE	MODIFIABLE
Age	Cigarette Smoking
Personal History	Nutritional Practices (High consumption of red meat, low consumption of fiber)
Family History/Inherited Genetic Risk	Less Physical Activities
Inflammatory Bowel Disease	High Alcohol Consumption

AGE

The risk of developing CRC increases as individuals get older. Ninety percent of patients diagnosed with CRC are 50 years and older. The average age at the time of diagnosis is 64.[3]

FAMILY HISTORY AND HEREDITARY HISTORY /INHERITED GENETIC RISK

Individuals with first degree relatives who had CRC are at 2-3x increased risk of developing the disease compared with people with no family history. The risk further increases if the CRC was acquired at a young age and more than one relative are afflicted with the disease.[4]

About 5% of patients with CRC have a genetic syndrome that causes the disease. The most common inherited conditions are: Hereditary Non-Polyposis Colorectal Cancer (HNPCC), also known as Lynch Syndrome, and Familial Adenomatous Polyposis (FAP).

HNPCC is inherited as an autosomal dominant trait and triggered by a mutation in one of the several DNA mismatch repair genes. MSH2 and MLH1 genes constitute for most of the mutations seen in HNPCC.[3,5] Patients with Lynch Syndrome can have colonic adenomas more frequently than the general population, however, colonic polyposis rarely occur.[6] Individuals with this syndrome are at increased risk of developing various types of cancers such as endometrial, ovarian, stomach and CRC. The average age at diagnosis is mid 40's with lesions more commonly occurring at the proximal colon.[3]

FAP accounts for 1% to 2% of patients with CRC.[3] FAP is caused by a germline mutation in the APC gene, a tumor suppressor gene. It is an inherited autosomal dominant trait and characterized by the development of hundreds to thousands of colonic adenomas which can commence early during adolescence and progress to CRC if untreated. The average age of diagnosis of CRC in patients with untreated FAP is 39 years old; 7% would develop CRC by age 21 and 95% by age 50.[6]

PERSONAL HISTORY OF COLON CARCINOMA

An individual with a previous history of CRC is at increase risk to have a second carcinoma (synchronous carcinoma) or can subsequently develop another carcinoma (metachronous carcinoma). Majority of patients with synchronous lesions will usually present with one lesion located at the proximal colon and the other lesion located at the distal colon. Several studies showed that 50% of metachronous

cancer can develop within 5 to 7 years from the initial lesion.[4]

PERSONAL HISTORY OF ADENOMATOUS POLYP

Adenomatous polyps are known to be precursor lesions of CRC. A patient with a previous history of adenomatous polyp is at increased risk. The natural history of CRC starts from an adenomatous polyp and progresses to carcinoma in a multi-step process in a span of 10-15 years. [7] The potential to progress to CRC depends on the degree of villous component in adenomatous polyps, polyp size and number of adenomatous polyps. In a Korean study among asymptomatic individuals, polyp size ≥1 cm and number of adenomas (≥3) are considered high-risk adenomas and are independent predictors of advanced neoplasia recurrence.[8] Adenomatous polyps have three histologic variants: tubular, tubulovillous, and villous adenomas. 75% to 85% of adenomatous polyps are tubular adenomas with < 5% chance of
malignancy. Tubulovillous adenomas constitute 10% to 15% of polyps with 20% to 25% chance of malignancy. While 5% to 10% are villous adenomas with 35% to 40% chance of malignancy.[3]

INFLAMMATORY BOWEL DISEASE (IBD)

Inflammatory Bowel Disease is one of the most important risk factors for the development of CRC. In patients with IBD, the longer the duration of the illness and the anatomical extensiveness of the disease predispose the patients to increased risk of developing CRC. The meta-analysis done by Eaden et al that included 116 studies showed the cumulative risk of CRC in patients with left-sided lesions or pancolitis was estimated at 1.6% in 10 years, 8.3% at 20 years, and 18% at 30 years after disease occurrence.[9] Pancolitis in Ulcerative Colitis confers 5-15% increase in risk compared to the general population, 8-10 years after initial diagnosis. Left-sided disease increases risk three-fold, while proctitis or proctosigmoiditis has no significant increase in risk. Data on CRC risk in Crohn's disease is less established. However, surveillance is recommended when 1/3 of the colon mucosa is involved.[10]

In recent years, there have been studies that showed a decreasing trend for the development of CRC in patients with IBD. This may be secondary to improvement in the management of IBD and screening methods to detect premalignant lesions.[11-14]

OTHERS

Abdominal radiation exposure of more than 30Gy for childhood malignancy increases adult risk for CRC. Thus, colorectal cancer screening and surveillance are recommended every 5 years,

starting 10 years after radiation treatment or at 35 years old, whichever comes first. Likewise, radiation for prostate and cervical cancer increase the risk for rectal cancer. The hazard ratios (HR) as baseline risk for CRC among men with prostate cancer are low (HR 1.14 and HR 1.36, for all CRC and for rectal cancer, respectively). However, the CRC risk doubles for men with prostate cancer who received radiation (HR 2.06; 95% CI, 1.42-2.99).[15,16] Diabetes mellitus (DM) is a chronic disease that is increasing in incidence in the Philippines and is an independent risk factor for colon and rectal cancer.[17] In a meta-analysis of 14 observational studies, analysis showed diabetes was associated with 38% higher risk of colon cancer (RR 1.38, 95% CI 1.26-1.51; n=14 studies) and 20% higher risk of rectal cancer (RR 1.20, 95% CI 1.09-1.31; n=12 studies), while controlling for the effects of smoking, obesity and physical exercise.[17] A growing body of literature indicates that alteration in the normal microbial flora on the large intestine may be etiologic for CRC. Factors such as antibiotic use and other host factors that modify the luminal microbe environment can contribute to CRC development.[18]

ENVIRONMENTAL RISK FACTORS

High consumption of red and processed meat shows strong evidence of increased risk.

There are modifiable environmental and dietary risk factors for CRC. High consumption of red and/or processed meat shows strong evidence of increased risk.[19] Probable underlying mechanism for the association between red meat and CRC includes cooking meat in high temperatures that may produce heterocyclic amines and polycyclic aromatic hydrocarbons which are deduced to have carcinogenic properties.[19,20]

The World Health Organization's International Agency for Research on Cancer (WHO-IARC) reviewed the evidence in 2015. Twelve of 18 cohort studies and 6 out of 9 case control studies found an association for consumption of processed meat and CRC. Seven of 14 cohort studies and 7 of 15 case control studies found a positive association for red meat consumption and CRC.[21]

CRC survivors are strongly encouraged to QUIT SMOKING

Cigarette smoking is a risk factor for essentially all types of colonic polyps. For adenomatous polyps, the risk is highest for more advanced adenomas and serrated colonic polyps. The risk association was stronger for cancer of the rectum than the colon.[22] Smoking may increase the risk in patients with Lynch syndrome. It is

recommended that CRC survivors should be strongly encouraged to quit smoking.

Consumption of >3 alcoholic beverages/day is associated with a 1.4 fold risk of CRC

High alcohol consumption increases risk for CRC. Consumption of more than 3 alcoholic beverages per day is associated with a 1.4-fold risk. The elevated risk may be related to interference of folate absorption by alcohol and decrease in folate intake. Risk is higher for Asian population with relatively high prevalence of the slow-metabolizing aldehyde dehydrogenase variant. In a Japanese study on alcohol and CRC involving 2,231,010 person-years of follow-up (from 1988 to 2004), 2,802 colorectal cancer cases are identified with RR of 1.42 (alcohol consumption of 23-46g/day) to 2.96 (alcohol consumption of ≥92g/day). The positive association is for men and women. One fourth of cases in men were attributable to an alcohol intake of > 23 g/day.[23]

Table 2: Diet, Nutrition, Physical Activity and Colorectal Cancer 2017

2017	DIET, NUTRITION, PHYSICAL ACTIVITY, AND COLORECTAL CANCER 2017		
		DECREASES RISK	INCREASES RISK
STRONG EVIDENCE	Convincing	Physical Activity [1,2]	Processed meat[3] Alcoholic drinks[4] Body fatness[5] Adult attained height[6]
	Probable	Wholegrain Foods containing dietary fibre[7] Dairy products[8] Calcium supplements[9]	Red meat[10]
LIMITED EVIDENCE	Limited-suggestive	Foods containing vitamin C[11] Fish Vitamin D[12] Multivitamin supplements[13]	Low intakes of non-starchy vegetables[14] Low intakes of fruits Foods containing haem iron[15]
	Limited-no conclusion	Cereals (grains) and their products; potatoes; animals fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrates; total fat; starch; glycaemic load; glycaemic index; folate;vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine beta- carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern	
STRONG EVIDENCE	Substantial effect on risk unlikely		

Source: Colorectal Cancer Report 2017, www.aicr.org[24]

1 Physical activity of all types: occupational, household, transport and recreational
2 The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.
3 The term 'processed meat', refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
4 Based on evidence for alcohol intakes above approximately 30 grams per day (about two drinks a day).
5 Body fatness marked by body mass index (BMI), waist circumference or waist-hip ratio.
6 Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional growth factors affecting growth during the period from preconception to completion of linear growth.
7 Includes both foods naturally containing the constituent and foods that have the constituent added. Dietary fibre is contained in plant foods.
8 Includes evidence from total dairy, milk, cheese and dietary calcium intakes
9 The evidence is derived from supplements at a dose of 200- 1,000 mg per day.

10 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
11 The Panel judges that the evidence for colon cancer is limited. No conclusion was drawn for rectal cancer.
12 Includes evidence from foods containing vitamin D, serum vitamin D, and supplemental vitamin D.
13 Definitions and categorisation of multivitamin supplements are not standardised.
14 Increased risk observed at low intakes (below 100 grams per day).
15 Foods include red and processed meat, fish and poultry.

For every 10g/ day increase in dietary fiber consumption, there was a significant reduction in the risk of colorectal cancer by 10%

There are environmental and dietary factors that may be protective against CRC. These include physical activity, diet, intake of fiber, folic/folate and Vitamin B6 supplementation, calcium and dairy, vitamin D and magnesium, garlic, and fish consumption. An inverse relationship has been reported between physical activity and risk for colon adenomas and CRC, especially in men. While moderate activity on a regular basis lowers the risk of CRC, vigorous activity may have an even greater benefit. Obesity is associated with elevated risk of CRC in both men and women. However, analysis of large epidemiological studies and randomized trials showed inconsistent to modest benefit, at best.[25] A meta-analysis funded by the World Cancer Research Fund found that for every 10 g/day increase in dietary fiber consumption, there was a significant reduction in the risk of colorectal cancer by 10%. Comparing unprocessed wheat bran to processed fiber showed that fiber from whole grains was associated with protection from CRC, while fruit, vegetable and legume-based fiber did not show protection.[26] A randomized, double-blind, placebo-controlled trial involving postmenopausal women, showed that there was no significant difference in the incidence of invasive CRC among women given calcium and vitamin D vs. those given placebo (HR 1.08; 95% CI 0.86 to 1.34; p = 0.5).[27] The role of folic and folate supplementation in the prevention of colorectal cancer is unclear.[28] Vitamin B6 supplementation has modest protective effect based on the meta-analysis of prospective studies, which showed pooled relative risk (RR) of colorectal cancer was 0.90 (95% CI 0.75-1.07) to 0.80 (95% CI 0.69-0.92). The risk of colorectal cancer decreased by 49% for every 100-pmol/mL increase (approximately 2 SDs) in blood pyridoxal 5' phosphate (PLP-active form of vitamin B6) levels (RR, 0.51; 95% CI, 0.38-0.69).[29] In a meta-analysis on the benefit of fish consumption, results showed that fish consumption was inversely associated with development of colorectal cancer. Two grams daily

of eicosapentaenoic acid (EPA) reduce the number of adenomas by a net change of 22.4% compared to placebo, and improve the global polyp burden, in familial adenomatous polyposis.[30]

Studies on statins and bisphosphonates as protective agents, showed conflicting results. Use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), particularly sulindac and celecoxib, have shown protection against CRC in the proximal colon. Regular use of aspirin and other NSAIDs showed 20 to 40 percent reduction in the risk of colonic adenomas and colorectal cancer in individuals at average risk. Proposed mechanism is the increased apoptosis and impairment of tumor cell growth by inhibition of cyclooxygenase-2. [31]

SUMMARY

CRC incidence is increasing. It remains one of the most common cancers and cause of death worldwide and in the Philippines. Established risk factors, such as hereditary syndromes, personal history of colon cancer and adenomas, age, IBD, abdominal radiation, all influence screening recommendations. There is sufficient evidence to classify processed meats (sausages, bacon, ham, beef jerky, corned beef, and other smoked, salted, fermented, or cured meats) as group 1 carcinogens. There are also possible protective environmental/dietary factors that may modify an individual's risk of developing the disease, such as fish consumption and high fiber intake. However, due to inconsistent results of the role of these protective factors, they have not changed the current screening and treatment recommendations for colorectal cancer.

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II Biology and Pathology

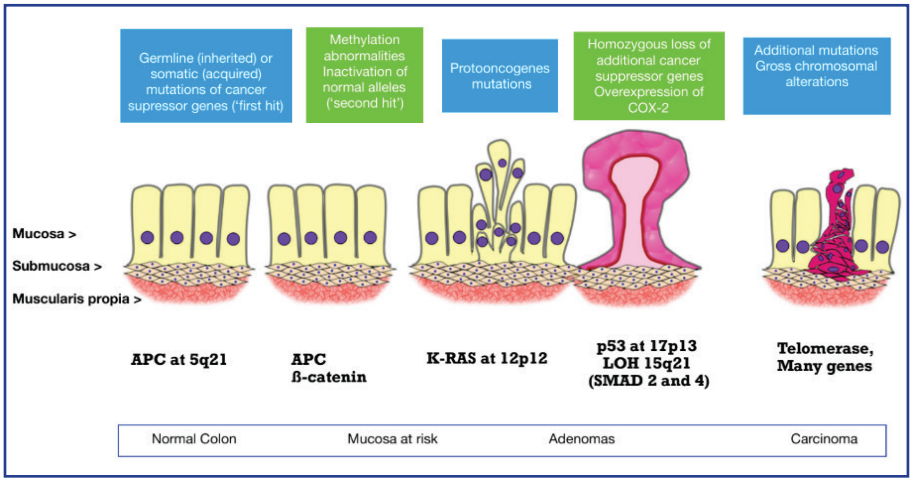
Pathogenesis of the Disease

Colorectal cancers arise from dysplastic adenomatous polyps in the majority of cases.[1] The development of CRC has been viewed as an ordered process in which three main phases can be identified: initiation, promotion and progression.[2] There is definite proof that stable alterations of the structure or sequence of DNA (mutations) represent the initiating event. These are followed by an uncontrolled expansion of the neoplastic clones which characterizes tumoral growth[2]. Several classes of genes have been identified (oncogenes, tumor suppressor genes and "mutator" genes) the alterations of which are important in the initiation as well as in the promotion and progression of tumors. CRC, therefore, results from a series of genetic changes which lead to the progressive and irreversible loss of normal control of cell growth and differentiation.[2]

Genetic changes that lead to the development of CRC traditionally have been categorized into 3 major classes: alterations in proto-oncogenes, loss of tumor suppressor gene activity, and abnormalities in genes involved in DNA mismatch repair (MMR).[3] Somatic mutations of the APC gene occur in 60% to 80% of sporadic CRCs and adenomas, including the smallest dysplastic lesions. Inactivation of the gene appears to be the gatekeeping event for the initiation of CRC.[3] Chromosomal instability, microsatellite instability and CpG island methylator phenotype pathways are responsible for genetic instability in CRC. Chromosomal instability pathway consists of activation of proto-oncogenes (KRAS) and inactivation of at least three tumor suppression genes, namely loss of APC, p53 and loss of heterozogosity of long arm of chromosome 18.[4]

Figure 1: Proposed sequence of molecular genetic events in the evolution of colon cancer

(from Sleisenger, M., Feldman, M., Friedman, L. and Brandt, L. (2015). Sleisenger and Fordtran's gastrointestinal and liver disease. Philadelphia, PA: Saunders/Elsevier.)



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Colorectal Cancer Staging

Once colon or rectal cancer has been diagnosed, several test are done to determine the size of the cancer tumour, its position and whether it has spread. This process is known as staging. Cancer staging is important in determining the optimal treatment for each patient.

One of the most commonly used staging systems is the American Joint Committee on Cancer (AJCC) TNM system. TNM classification for colorectal cancer classifies the extent of the primary tumor (T), the status of regional lymph nodes (N), and the presence or absence of distant metastases (M).

The extent of the primary tumor (T) is determined by the depth of penetration of the tumor into the layers bowel wall and if it has spread to an adjacent or nearby organ. The presence of lymph nodes (N) near the colon and rectum are called regional lymph nodes. All others are distant lymph nodes that are found in other parts of the body. Metastases (M) refer to spread of the cancer cells to other distant organs.

Colon cancer has 5 stages: stage 0 and stages I through IV. Stage 0 is the earliest stage. This stage is also known as carcinoma in situ or intramucosal carcinoma (Tis). The tumor has not grown beyond the inner layer (mucosa) of the colon or rectum. In Stage 1 the cancer has grown through the muscularis mucosa into the submucosa (T1), and it may also have grown into the muscularis propria (T2). It has not spread to nearby lymph nodes (N0) or to distant sites (M0). In Stage 2 the cancer has either grown into the outermost layers of the colon or rectum but has not gone through them (T3) or has grown through the wall of the colon or rectum but has not grown into other nearby tissues or organs (T4a) or the cancer has grown through the wall of the colon or rectum and is attached to or has grown into other nearby tissues or organs (T4b). In stage 2 there is no spread to lymph nodes (N0) or to distant sites (M0). In Stage 3 cancer the tumor has penetrated into the submucosa or the deeper layers of the bowel wall with the presence of one or more regional lymph nodes. Stage 4 is the penetration of the tumor into any layer of the bowel wall with or without regional lymph nodes but with tumors in one or more distant sites or organs or in the peritnoneum.

In 1929, Cuthbert Dukes proposed a staging classification for cancers of the rectum and colon; it has since been modified many times to increase its prognostic value.[1]

The American Joint Committee on Cancer (AJCC) introduced the TNM classification for colorectal cancer which classifies the extent of the primary tumor (T), the status of regional lymph nodes (N), and the presence or absence of distant metastases (M).

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or or intramucosal carcinoma (involvement of lamina propria with no extension through the muscularis mucosa)
T1	Tumor invades submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor 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 (tumor in lymph nodes measuring ≥0.2 mm) or any number of tumor deposits are present and all identifiable nodes are negative
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized, pericolic, or perirectal/mesorectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more 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 by imaging or other studies, no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis
M1a	Metastasis confined to 1 organ or site (eg, liver, lung, ovary, nonregional node) without peritoneal metastasis
M1b	Metastasis to two or more sites or organs without peritoneal metastasis
M1c	Metastasis to the peritoneal surface alone or with other site or organ metastases

Anatomic Stage				
Stage	T	N	M	Dukes
0	Tis	N0	M0	--
I	T1	N0	M0	A
	T2	N0	M0	A
IIA	T3	N0	M0	B
IIB	T4a	N0	M0	B
IIC	T4b	N0	M0	B
IIIA	T1-T2	N1/N1c	M0	C
	T1	N2a	M0	C
IIIB	T3-T4a	N1/N1c	M0	C
	T2-T3	N2a M0	M0	C
	T1-T2	N2b	M0	C
IIIC	T4a	N2a	M0	C
	T3-T4a	N2b	M0	C
	T4b	N1-N2	M0	C
IVA	Any T	Any N	M1a	--
IVB IVC	Any T Any T	Any N Any T	M1b M1c	--

Prognosis by Stage

Rectal Cancer

In Asia, the overall cure rate of colorectal cancer has not improved dramatically in the last decade, the overall 5-year survival rate is approximately 60%3. Colorectal cancer survival time has increased in recent years, but mortality rate remains high. It seems that among the prognostic factors explored so far, the most important are those that relate to early diagnosis3.

The numbers below come from the National Cancer Institute's SEER database, looking at people diagnosed with colon cancer between 2004 and 2010.

The 5-year relative survival rate for people with stage I colon cancer is about 92%. Stage IIA colon cancer around 87%. For stage IIB cancer, 65%. Stage IIIA colon cancers is about 90%. For stage IIIB cancers the survival rate is about 72%, and for stage IIIC cancers the survival rate is about 53%. Metastatic, or stage IV colon cancers, have a 5-year relative survival rate of about 12%.

For rectal cancers the 5-year relative survival rate for people with stage I rectal cancer is about 88%. Stage IIA rectal cancer about 81%, stage IIB cancer 50% and stage IIIA rectal cancers is about 83%. Survival rate for stage IIIB around 72%, and for stage IIIC cancers the survival rate is about 58%. Rectal cancers that have spread to other parts of the body are often harder to treat and tend to have a poorer outlook. Metastatic, or stage IV rectal cancers, have a 5-year relative survival rate of about 13%.

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III Clinical Features

Symptoms

KEY NOTES

• Symptoms of CRC may be minimal or non-existent during the early stages of the disease

• Regular screening tests are recommended to help prevent the disease.

• Warning signs and symptoms of CRC include:
- Altered stool habits (alteration of constipation and diarrhea)
- Rectal bleeding or presence of blood in the stool
- Abdominal discomfort (cramps or gas pain)
- Unexplained weight loss
- Anemia
- Body weakness and fatigue
- Abdominal distension or abdominal bloatedness
- Decrease caliber of stools or narrow stools

• 60% of cancers arise in the descending colon and rectosigmoid, but there has been a shift towards right-sided tumors (cecum, ascending colon) and transverse colon during the past few decades.

Colon cancer does not develop in a few weeks. It takes months, sometimes years, to grow. Most cases of colon cancer begin as small polyps. Over time some of these polyps can become cancerous. Symptoms may be minimal or non-existent during the early stages of the disease. For this reason, guidelines recommend regular screening tests to help prevent the disease by removing polyps before they progress into cancer.

The following signs and symptoms can occur with CRC:

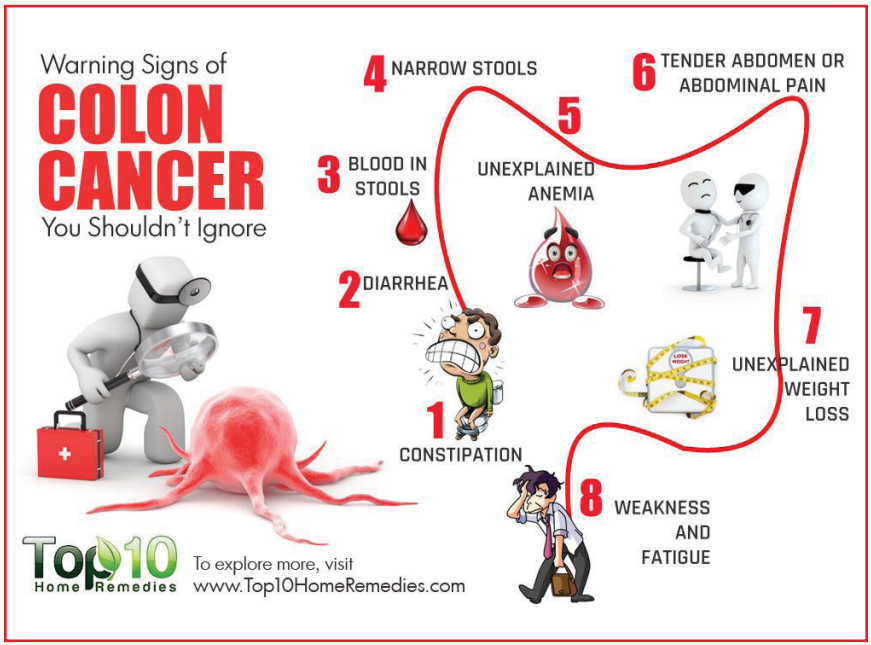
• **Altered stool habits**

Regular bowel movement may be changed initially to constipation, goat stool-like stools, or difficult passage of stools. Later on, with more advanced disease, bowel movement may be characterized by alternating constipation and diarrhea, or purely liquid, low volume, frequent stools.

In the left side of the colon where the lumen is narrow, and the stools are more formed, changes in bowel habits are exhibited earlier than right-sided malignancies.
Ribbon-shaped stools are seen more in cancers low in the rectum.

- **Rectal bleeding or blood in the stools**
- **Abdominal discomfort**, including cramps and gas pains
- **Bloatedness** or noticeable **abdominal distention**
  Abdominal distention happens when there is moderate to high grade obstruction produced by the tumor.
- **For large masses**, or for thin individuals, a **palpable mass** in the abdomen may be appreciated
- **Body weakness** or **fatigue**
- **Unexplained iron-deficiency anemia**
  In right-sided lesions, anemia may be the initial manifestation, even before changes in bowel patterns occur. This usually manifest as iron-deficiency anemia.
- **Loss of appetite and weight loss**
  Weight loss is usually associated with more advanced malignancy.

The symptomatology mentioned above may also be seen in other colonic pathologies. Therefore, if there is suspicion of malignancy, immediate diagnostic testing should be done.



Source: www. Top10HomeRemedies.com
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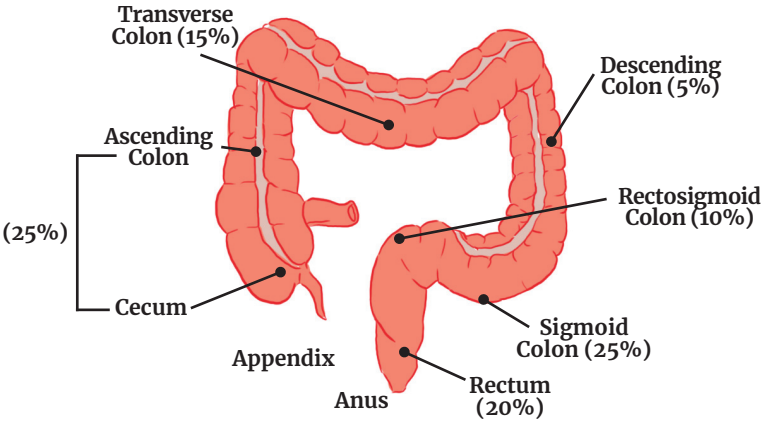
About 60% of cancers arise in the descending colon and rectosigmoid, but there has been a shift towards right-sided tumors (cecum, ascending colon) and transverse colon during the past few decades.

Location of Colorectal cancers at diagnosis



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IV Screening and Diagnosis

Diagnostic approach to symptomatic patients

Colon cancer may be suspected from one or more of the signs and symptoms previously discussed, or may be asymptomatic and discovered by routine screening through tests such as colonoscopy or fecal occult blood testing.

There are no symptoms in the majority of patients with early stage colon cancer. Although screening procedures have led to diagnosis during the asymptomatic period, most cases are diagnosed after the onset of symptoms. Clinical manifestations include rectal bleeding, change in bowel habits, abdominal pain and unexplained anemia. These are related to growth of the tumor into the lumen or adjacent structures. As a result, symptomatic presentation is usually associated with relatively more advanced disease.

Once colon cancer is suspected, various tests can be done to confirm and establish the diagnosis. Colonoscopy is considered the most accurate diagnostic test. It has the advantage of localizing the lesion and getting a tissue biopsy, detect synchronous neoplasms and remove polyps.

In situations where colonoscopy cannot be done, radiologic evaluation such as CT colonography or "virtual colonoscopy" may be considered as an option. Air-contrast barium enema in conjunction with flexible sigmoidoscopy used to be done in the past but due to its low sensitivity made it less utilized as diagnostic option.

Principles of Screening

Colorectal Cancer screening is a type of ***secondary prevention*** to identify existing preneoplastic and early neoplastic lesions and to treat them thoroughly and expeditiously. The assumption is that early detection improves prognosis.[1]

The prolonged natural history of CRC affords time to detect and eliminate early neoplastic lesions before they reach an advanced, incurable stage.

Various studies and guidelines group screening tests into:[2-3]

1. those that primarily detect cancer - annual fecalysis with occult blood (FOBT) including those that are guaiac-based or immunochemical tests, and stool DNA tests
2. those that can detect early cancer and adenomatous polyps - flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, double contrast barium enema (DCBE) every 5 years, or CT colonography (CTC) every 5 years.[2-3,22]

The joint Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endoscopy (PSDE) consensus guideline on the management of colorectal carcinoma of 2017 recommends FOBT preferably Fecal Immunochemical Testing (FIT), flexible sigmoidoscopy and colonoscopy as screening examinations for CRC and discourages the use of stool DNA, DCBE and CTC due to its costs, lower sensitivity and practical applicability in detecting CRC and pre-cancerous lesions.[2]

Although most physicians agree in principle with guidelines for screening, many do not follow them for all patients. Reluctance to perform what is perceived as an uncomfortable and invasive procedure in asymptomatic persons, requirements for training, and limitations of time and resources contribute to reluctance on the part of primary care physicians.[2]

FECAL OCCULT BLOOD TEST (FOBT)

Annual fecal based occult blood testing (FOBT), preferably fecal immunochemical testing (FIT), is the recommended first line screening test for CRC in average risk individuals 50 years old and above.

FOBT is known to detect cancer more than adenomas. It is a non-invasive and simple test that needs to be repeated annually or at least every two years to increase its sensitivity and specificity. FOBT is further differentiated as gFOBT (guaiac-based fecal occult blood test) or iFOBT/ FIT (fecal immunochemical test). iFOBT/FIT does not need the dietary restrictions imposed by gFOBT thus, improving patient compliance. It is also better than gFOBT in detecting adenomas.[4-11]

Annual FIT is universally accepted as the first line CRC screening tool including the 2017 Philippine Joint Consensus Guidelines.

FLEXIBLE SIGMOIDOSCOPY (FS) AND COLONOSCOPY

Significant reduction in CRC incidence and mortality has been reported using flexible sigmoidoscopy (FS) as screening tool. Studies suggested FS in asymptomatic average-risk persons might detect early-stage cancers, and that detection and removal of adenomas could result in a lower than expected frequency of rectosigmoid cancers in the screened population.[12-16]

Colonoscopy is the gold standard for detecting and treating colonic neoplasms. However,it is an invasive procedure, relatively expensive and requires availability of well-trained endoscopists. In resource-limited countries like the Philippines, colonoscopy may not be feasible as a population-based screening test. However, when there is a positive finding with other modalities such as FS, DCBE, FOBT, CTC, stool DNA (sDNA is not yet available locally), and capsule endoscopy (CE), colonoscopy provides that enviable opportunity for a non-operative removal of adenomas and/or early CRC.[17-19]

DOUBLE CONTRAST BARIUM ENEMA (DCBE)

DCBE is recognized as an option in various screening guidelines. Several studies have indicated that the sensitivity of DCBE is far less than that of colonoscopy, especially for detecting lesions smaller than 1 cm.[1-20]

CT COLONOGRAPHY (CTC)

CTC or virtual colonoscopy, uses helical CT to generate high-resolution, 2-dimensional images of the abdomen and pelvis. Three-dimensional images of the colon can be reconstructed by computer generation offline and has the potential advantage of being a rapid and safe method of providing full structural evaluation of the entire colon.[1]

CAPSULE ENDOSCOPY

Capsule endoscopy employs an ingested capsule that allows imaging of the colon without the need for sedation or gas insufflation although a bowel preparation is required. There is a lack of specific studies based in the screening setting.[1]

MR COLONOGRAPHY

MR colonography is a radiation-free, IV contrast-enhanced examination of the abdomen with high resolution. There are limited studies, to date, that have examined this modality for CRC screening, but recent data indicate that this modality can detect colorectal adenomas 6 mm or larger and advanced neoplasia with high levels of sensitivity and specificity, albeit with lower levels of sensitivity than colonoscopy.[1]

PLASMA AND SERUM BASED TUMOR MARKERS

CEA may be useful in the preoperative staging and postoperative follow-up of patients with colon cancer, but it has a low predictive value for diagnosis in asymptomatic patients. The relatively low sensitivity and specificity of CEA combine to make it unsuitable for screening large asymptomatic populations.[1]

FECAL DNA AND GENETIC TESTING

A molecular approach to CRC screening is attractive because it targets biological changes that are fundamental to the neoplastic process.

The fecal DNA panel consists of 21 mutations: 3 in theK-ras gene, 10 in the APC gene, 8 in the TP53 gene, the MSI marker BAT-26, and a marker of long DNA thought to reflect disordered apoptosis of cancer cells sloughed into the colonic lumen. Presently this test is not available in the Philippines.

Table 1: Advantages and disadvantages of different tests to detect and treat premalignant colonic lesions:

Tests	Advantages	Limitations
Double contrast Barium enema	Non-invasive, almost always evaluates the entire colon, useful when colonoscopy is incomplete	Lack of RCTs to reduce incidence or mortality from CRC in average risk adults, requires bowel preparation, expertise, exposure to radiation, no opportunity for polypectomy, findings of polyp >6mm requires colonoscopy; perforation rate: 1 in 25,000
CT colonography	Less invasive, high sensitivity for the detection of lesions >10mm	No evidence of reduction in CRC incidence, requires bowel preparation, special resources and expertise, treatment of patients with <6mm polyps uncertain, detection of flat polyp uncertain, repeat testing unknown
Flexible sigmoidoscopy	Office-based, sedation not necessary, pre-malignant colonic lesions can be removed, case control studies showed 60% reduction in mortality from distal colon cancers	Does not detect proximal lesions, less effective in elderly and in women, sensitivity and specificity in clinical practice unknown
Colonoscopy	90% sensitivity for lesions >10mm, case-control studies show a 53-72% reduction in incidence of CRC and 31% reduction in mortality, premalignant colonic lesions can be removed and is the recommended test to evaluate the colon when other screening tests show positive result	Lack of RCTs showing reduced incidence or mortality from colorectal carcinoma. Requires bowel preparation, special resources and expertise, Expensive, invasive, 3-5 adverse events per 1000 examinations and sensitivity and specificity in clinical practice unknown

Source: Sollano JD, et al The Joint Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endoscopy (PSDE) Consensus Guidelines on the Management of Colorectal Carcinoma. PJIM 2017[2]
(Published with persmission from source)

CAPSULE ENDOSCOPY

Approach to Screening

Screening and case-finding approaches are different for patients in average-risk and high-risk groups.

Table 2: Categories of colorectal cancer risk groups

Average-risk Group	High-risk Group
• More than 50 years old • No personal or family history of colorectal adenoma or CRC • No personal history of IBD	• Familial colon cancer • Long-standing Ulcerative Colitis • Previous CRC • Previous adenomas • Female genital cancer • Familial polyposis • HNPCC

Screening for CRC should start at 50 y/o for average-risk and earlier for high-risk individuals.

However, recent studies showed the neoplasia detection rate was 8% percent higher in people aged between 45-49 than it was between 50-54, leading to calls for CRC screening programmes to begin at 45 years of age.[21]

AVERAGE RISK GROUP

Patients 50 years old and older with no personal or family history of colorectal adenoma or CRC and no personal history of IBD are classified as average risk individuals.[17]

FOBT preferably FIT annually, flexible sigmoidoscopy every 5 years and colonoscopy every 10 years are the recommended screening examinations for CRC.

FOBT preferably FIT annually, flexible sigmoidoscopy every 5 years and colonoscopy every 10 years are the recommended screening tests.[2]

Colonoscopy should be performed for patients who have positive findings on sigmoidoscopy, FOBT, CTC, or DCBE.

A diagnostic evaluation is indicated for persons with a positive FOBT or distal neoplasm (adenoma, carcinoma) found at sigmoidoscopy. Colonoscopy is the diagnostic modality of choice. If colonoscopy is unavailable, not feasible, or not desired by the patient, CT colonography is an acceptable alternative to evaluate a positive FOBT result.[20]

HIGH RISK GROUP

The approach to patients with a suggestive family history (e.g., 1 first-degree relative with colon cancer) is not firmly established, but existing data suggest that these patients should be monitored more rigorously than average-risk persons.

It is recommended that if CRC or adenomatous polyps occurred in any first- degree relative before age 60 years, or in 2 or more first-degree relatives at any age, then colonoscopy should be performed every 5 years, beginning at age 40 years or beginning 10 years before the youngest case in the immediate family.

PRIOR ADENOMA OR COLON CANCER

These guidelines suggest that those whose index lesion consists of 1 or 2 small tubular adenomas with low- grade dysplasia should have a follow-up colonoscopy 5 to 10 years after the initial polypectomy. The precise timing within this interval should be based on clinical factors such as prior findings, family history, and patient and physician preferences.[3,22]

In patients with a large (>1 cm) adenoma, multiple (3 to 10) adenomas, or adenomas with high-grade dysplasia or villous change, colonoscopy should be repeated within 3 years of the initial polypectomy. If repeat examination is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years. Patients with more than 10 adenomas on a single examination should have a follow-up colonoscopy less than 3 years after the initial polypectomy, and the existence of an underlying familial syndrome should be considered.

Surveillance is recommended after resection of colorectal cancer.

Colonoscopy should be performed 1 year after surgery.

If the examination performed at 1 year is normal, then the next colonoscopy should be done 3 years after.

If the examination on the 3rd year is normal, the next colonoscopy should be at 5 years.

Patients with colon or rectal cancer should have high- quality perioperative clearing. Colonoscopy should be performed preoperatively, intraoperatively, or within 3 to 6 months after cancer resection. Those who have had a colon cancer resected should have colonoscopy performed 1 year after surgery or the original clearing colonoscopy. If the examination performed at 1 year is normal, then the

interval before the next colonoscopy should be 3 years; if that examination is normal, the next colonoscopy should be at 5 years.[1] Periodic examination of the rectum to identify local recurrence usually is performed at 3- to 6-month intervals for the first 2 or 3 years after low anterior resection for rectal cancer. Serum CEA levels should be measured at regular intervals because postoperative CEA determinations may be cost-effective for detecting recurrent cancers.

SCREENING IN ELDERLY PATIENTS

Screening for patients >75 years old should be individualized depending on life expectancy and associated risks

Screening beyond 75 years after consecutive negative screenings from age 50 adds very little benefit because the chance of having a missed adenoma or developing a new lesion that can progress to cancer is very small.[23-24] The survival benefit of routine CRC screening may be observed not earlier than five years after its performance thus, limiting its value among the elderly with short life expectancy.[25]

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Tumor Markers and Genetics Testing

Tumor Markers

No diagnostic circulating biomarker is currently available. Carcinoembryonic antigen (CEA) is not recommended for screening test but may be used for disease monitoring

Genetic Testing

Approximately 5-10% of CRC are hereditary and are often categorized by presence or absence of polyposis a predominant feature.

Genetic Testing in Polyposis Syndromes

A. Adenomatous Polyps

A.1 Familial adenomatous polyposis (FAP)

- autosomal-dominant disease caused by a defect in the APC gene

- leads to colon cancer in 100% of patients by the age of 40 years if untreated
- Lifetime cancer risks
  - Colorectal (100%), duodenum (5%), stomach (≤1%), thyroid (1-2%), pancreas (1-2%), hepatoblastoma (1-2%), medulloblastoma (<1%)
- Screening:
  - Annual colonoscopy/sigmoidoscopy by 10-12 years of age until colectomy
  - Upper endoscopy every 1-4 years by 25-30 years of age
  - Annual thyroid physical examination
- Presentation:
  - 100-1000 of colorectal adenomas
  - fundic gland polyposis
  - duodenal polyposis
  - CHRPE, epidermoid cysts, osteomas
  - Dental abnormalities
  - Desmoid tumors
- Genetic Testing:
  - APC mutation
- Management:
  - Proctocolectomy with ileal pouch anal anastomosis by 30 years of age.
  - If with limited rectal involvement, total colectomy with ileorectal anastomosis
- Pre-colectomy screening for the development of cancer is also indicated.
- Associated with this syndrome are other cancers such as medulloblastoma, papillary thyroid carcinoma, hepatoblastoma, pancreatic cancer, and gastric cancer.

A.2 Attenuated FAP (AFAP)

- Lifetime Cancer risks:
  - Colorectal (70%), duodenum (5%), stomach (≤1%), thyroid (1-2%), pancreas (1-2%)
- Screening:
  - Colonoscopy every 1-2 years by 19-20 years of age
  - Upper endoscopy every 1-4 years by 25-30 years of age
  - Annual thyroid physical examination
- Presentation:
  - 10-100 colonic adenomas (range, 0-100s)
  - fundic gland polyposis
  - duodenal polyposis
- Genetic Testing:
  - APC mutation

- Management
  - Total colectomy with ileorectal anastomosis

A.3 MUTYH (MutY human homolog)-associated polyposis (MAP)
- Caused by germ-line mutation in MUTYH gene
- Autosomal-recessive pattern
- Lifetime Cancer risks:
  - Colorectal (80%), duodenum (4%)
- Screening:
  - Colonoscopy every 3 years by 25-30 years of age
  - Upper endoscopy every 3-5 years by 30-35 years of age
- Presentation:
  - 10-100 colonic adenomas (range, 0-100s)
  - multiple hyperplastic and sessile serrated polyps possible
  - duodenal adenomatous polyposis
- Genetic Testing
  - APC gene mutation testing then
  - Biallelic MUTYH mutation
- Management
  - Colectomy

B. Hamartomatous Polyps

B.1 Peutz-Jeghers Syndrome (PJS)
- STK11/LKB1 gene mutation
- Autosomal dominant
- Lifetime Cancer Risks:
  - Breast (54%), colon (39%), pancreas (11-36%), stomach (29%), small bowel (13%), ovary (21%), uterine/cervix (11%), lung (15%), testicle (<1%)
- Presentation:
  - Mucocutanous pigmentation
    - Peutz-Jeghers polyps
    - Intussuception or obstruction
  - Clinical Diagnosis of PJS is considered when any of the following are met:
    - ≥3 histologically confirmed Peutz-Jeghers polyps
    - any number of Peutz-Jeghers polyps and a family history of PJS
    - characteristic, prominent, mucocutaneous pigmentation and a family history of PJS
    - ≥1 Peutz-Jeghers polyp and characteristic, prominent, mucocutaneous pigmentation
- Screening
  - Annual mammogram and breast magnetic resonance imaging by 25 years of age
  - Colonoscopy every 2-3 years by 25 years of age

- •CA19-9 and magnetic resonance cholangiopancreatography and/or endoscopic ultrasound every 1-2 years
- • Upper endoscopy by 25-30 years of age; consider small-bowel visualization (computed tomography enterography, small-bowel enterocylsis) by 8-10 years of age.
- • Annual pelvic examination and Pap smear
- • Annual testicular examination

• Management
- • Colectomy

B.2 Juvenile Polyposis Syndrome (JPS)

• SMAD4 or BMPR1A gene mutation
• Autosomal dominant
• Lifetime Cancer Risks
- • Colon (40-50%), stomach (21% if gastric polyps are present)

• Presentation
- • Juvenile polyps
- • Features of hereditary hemorrhagic telangiectasia
- • Congenital defects
- • Intussuception or obstruction
- • hematochezia

• Clinical Diagnosis of JPS is considered when any of the following are met:
- • 3-5 juvenile polyps of the colorectum
- • juvenile polyps throughout the gastrointestinal tract
- • ≥1 juvenile polyp in an individual with a family history of JPS

• Screening
- • Colonoscopy by 15 years of age, repeating annually if polyps are present and every after 2-3 years if no polyps detected
- • Upper endoscopy by 15 years of age, repeating annually if polyps are present, and every 2-3 years if no polyps detected

• Management
- • Colectomy

B.3 Cowden Syndrome (CS)

• PTEN gene mutation
• Presentation
- • Multisystem disorder associated with characteristic mucocutaneous features, macrocephaly, and a variety of cancers and GI presentations
- • GI polyps – diffuse polyposis (from esophagus to rectum)

• Genetic testing for CS is considered in individuals meeting any of the following criteria:
- • Adult onset Lhermitte-Duclos disease
- • Autism spectrum disorder and marocephaly
- • ≥2 major criteria (one must be macrocephaly)

- ≥3 major criteria without macrocephaly
- Bannayan-Riley-Ruvalcaba syndrome
- One major and ≥3 minor criteria
- ≥2 biopsy-proven trichilemmonmas
- ≥4 minor criteria

- Major Criteria
  - •Multiple gastrointestinal hamartomas/ ganglioneuromas
  - Nonmedullary thyroid cancer
  - Breast cancer
  - Endometrial cancer
  - Mucocutaneous lesions
  - One biopsy proven trichilemmoma
  - Multiple palmoplantar keratosis
  - Multiple cutaneous facial papules
  - Macular pigmentation of glans penis
  - Mutifocal/extensive oral mucosal papillomatosis
  - Macrocephaly (megalocephaly) (at least 97th percentile)
- Minor Criteria
  - A single GI hamartoma/ ganglioneuroma
  - Thyroid adenoma or multinodular goiter
  - Fibrocystic disease of the breast
  - Mental retardation (i.e., Intelligence Quotient ≤75)
  - Autism spectrum disorder
  - Fibromas
  - Renal cell carcinoma
  - Uterine fibroids
  - Lipomas
- Genetic Testing
  - PTEN mutation

Genetic Testing in Nonpolyposis Syndromes

A. Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch Syndrome (LS)

- Autosomal-dominant disease
- Mutation in one of four mismatched repair genes (MLH1, SMH2, MSH6, and PMS2)
- Often leads to malignancies with mucinous histology in the right side of the colon
- May arise without going through a polyp phase (often detected as flat adenomas)
- Associated with cancers of the endometrium, ovary, stomach, hepatobiliary system, urothelium, brain and small bowel
- Revised Amsterdam Criteria
  - ≥3 relatives with colorectal, endometrial, small bowel, urter and/or renal pelvis cancer AND

- One of these relatives is a 1st-degree relative (parent, sibling, or child) of the other 2 AND
- ≥2 successive generations are affected AND
- at least one diagnosis is at the age of <50yyears
- Familial adenomatous polyposis is excluded
- Tumor should be verified pathologically/histologically

- Revised Bethesda Guideline
  - Individuals with CRC should be tested for Microsatellite Instability (MSI) if they have the following:
    - CRC at age of <50years
    - Synchronous CRC (>1 CRC at the same time) or metachronous CTC (>1 CTC diagnosed at different times) or other LS-associated tumors*)
    - CRC with MSI-H histology (tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous or signet-ring differentiation, medullary growth pattern) in a patient aged <60 years
    - CRC or LS associated tumors* diagnosed at the age of <50 years in 1st-degree relative
    - CRC or LS associated tumors* diagnosed in two (2) 1st-degree relative and or 2nd-degree relative at any age

    *LS associated tumors: CRC, Endometrial Cancer, Stomach Cancer, Small Bowel Cancer, Ovarian cancer, Pancreatic Cancer, Ureteral Cancer, Renal Pelvis Cancer, Biliary Tract Cancer, Brain Tumor, Sebaceous Adenomas, Keratoacanthomas
- Screening:
  - Immunohistochemistry to determine presence of absence of MMR proteins in a tumor specimen
    - The absence of one or more MMR proteins indicated dysfunction of the corresponding MMR gene.
  - Colonoscopy is recommended at 1-2 years beginning at age 20 years or 2 to 5 years earlier than the youngest CRC in the family if diagnosed before 25 years of age.
  - To screen for gastric and small bowel cancers, individuals with Lynch Syndrome should consider esophagogastroduodenoscopy with extended duodenoscopy and capsule endoscopy every 2-3 years starting age 30-35.
  - To screen for urothelial cancer, annual urinalysis starting at age 25- 30
  - Annual physical examination for symptoms of CNS tumors.
  - Genetic Testing:
    - IHC testing for MMR proteins or
    - Testing for mutations in MLH1, MSH2, MSH6, PMS2
    - If negative from above, test for deletions in TACSTD1 (aka

EPCAM)

- Management:
  - Prophylactic subtotal colectomy
  - Consider prophylactic hysterectomy and bilateral salpingo-oophorectomy upon completion of childbearing, among women.
- Genetic Counseling for Lynch Syndrome:
  - 1st degree relatives of individuals with lynch syndrome have 50% chance of having inherited the syndrome
- Chemoprevention:
  - According to a study by Burn, et al, daily use of Aspirin 600mg for a inimum of 25 months reduced the risk of CRC in patients with Lynch Syndrome. Optimum dose and duration still needs to be established.

Other inherited syndromes associated with an increased risk of CRC include MYH-associated polyposis, Gardner syndrome, Turcot syndrome, Muir–Torre syndrome, and Peutz–Jeghers syndrome.

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Persons who can benefit from CRC Genetic counselling and testing :

1. Persons with family history of colorectal polyps or colorectal cancer
   a. A strong family history of CRC increases the risk.
   b. A family history of CRC in first-degree relatives (parents and siblings) poses a higher risk.
   c. Presence of CRC in 2 or more distant relatives further increases the risk compared if only one relative had the disease.
   d. Risk is also higher if the relative with CRC was diagnosed at a younger age than usual.
2. Persons with known inherited cancer syndromes
   a. Lynch Syndrome

i. Lynch Syndrome are at increased risk for cancers such as cancer of the small bowel, ovaries, uterus, stomach, pancreas, kidneys, brain, ureters, and bile duct.

ii. The following are characteristics of Lynch Syndrome using the Amsterdam Criteria (based on family history) who might benefit from Genetic counselling and testing:

1. There is at least 3 relatives who have a cancer associated with Lynch Syndrome.
2. One is a first-degree relative (parent, sibling, or child) of the other 2 relatives.
3. At least 2 successive generations are affected by the syndrome.
4. At least 1 relative had their cancer diagnosed at a young age <50.

iii. Characteristics of Lynch Syndrome using Revised Bethesda Guidelines (for persons diagnosed with colorectal cancer) who might benefit from Genetic counselling and testing to detect gene changes keen to Lynch Syndrome (Microsatellite Instability). These criteria include at least one of the following:

1. The person is diagnosed with CRC at a younger age (<50).
2. The person has or had a second CRC or another cancer (uterus, ovary, stomach, small bowel, pancreas, kidney, ureters, brain or bile duct) associated with Lynch Syndrome.
3. The person is younger than 60 years old and the cancer has characteristics of Lynch syndrome as seen under a microscope.
4. The person has a first-degree relative (parent, sibling, or child), younger than 50 years old, who was diagnosed with CRC or a cancer associated with Lynch Syndrome.
5. The person has 2 or more first- or second-degree relatives (uncles, aunts, nephews, niece or grandparents) who had CRC or another cancer connected to Lynch at any age.

b. Familial Adenomatous Polyposis (FAP)

i. FAP is characterized by the presence of multiple colonic polyps/adenomas which can progress to CRC over a period of time.

ii. Genetic counselling and testing is recommended for people who may have

1. Familial Adenomatous Polyposis
2. Presence of multiple polyps detected during a colonoscopy.

3. Genetic testing is also recommended for first degree relatives (siblings and children) of patients noted to have genetic changes in the gene that causes FAP.

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V Therapeutic Management

Surgical Treatment

KEY NOTES

• The management of colorectal cancer is stage-specific.

• TNM Classification is the recommended staging system.

• The treatment for colon cancer without distant metastasis and early-stage rectal cancer is surgical resection.

• Stage-specific surgical treatment of COLON cancer:

1. Carcinoma-in-situ (Stage 0)
- Most pedunculated and sessile colonic polyps with high grade dysplasia may be completely removed endoscopically.
2. Malignant polyp (Stage I)
- This carries a high risk of nodal involvement thus is best treated with surgical resection.
3. Localized colon cancer (Stage I and II)
- Majority of localized colon adenocarcinoma will be cured with oncologic surgical resection alone.
- Adjuvant chemotherapy has been suggested for selected "high risk" stage II disease.
4. Colon cancer with lymph node metastasis (Stage III)
- Mainstay of treatment is oncologic surgical resection.
- Adjuvant chemotherapy has been routinely recommended due to increased risk for local and distant metastasis.
5. Unresectable colon cancer without distant metastasis
- Chemotherapy is recommended for locally unresectable colon cancer with a goal to convert to a resectable lesion.
6. Colon cancer with distant metastasis (Stage IV)
- Chemotherapy is the first line treatment for patients with metastatic colon cancer and an asymptomatic primary tumor.
- For highly selected patients, surgical resection of primary tumor and resectable distant metastasis combined with systemic chemotherapy may significantly improve survival.

• Surgical resection remains the cornerstone in the treatment of rectal cancer.

• Oncologic surgical resection for rectal cancer may be performed using open, laparoscopic, and robot-assisted techniques.

•Stage-specific surgical treatment of RECTAL cancer:

1. Carcinoma in situ (Stage 0)
- Rectal polyp with high-grade dysplasia is treated with local excision.
2. Malignant polyp (Stage I)
- Management of malignant rectal polyp follows the same principles of treatment for malignant colon polyp.
3. Localized rectal cancer (Stage I)
- Early stage localized rectal cancer may be cured with oncologic surgical resection alone.
4. Resectable locally-advanced rectal cancer (Stage II and III)
- Recommended sequence of treatment is neoadjuvant radiation therapy, followed by surgery, then administration of adjuvant chemotherapy.
- Initial placement of proximal stoma must be considered for obstructing and potentially obstructing locally-advanced rectal cancer prior to starting sequence of treatment.
5. Unresectable locally-advance rectal cancer (Stage II and III)
- Pre-operative combined chemotherapy and radiation treatment are needed to possibly convert unresectable locally-advanced rectal cancer to a resectable disease.
6. Rectal cancer with distant metastasis (Stage IV)
- Multidisciplinary approach to treatment is recommend at present.

INTRODUCTION

The management of colon and rectal cancer is stage–specific. Currently, the AJCC Cancer Staging Manual (7th Edition), which assesses the depth of tumor penetration into the bowel wall as well local invasion of tumor to adjacent organs (T stage), the involvement of locoregional lymph nodes (N stage), and the presence of distant metastasis (M stage) is the recommended staging system.[1-3]

Multidisciplinary Team management is recommended in managing locally-advanced and metastatic colorectal cancer patients

Generally, the treatment for resectable colon cancer without distant metastasis and early-stage rectal cancer is surgical resection. Because of the complexity in the decision-making for locally-advanced and metastatic colorectal cancer with regard to the optimal timing and sequence of surgery, radiation treatment, and chemotherapy; the best recommendation at present is to subject patient to Multidisciplinary Team management to discuss the best treatment plan. The Multidisciplinary Team is usually composed of surgeon (colorectal surgeon, surgical oncologist, or general surgeon with extensive

experience in colorectal cancer management), medical oncologist, radiation oncologist, gastroenterologist, pathologist, palliative care physician, and specialist depending on the organ invaded by the tumor (urologist, vascular surgeon, gynecologist) or the site of distant metastasis (liver surgeon, thoracic surgeon, orthopedic surgeon, or neurosurgeon).

THE SURGICAL MANAGEMENT OF COLON CANCER

Surgical resection is the mainstay of treatment for colon cancer without distant metastasis.

Surgical resection is the mainstay of treatment for resectable colon cancer without distant metastasis.[3-5] The principles of oncologic surgical resection include removal of the primary tumor along with its lymphovascular supply, performing complete mesocolic excision, ligation of the primary vessel at its origin, wide mesenteric resection with a minimum of twelve harvested pericolic lymph nodes, and at least a five-centimeter resection margins.[3] Any adjacent organ or structure that has been grossly adherent or directly invaded must be resected en bloc with the tumor with the goal of attaining negative resection margins.[4,5] There is no difference in cancer-related outcomes between open and laparoscopic oncologic colon resections.[4] Debulking or incomplete surgical resection is rarely effective and not recommended in the surgical treatment of unresectable colon cancer.[4]

For stage IV disease, Multidisciplinary Team approach is recommended to determine the optimal sequence of treatment. In general, systemic chemotherapy is the first line treatment for patients with metastatic colon cancer with asymptomatic primary tumor.[3] However, palliative approaches for symptomatic tumor may be necessary prior to chemotherapy. Highly selected patients with isolated and resectable distant metastases may benefit from metastasectomy.[1,3-5]

STAGE-SPECIFIC SURGICAL TREATMENT OF COLON CANCER

CARCINOMA IN SITU: Stage 0 (Tis, N0, M0)

Colonic polyps with high-grade dysplasia or carcinoma-in-situ carry no risk of lymph node metastasis, thus, most pedunculated and sessile polyps may be completely removed endoscopically. Successful endoscopic resection should be followed with surveillance colonoscopy to ensure that the polyp has not recurred nor an invasive adenocarcinoma has not developed. In cases where endoscopic resection is not possible to completely remove flat

lesion or large polyp, a segmental colectomy is recommended.[4]

THE MALIGNANT POLYP: Stage I (T1, N0, M0)

The risk of lymph node metastasis depends mainly on the depth of tumor invasion into the bowel wall (T stage). Invasive adenocarcinoma in the head, neck, or stalk of a pedunculated malignant polyp carries less than one per cent risk of nodal metastasis, hence, may be completely resected endoscopically.[4] On the other hand, invasive adenocarcinoma arising from the base of a pedunculated malignant polyp or occurring from sessile malignant polyp carries high risk of nodal metastasis, hence, is usually best treated with surgical resection.[4,5]

LOCALIZED COLON CANCER: Stage I and II (T1-4, N0, M0)

The majority of localized colon adenocarcinoma will be cured with oncologic surgical resection alone. Although adjuvant chemotherapy has been suggested for selected "high risk" stage II disease[1,3,4] it remains controversial as to whether chemotherapy essentially improves survival rates in these patients.

COLON CANCER WITH LYMPH NODE METASTASIS: Stage III (Tany, N1-2, M0)

The mainstay of treatment for stage III colon cancer is oncologic surgical resection. Since patients with lymph node metastasis are at significant risk for both local and distant recurrences, adjuvant chemotherapy has been routinely recommended in these patients.[3,4]

UNRESECTABLE COLON CANCER WITHOUT DISTANT METASTASIS

For colon cancer that is locally unresectable because of involvement of critical structures such as major vascular structures, chemotherapy is recommended, with the goal of converting the lesion to a resectable condition.[1]

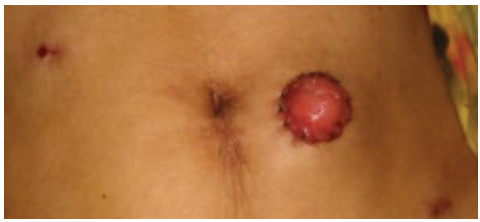
COLON CANCER WITH DISTANT METASTASIS: Stage IV (Tany, Nany, M1)

The first line treatment for patients with metastatic colon cancer and an asymptomatic primary tumor is chemotherapy.[3] But for highly selected patients, surgical resection of resectable primary tumor and metastasectomy of resectable distant metastasis combined with systemic chemotherapy may significantly improve survival.[1,4]

For most patients with stage IV colon cancer that cannot be cured surgically because complete resection of either the primary tumor or the distant metastasis is not feasible, palliative approaches for

symptomatic disease may be necessary prior to chemotherapy. These may include endoscopic deployment of intraluminal stent, creation of intestinal bypass, placement of stoma, or performing partial colectomy for obstructing lesions; application of external beam radiation, angiographic intervention or partial colectomy for massively bleeding tumor; and placement of stoma or performing partial colectomy for perforated cancer.[1,3,4]

Stoma, a greek word, meaning "mouth" or "opening" is a surgically created opening in the abdominal wall for allowing the passage of stool from a section of the bowel.



THE SURGICAL MANAGEMENT OF RECTAL CANCER

Surgical resection remains the cornerstone and important facet in the treatment of rectal cancer. Depending on the exact location of the tumor from the anal verge and the extent of disease, a variety of surgical approaches are used to treat primary rectal cancer. Local transanal excision or endoscopic resection may be performed to treat carcinoma-in-situ or even early – stage rectal cancer.[6-7] Low anterior resection, a sphincter – preserving operation, is typically recommended for mid and high distal rectal cancer. While abdominoperineal resection, which involves removal of the entire rectum, anal canal, and anus with consequent construction of a permanent stoma, is indicated for very low rectal cancer that invades the anal sphincter complex, levator muscles, or perianal skin.[8-10]

The operative principles involve complete resection of the primary tumor with total mesorectal excision technique and en bloc resection of locally invaded organs.[2,4,11,12] Achieving adequate circumferential resection margins, an important pathologic staging parameter in rectal cancer, is very critical in the surgical management, as it has been shown to be a strong predictor of both local recurrence and overall survival.[2,11] Oncologic surgical resection for rectal cancer may be performed using open, laparoscopic, and robot-assisted techniques.

STAGE-SPECIFIC SURGICAL TREATMENT OF RECTAL CANCER

CARCINOMA-IN-SITU: Stage 0 (Tis, N0, M0).

Rectal polyp harboring high-grade dysplasia or carcinoma-in-situ is incapable of regional nodal metastasis, hence, is ideally treated

with local excision. Successful local excision should be followed by frequent clinical evaluation with digital rectal examination and proctoscopy to ensure that the polyp has not recurred nor an invasive adenocarcinoma has not developed.

Rarely, radical resection will be necessary if local excision is not technically feasible such as in large and circumferential lesions. [4,6,7]

THE MALIGNANT POLYP: Stage I (T1, N0, M0).

The management of malignant rectal polyp follows the same principles of treatment for malignant colon polyp as described earlier, except other than endoscopic resection, transanal technique may be employed.

LOCALIZED RECTAL CANCER: Stage I (T1-2, N0, M0).

The majority of early-stage localized rectal cancer may be cured with oncologic surgical resection alone. [2,4,11]

RESECTABLE LOCALLY-ADVANCED RECTAL CANCER: Stages II and III (T3-4a, N any, M0).

For clinically diagnosed locally – advanced rectal cancer, the recommended sequence of treatment is application of neoadjuvant radiation therapy, then followed by surgery, and followed by administration of adjuvant chemotherapy. [2,4,11] However, initial placement of proximal stoma must be considered for obstructing and potentially obstructing locally advanced rectal cancer prior to starting the recommended sequence of treatment.

UNRESECTABLE LOCALLY-ADVANCED RECTAL CANCER: Stages II and III (T4b, N any, M0).

Pre-operative combined chemotherapy and radiation treatment is necessary to possibly convert unresectable locally-advanced rectal cancer to a resectable disease. [2] En bloc resection of locally invaded organ or structure should be performed with the goal of attaining negative resection margins. [2,4]
Debulking or incomplete resection is not recommended. [4]

RECTAL CANCER WITH DISTANT METASTASIS: Stage IV (T any, N any, M1).

Because of the complexity in the decision-making for stage IV rectal cancer that may include the optimal timing and sequence of surgery, radiation treatment, and chemotherapy; the best recommendation at present is to subject patient to Multidisciplinary Team approach to cancer care.

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Systemic Treatment

KEY NOTES

- Surgery is the primary treatment for almost all localized cancers except hematologic malignancies such as lymphomas and leukemias.
- For patients who have undergone complete resection, the risk for recurrence persists. This risk increases as the stage of disease progress.
- The presence of microscopic circulating tumor cells is responsible for recurrence. The administration of adjuvant treatment is intended to eliminate these circulating tumor cells and therefore, reduce recurrence risk.
- Adjuvant treatment is given after surgery; while neoadjuvant treatment is given before surgery.
- Adjuvant and neoadjuvant treatment can be in the form of: chemotherapy, hormonal, targeted, and radiotherapy.
- Adjuvant treatment is recommended for patients with stage III completely resected colon cancer.
- Stage II colon cancer is a gray area where outright adjuvant chemotherapy will not benefit all patients.
- There is a role for radiation therapy among selected patients with early stage rectal cancer. The rationale behind the use of radiation for rectal cancers is the relatively high risk of locoregional recurrence.
- When administering systemic treatment for metastatic disease, the goals of treatment have to be identified and discussed properly with the patient.
- Systemic therapies that are active for colon and rectal cancers are chemotherapy and targeted therapies.

Surgery is the primary treatment for almost all localized cancers except hematologic malignancies such as lymphomas and leukemias. For patients with localized (Stage I-III) colorectal cancers, surgery with or without adjunctive treatments constitute the path to curative treatment. Involving a multidisciplinary approach will often lead to better outcomes whether patients are in the early or advanced stages of cancer.

Survival with surgery alone for localized disease are as follows[1]:

Table 1: 5-Year Survival for Localized Disease

Disease Stage	5-Year Survival
Stage I (T1-2 N0)	93%
Stage IIA (T3N0)	85%
Stage IIB (T4N0)	72%
Stage IIIA (T1-2N1)	83%
Stage IIIB (T3-4N1)	64%
Stage IIIC (N2 disease)	44%

Surgical resection can still have potential long term survival benefits even for patients who develop isolated liver or lung recurrences from colorectal cancer.[2,3] Five and 10-year median survival for patients who underwent surgical resection for isolated liver metastases are 38% and 26%, respectively.[2] Up to 50% of patients may have a 5-year survival for those who underwent pulmonary metastasectomy[3].

After complete resection of all macroscopic disease, the risk for recurrence persists, especially within the 2-3 years after surgery, and this risk increases as the stage of disease progress. The presence of microscopic circulating tumor cells is potentially responsible for this recurrence. The administration of adjuvant treatment is intended to eliminate these circulating tumor cells and therefore reduce recurrence risk.

Colon and rectal cancers have somewhat differing patterns of recurrence. Cecum, transverse and sigmoid colon have tendency to develop a higher risk for peritoneal seeding due to their intraperitoneal location while the ascending and descending colon, hepatic and splenic flexures are extraperitoneal resulting in metastases that infiltrate retroperitoneal organs and soft tissues[4]. The venous drainage of the colon goes to the portal vein passing through the liver before going into the systemic circulation which makes patients with colon cancer at high risk of developing metastases to the liver.

Rectal cancers, lacking serosa, often extend into the perirectal tissues involving the bladder, prostate and vagina. The venous drainage of the upper rectum is similar to that of the colon. The lower rectum drains into the inferior vena cava without passing through the portal vein which accounts for a higher incidence of

lung metastases. Low rectal cancers can also have a higher risk of vertebral metastases due to the connections of the lower pelvic veins with the vertebral venous plexus.[4]

ADJUNCTIVE THERAPIES

NEOADJUVANT
Treatment is given BEFORE surgery

ADJUVANT
Treatment is given AFTER surgery

Adjuvant treatment refers to Treatment (chemotherapy, hormonal, targeted therapy and radiotherapy) given after surgery while neoadjuvant treatment refers to treatment given prior to surgery. Adjuvant treatment is generally given to reduce the risk of recurrence and improve survival. Chemotherapy, hormonal and targeted therapies are examples of systemic treatments while radiation therapy is a local treatment which is often given to reduce the risk of local recurrence.

For colon cancer, only chemotherapy is given in the adjuvant setting while neoadjuvant treatment, consisting of combination chemotherapy and radiation therapy, may be recommended for rectal cancer. If neoadjuvant treatment were not given for rectal cancer, combination chemotherapy and radiation therapy is often given post operatively.

In the adjuvant setting, for both colon and rectal cancer, the only systemic treatment which has been shown to provide benefit is chemotherapy. Targeted therapies have not been proven to be beneficial in the adjuvant or neoadjuvant setting and some studies have even shown detriment when targeted therapies are added to chemotherapy.[5,8]

ADJUVANT TREATMENT FOR RESECTED EARLY STAGE COLON CANCER

Chemotherapy should ideally be started within 4-6 weeks after surgery

Adjuvant treatment is recommended for patients with stage III completely resected colon cancer.[6,8] Chemotherapy should ideally be started within 4-6 weeks after surgery.

On the other hand, stage II colon cancer is a gray area where outright adjuvant chemotherapy will not benefit all patients. Stage II Colon Cancer patients that may benefit from adjuvant chemotherapy include those with inadequately sampled nodes, T4 lesions, perforation, or poorly differentiated histology.[7]

NEOADJUVANT AND ADJUVANT TREATMENT FOR EARLY STAGE RECTAL CANCER

Unlike colon cancer, there is a role for radiation therapy among selected patients with early stage rectal cancer. Radiation therapy (RT) may be given pre or post-operatively.

When RT is administered, this is usually given concurrent with either infusional or bolus 5-FU or capecitabine. In the neoadjuvant setting, concurrent chemotherapy and radiation are done prior to surgery while in the adjuvant setting, concurrent chemo-RT is sandwiched between chemotherapy given for 2 months before and after chemo-RT[10].

The rationale behind the use of radiation for rectal cancers is the relatively high risk of locoregional recurrence[10]. An adequately performed total mesorectal excision(TME) significantly reduces the risk of recurrence. The current guidelines still recommend that radiation therapy form part of the treatment for patients with T3 or higher or node positive rectal cancers[10].

APPROACH TO TREATMENT FOR METASTATIC COLORECTAL CANCER

Distant metastases for colorectal cancer has been subdivided into 2 categories as follows:
M1a – metastasis confined to one organ or site
M1b – metastases in more than one organ/site or the peritoneum

Patients with M1a disease should be considered for surgery, if feasible, for complete resection of the metastasis.

The liver is the most common organ affected by metastases due to the anatomy of venous drainage as explained above. If surgical resection were not feasible, other liver directed therapies are available such as radiofrequency ablation, stereotactic body radiation therapy (SBRT) and transarterial chemoembolization (TACE)[8].

For patients with more disseminated disease that are not amenable to the interventions identified above, systemic treatment with chemotherapy with or without targeted therapy is recommended.

When administering systemic treatment for metastatic disease, the goals of treatment have to be identified and discussed properly with the patient. Factors such as performance status, comorbid conditions, chemotherapy used in the adjuvant setting,

Factors to consider before starting chemotherapy:

- Performance status
- Co morbid conditions
- Chemotherapy used in the adjuvant setting
- RAS testing
- Side effect profile of the chemotherapy
- Patient tolerability
- Cost of treatment

molecular profile of the tumor (RAS testing), side-effect profile of the treatment, patient tolerability and cost of treatment should be considered in choosing the appropriate treatment.

Studies have shown benefit for maintenance treatment in metastatic disease[13]. Maintenance treatment entails administering an intensive regimen initially to be followed by a less intensive regimen consisting of chemotherapy such as capecitabine or infusional 5-FU plus targeted therapy, usually bevacizumab, until disease progression or intolerability.

SYSTEMIC TREATMENT FOR COLORECTAL CANCER

Systemic therapies that are active for colon and rectal cancers are chemotherapy and targeted therapies. The chemotherapy agents that are active for colorectal cancers include oxaliplatin, irinotecan, leucovorin, 5-fluorouracil and capecitabine. Targeted therapies that are active include bevacizumab, cetuximab, regorafenib, panitumumab, ramucirumab and ziv-aflibercept.

5-fluorouracil (5-FU) has been the oldest currently active drug used for colorectal cancers. This is given intravenously either as a continuous infusion or iv bolus. It is used in a variety of schedules but nowadays, it is most often used in combination with either oxaliplatin or irinotecan and leucovorinbecause these combinations were shown to provide enhanced tumor response as well as improvement in survival compared to 5-FU alone or 5-FU in combination with leucovorin[6,14-18]. The 3-drug combinations that are very active for colorectal cancers are Oxaliplatin, leucovorin and 5-FU also known as the FOLFOX regimen and Irinotecan, leucovorin and 5-FU also known as the FOLFIRI regimen.

Capecitabine is an oral drug which mimics the action and efficacy of infusional 5-FU[19-20]. This may be given as a single agent or combined with oxaliplatin in the adjuvant and metastatic setting[21]. It can also be used as a single agent with the targeted therapy bevacizumab in the metastatic setting[8,19]. However, more caution should be exercised when capecitabine is combined with irinotecan. This combination is associated with higher rates of severe vomiting, diarrhea and dehydration[22].
Regarding chemotherapy in the adjuvant setting, all of the above agents are active except for irinotecan. The addition of irinotecan to leucovorin and 5-FU did not confer any improvement in survival for patients with resected Stage III colon cancer[23]. Irinotecan is only

beneficial for patients in the metastatic setting.

Bevacizumab is a monoclonal antibody that binds the vascular endothelial growth factor (VEGF). It reduces blood vessel formation in the tumor which is essential for their growth and survival.

Cetuximab and Panitumumab are an anti-epidermal growth factor receptor (anti-EGFR) antibodies. They block a pathway that facilitates growth and survival of the cancer. It is necessary to perform the RAS test on the tumor before using anti-EGFR. Only patients that are found to be harboring RAS wild type tumors are candidates for the use of these drugs. Those patients harboring RAS mutations should not be given an anti-EGFR antibody. These drugs may be given alone without chemotherapy for RAS wild type patients who are not capable of tolerating chemotherapy.

Regorafenib is an oral targeted therapy which is used for patients who have progressed after use of oxaliplatin and irinotecan containing combination chemotherapies with or without targeted agents. It targets multiple pathways that are important in the proliferation, growth and survival of cancers. Similar to bevacizumab, it also has an effect on inhibiting tumor blood vessel formation.

Table 2: Common Side-effects of Systemic Treatment

Drug	Side effects
5FU Capecitabine	stomatitis, diarrhea, hand-foot syndrome, nausea/vomiting, fatigue/weakness
Oxaliplatin	peripheral sensory neuropathy and swallowing difficulty
Irinotecan	nausea/vomiting, diarrhea, alopecia, myelosuppression
Bevacizumab	perforation or fistula, arterial and venous thromboembolic events, hypertension, proteinuria
Cetuximab	rash, hypomagnesemia
Panitumumab	infusion related reactions
Regorafenib	fatigue/weakness, decreased appetite, hand foot syndrome, diarrhea, hypertension and the other side-effects associated with bevacizumab

A recent advance in the systemic treatment of colorectal cancers is the use of immunotherapy. The use of immunotherapy is based on the assumption that the immune system is involved in the surveillance and eradication of cancer cells. However, cancer cells develop ways to escape these mechanisms to allow their survival.

Immunotherapy (Nivolumab and Pembrolizumab) is indicated for patients with unresectable metastatic colorectal cancers whose tumors have progressed following conventional chemotherapy. However, these therapies are only effective on tumors that harbor deficient mismatch repair genes (dMMR) or high levels of microsatellite instability (MSI-H). Only a small percentage of patients with Stage IV colorectal cancer harbor these mutations (3.5-5%).

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Endoscopic Treatment

INTRODUCTION

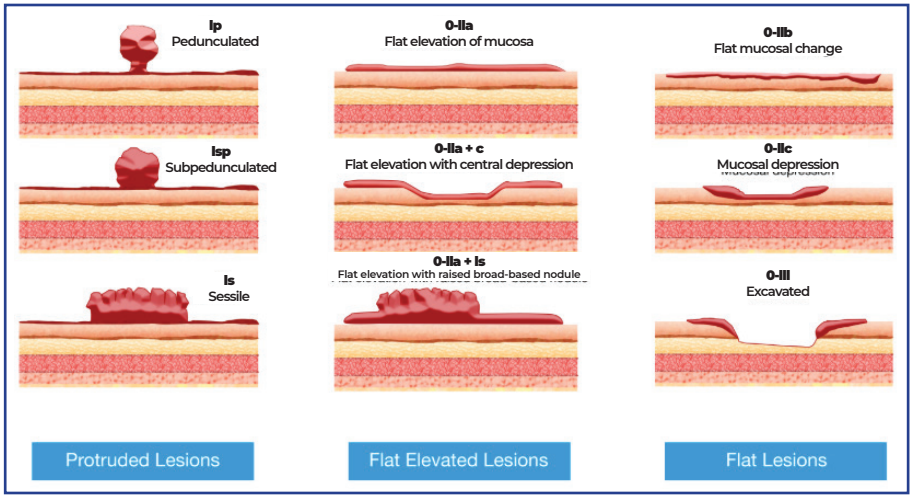
Colonoscopy has an established role in the early diagnosis and prevention of colorectal cancer. Traditionally, the removal of precursor lesions, the adenomatous polyps, is its only therapeutic use. As we move well into the era of minimally invasive surgery, the role of colonoscopy in the diagnosis of early colorectal cancer is now being discovered and the technique being perfected in our country.

INDICATIONS & TECHNIQUES IN SCREENING

Endoscopic resection of tumors is indicated in early colorectal cancer, which is defined as lesions that are confined in the mucosa or submucosa without invasion of the muscularis propia. We must be adept in the proper characterization of the lesion prior to decision to proceed to endoscopic resection. Lesions are generally classified as polypoid or non-polypoid lesions. Polypoid lesions can be removed via standard polypectomy techniques using a specialized snare. On the other hand, flat lesions should be carefully characterized. Size, localization, macroscopic features, color, surface (pit pattern), presence of fold conversion and wall deformation are used as part of the complete assessment of flat polyps.

Flat lesions are generally classified into, in order of increasing malignancy rates: sessile lesions (height is greater than the width), depressed lesions (flat lesions with ulcerated or depressed centers), flat lesions (less than 10mm circumference) and laterally spreading lesions (more than 10mm in circumference).[1] The Paris classification is used to grossly characterize the lesions.[2] In general, flat lesions with ulcerations or depressed regions are more likely to invade deeper layers and harbor invasive neoplasia.

Figure 1: Paris classification for Mucosal Neoplasia



The surface assessment also helps determine the depth of invasion. This may be done by examining the pit pattern or the vasculature can be achieved with the use of either digital (digital manipulation of the processor) or chemical chromoendoscopy (using indigo carmine). Several classifications are used like the Kudo and Sano classification among others.

ENDOSCOPIC TREATMENT

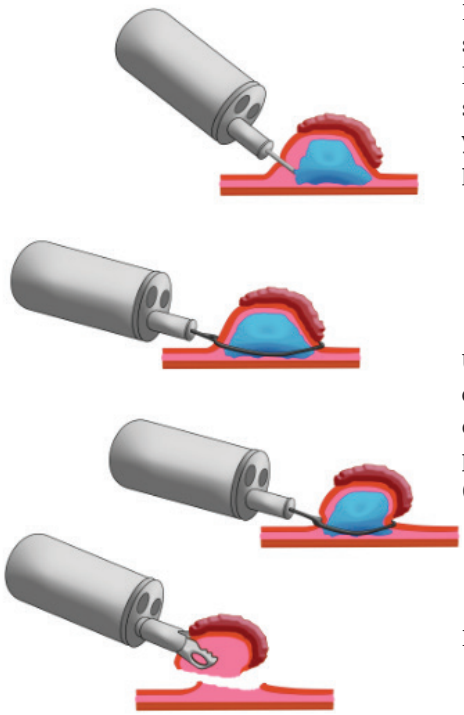
Endoscopic resection is performed by a trained therapeutic endoscopist in a well-equipped endoscopy unit with adequate support and assistance. Before this is carried out, informed consent should be collected. Ideally this procedure should be done in close collaboration with a surgeon, anesthesiologist and pathologist. The method will depend on the initial assessment described above.

ENDOSCOPIC MUCOSAL RESECTION (EMR)

EMR is indicated in superficial, flat, non-polypoid lesions measuring 20mm and less; and are not amenable to snare polypectomy. After characterization of the polyp, 5-20 ml of saline is injected in the submucosal layer using a standard G 25 needle inserted adjacent to the polyp base. The lesion is caught as a whole using a polypectomy snare and completely resected using pure cutting or blended current (depending on operator preference). Standard hemoclips are used for hemostasis. Any residual lesion can be removed via piecemeal method.

Technical success of EMR in large volume centers is reported at 90-100%with complication rates 0-9% .[3] Common complications

are perforation and bleeding which can be controlled by endoscopic methods. Complications are reported to be higher in older patients, patients with co morbidities and on anti-coagulation.



Inject saline solution into the submucosal space to lift the lesion and protect the underlying submucosa and muscularis. If you see complete lifting, you may proceed with EMR.

Using a polypectomy snare, may completely catch the polyp or may do so in a piecemeal fashion using pure cutting or blended current (depending on operator preference).

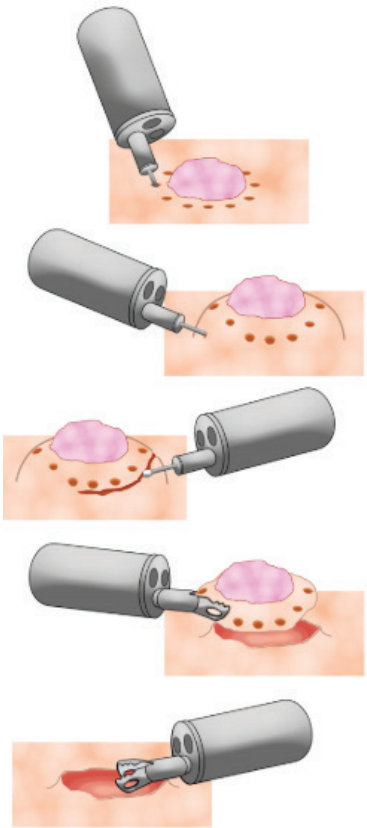
Retrieve the specimen.

Figure 2: Endoscopic Mucosal Resection (EMR)

ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD)

ESD is indicated in superficial, non-polypoid lesions or laterally spreading lesions measuring more than 20mm and allows en-bloc resection of these lesions. After identifying that the lesion is amenable for ESD by the techniques described above, injection of saline or glycerol or fructose with a small amount of indigo carmine into the submucosa is done. This is to separate the submucosal area from the muscularis propia and in effect protect the latter during the procedure. Once the lesion is fully lifted, careful resection is done using different types of electrosurgical knives and counter-traction methods to expose the submucosal plane throughout the procedure. There are different techniques and methods in different

centers however the outcomes are not significantly different.[4] The goal of ESD is complete resection of the lesion which is reported in 60-90%. Bleeding and perforation are also reported and slightly higher in ESD than in EMR.[4]



Creation of markings around the lesion to be resected.

Injection of saline/glycerol/fructose with a small amount of indigo carmine into the submucosal space to lift the lesion. This is done to seperate the submucosal area from the muscularis propia and protect the latter during the procedure.

One lesion is fully lifted, careful en bloc resection is done within the submucosal pocket using a special endoscopic knife.

The lesion is removed.

Figure 3: Endoscopic Submucosal Dissection (ESD)

OTHER ENDOSCOPIC TREATMENT

Argon Plasma Coagulation (APC)

APC is a non-contact method initially designed for thermocoagulation for the control of bleeding using argon gas. In a small study of 10 patients, it has been shown to be an option for T1 tumors and was shown to have positive local response in 9 of 10 patients in a period of 9 months. On the other hand, APC may have a role for tumor debulking with a goal of colonic recanalization for symptom relief in patients who are too ill to undergo surgery.[5]

Colonic Stenting

Self-expandable metal stents which are deployed under endoscopic and fluoroscopic guidance may be used generally in left sided colonic tumors. It is not recommended in rectal tumors or those proximal to the splenic flexure due to low success and high perforation rate. Recent data shows that the use of colonic stenting may be considered as an alternative to surgery in acute colonic obstruction if the medical risks of the patient (ie co morbidies, poor performance status or high ASA scores) outweigh the benefit of surgery; and in relief of obstruction in palliative settings.[6]

SUMMARY

Colonoscopy is no longer limited to screening and basic polypectomy in patients with colonic neoplasms. After proper screening and characterization of early colorectal lesions, one may opt to do EMR or ESD. The endoscopist must be trained and the endoscopy unit must be equipped for the procedure and ready to handle any possible complications.

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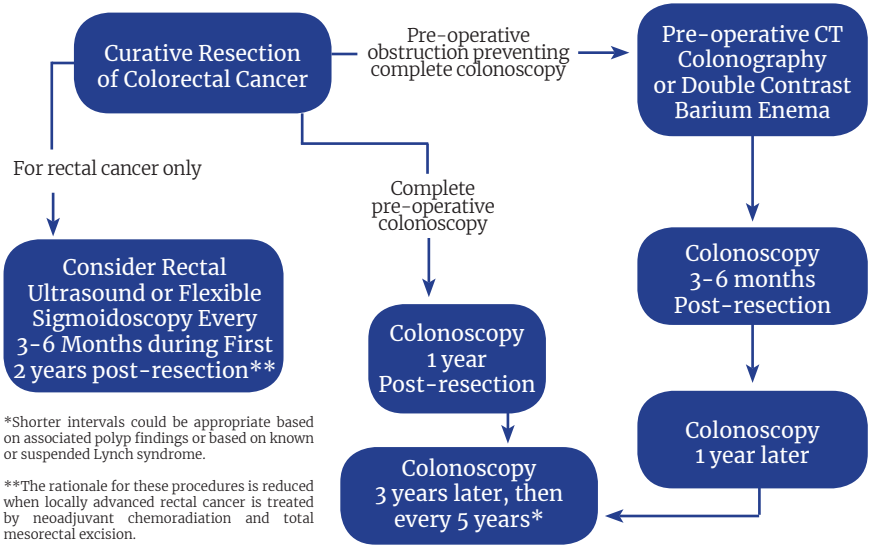
VI Surveillance

After a definitive management for CRC, it is recommended to do surveillance to screen for possible tumor recurrence and emerging pre-cancerous polyps. The American Gastroenterology Association (AGA) has formulated guidelines for the endoscopic monitoring of colon cancer post-surgical resection.

AGA INSTITUTE GUIDELINES FOR

Colonoscopy Surveillance After Cancer Resection
CLINICAL DECISION SUPPORT TOOL



*Shorter intervals could be appropriate based on associated polyp findings or based on known or suspended Lynch syndrome.

**The rationale for these procedures is reduced when locally advanced rectal cancer is treated by neoadjuvant chemoradiation and total mesorectal excision.

Source: Douglas K. Res, et. al. Guidelines for Colonoscopy Surveillance After Cancer Resection: A Consensus Update by the American Cancer Society and the US Multi- Society Task Force on Colorectal Cancer (Published with permission from source)

Post cancer Resection Surveillance Colonoscopy Recommendations
1. Patients with colon and rectal cancer should undergo high quality perioperative clearing (Good bowel preparation). In the case of non-obstructing tumors, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, computed tomography colonography with intravenous contrast or double-contrast barium enema can be used to detect neoplasms in the proximal colon. In these cases, a colonoscopy to clear the colon of synchronous disease should be considered 3 to 6 months after the resection if no unresectable metastases are found during surgery. Alternatively, colonoscopy can be performed intraoperatively.
2. Patients undergoing curative resection for colon or rectal cancer should undergo a colonoscopy 1 year after the resection (or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease). This colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumors.
3. If the examination performed at 1 year is normal, then the interval for the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval for the next subsequent examination should be 5 years.
4. Following the examination at 1 year, the intervals for subsequent examinations may be shortened if there is evidence of hereditary non -polyposis colorectal cancer or if adenoma findings warrant earlier colonoscopy.
5. Periodic examination of the rectum for the purpose of identifying local recurrence, usually performed at 3- to 6-month intervals for the first 2 or 3 years, may be considered after low anterior resection of rectal cancer. The techniques utilized are typically rigid proctoscopy, flexible proctoscopy, or rectal endoscopic ultrasound. These examinations are independent of the colonoscopic examinations described above for detection of metachronous disease.
Guidelines for Colonoscopy Surveillance After Cancer Resection: A Consensus Update by the American Cancer Society and the US Multi-Society Task Force on Colorectal CancerDouglas K. Rex, et. al.[1]

(Published with permission from source)

Stage I disease

The recommended postoperative surveillance strategy only includes colonoscopy.[1,2,4,6] In general, aggressive surveillance other than colonoscopy has generally not been recommended in patients with resected stage I tumors, since over 95 percent are cured by surgery alone.[2] The number of patients who can be cured as a result of routine periodic CEA and imaging surveillance is very small: less than 1 percent.[7]

- Colonoscopy at 1 year; subsequent studies dictated by prior findings. If negative, every 5 years. Proctosigmoidoscopy every 2 to 5 years if rectal cancer and no pelvic radiotherapy. (ASCO)
- Colonoscopy at 1 year; subsequent studies dictated by prior findings. If no advanced adenoma, repeat at 3 years, then every 5 years; if advanced adenoma at 1 year, repeat at 1 year. (NCCN)

Stage II and III disease

The recommended postoperative surveillance for resected stage II or III colorectal cancer patients are the following[1,2,4,6] Consistent with the guidelines provided by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN):

- CEA monitoring
  - Every three to six months for the first three years
  - An elevated CEA should be retested for confirmation if values lie between 5 to 10mg/ml
- Colonoscopy
  - Colonoscopy at 1 year; subsequent studies dictated by prior findings. If negative, every 5 years. Proctosigmoidoscopy every 2 to 5 years if rectal cancer and no pelvic radiotherapy. (ASCO)
  - Colonoscopy at 1 year; subsequent studies dictated by prior findings. If no advanced adenoma, repeat at 3 years, then every 5 years; if advanced adenoma at 1 year, repeat at 1 year. (NCCN)
- Annual CT scans of the chest and abdomen for the first 3 years
- Annual pelvic CT scan for patients with rectal cancer who did not undergo radiation therapy

Resected Stage IV disease

The recommended postoperative surveillance for resected stage IV disease provided by the National Comprehensive Cancer Network is only consensus- based.[1,2]

- The consensus suggests the surveillance strategy used for patients with stage II and III disease also be used for resected stage IV disease. [1,2,4]
- A frequent schedule for CT scans is also advised.[1]
- Post-treatment surveillance strategy for this group of patients should be individualized.[1,2]

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ADDENDUM

Genetic testing services in the Philippines are available in (1) Department of Pedriatics, Philippine General Hospital; (2) Department of Obstetrics and Gynecology, Philippine General Hospital; (3) Department of Internal Medicine, Philippine General Hospital; (4) Department of Pathology and Microbiology, University of the East-Marcos Magsaysay Memorial Medical Center