CURRENT CONCEPT

BJS

*BJS, September, **5,** 1999*

COLORECTAL CANCER

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One in 20 individuals is at risk for developing colonerctal cancer. This risk is age dependent with almost an 18-fold increase after the age of 65. In 1996 colorectal cancer affected 133.000 person in USA and 55000 died of the disease.

Aetiology

The exact cause of colon and rectal cancer is not known but there are inherited (genetic and familial) and environmental[1,2,3,4] (Dietary and others) factors as well as certain preexisting conditions have been implicated[2,3,4].

A- The inherited factors

1-Some cases are caused by known genetics disorders e.g. (APC gene in FAP syndrome)

2-Other cases have very strong familial tendecies e.g. (Lynch syndrome)

3-Other cases related to specific pre malignant disease such as ulcerative colitis and Crohn's disease[3,4].

Genetic predisposition

Genes play role in the development of colo-rectal cancer and 15% of cases of colo-rectal cancer are genetically predisposed[1,3,4,5].

I-First observations are in the patients with familial adenomatous polyposis (FAP) syndrome. The syndrome is an autosomal dominant. The gene responsible is APC gene (adenomatous polyposis coli) gene. This gene is located on chromosome 5 near q 21.22 locus[1,3,4,5,6].

II-Hereditary non-polyposis colon cancer (HNPCC). This is Lynch syndrome, which is of two types Lynch I and Lynch II syndromes. The gene responsible for this syndrome is mapped to chromosome [2,3,4,5].

III-Other genes have been implicated in colon cancer development. These are:

1-Myc on chromosome 8.

2-K.ras on chromosome 12.

3-P_{53} & neu/ HER_2 on chromosome 17.

4-DCC on chromosome 18q.

K-ras, neu/HER2 and myc are known oncogenes. APC, DCC and P_{53} are known suppressor genes[1,3,4,5].

B-Environmental factors

These include the diet and other factors in the environment.

Diet: the association of high fat, low fiber diet with colorectal cancer has long been suspected, a sedentary life style, obesity and high level of dietary fat have been implicated as factors predisposing to large bowel cancer[1,3,4].

1-Fat is toxic to colonic mucosa, diet rich in saturated and polyunsaturated fats is carcinogenic to colorectal mucosa.

2-Increased dietary fibers decreases the incidence of colorectal cancer due to rapid evacuation of diet, dilution of dietary carcinogens and reduction of mucosal contacts to these carcinogens.

3-Bile acids and alcohol promote a mutational changes in the colo-rectal mucosa[3,4].

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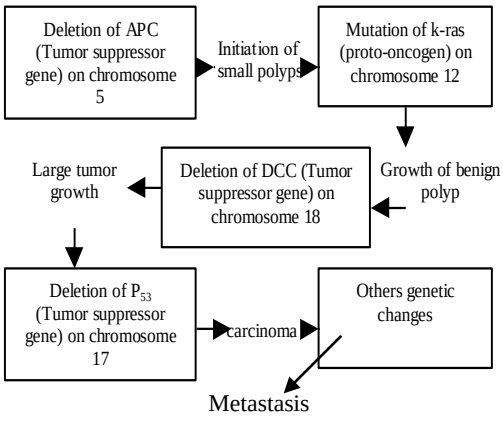
Fearon and Vogelstein have proposed a model for genetic changes leading to colorectal cancer[4,5,7].



Diagnosis

Screening programme is used for early detection of colo-rectal cancer in patients with high risk factors for developing colo-rectal cancer, which includes:

1-digital examination for every person>40.
2-FOT (faecal occult test) for every person >50.
3-fibreoptic sigmoidoscopy for every person > 50.
4-either colonoscopy or barium enema (double contrast) for person with high risk factors.
5-serological tumor-markers are of no value now[3,9].

Those patients with risk factors for colo-rectal cancer are:

a-FAP and associated syndrome (Gardner, Turcot's).
b-longstanding pancolitis.
c-longstanding left side colitis.
d-HNPCC
e-those with history of pelvic radiation.
f-those patients with uretero-sigmoidostomy for urinary diversion[3,4,9].

There are a lot of measures to be done for diagnosis of colorectal cancer and to see its local extension, lymphatic and distant metastases which are necessary for staging, treatment and prognosis of the disease.

*In spite of *digital examination* of anus and rectum, *pelvic examination* under general anaesthesia is necessary especially in female patients to evaluate the tumor, its size, extent and fixity with epi or para rectal lymph nodes enlargement if present.

**Fibreoptic colonoscopy* which can identify and biopsy even small lesions (<0.5 cm). However, in up to 10% of examination the proximal colon can not be reached[1,3].

**Double contrast barium enema* is necessary especially for those patients with colonoscopic failure also to evaluate the bowel proximal to the lesion (synchronus tumors).

**Ultrasound to the abdomen, pelvis* and transrectal ultrasound in cases of rectal cancer.

**CT scan to the pelvis and abdomen*

**MRI to the pelvis, abdomen and transrectal MRI.*

To determine the local extension of tumor in cases of rectal and sigmoid colon cancer, and that of the abdomen to determine para-aortic lymph node and liver metastases.

**Liver function test*, alkaline phosphatase, SGGT, SGOT, SGPT, LDH.

**Chest x-ray*

To detect any metastasis.

**Tumor markers*

CEA still remains the most widely diagnostic marker for colorectal cancer. Despite discovery of other markers such as CA 19-9 or CA –50 or TAG-72 have not been widely accepted.

CEA	0-2.5ng/ml	Normal
CEA	<10ng/ml	Benign condition
CEA	>10ng/ml	In colorectal cancer

**Immuno scintigraphy*.

Radio labeled antibody to target tumor. Indolium 111 (In^{111})- labeled anti TAG 72 for imaging colorectal cancer.

**Urinary system evaluation by.*

IVU, radio opaque enhanced CT and cystoscopy.

All these investigations aid to determine the following:

I-The depth of tumor penetration into bowel wall

II-The involvement of regional lymph nodes.

III-The presence of distant metastasis.

Staging of colorectal cancer

TNM staging[1,3,4,8,9] is now usually used.

1)Primary tumor (T)

Tx-primary tumor can not be assessed.
To-no evidence of primary tumor.
Tis-carcinoma in situ.
T1-tumor invades submucosa.
T2-tumor invades muscularis properia.
T3-tumor invades subserosa., serosa., pericoloic or rectal fat.
T4-tumor invades the visceral peritonium and adjacent structures.

2)Regional lymph nodes (N)

Nx-lymph nodes can not be assessed.
No-no evidence of lymph nodes metastasis
N1-metastasis in 1-3 peri-colic or perirectal lymph nodes.
N2-metastasis >4 peri-colic or perirectal lymph nodes.
N3-Metastasis in any lymph nodes along named vascular trunk.

3)Distant metastasis (M)

Mx-presence of distal metastasis can not be assessed.
Mo-no distant metastasis
M1-distant metastasis.

The stage of TNM system is as follows:

Stage 0	Tis	No	Mo
Stage I	T1,T2	No	Mo
Stage II	T3, T4	No	Mo
Stage III	Any T	Any N	Mo
Stage IV	Any T	Any N	M1

Prevention[9]

This can be done by the following steps:

1-Periodic colonoscopy and polypectomy especially for high-risk patients.

2-Prophylactic colectomy or proctocolectomy will be done in some cases of polyposis, and some cases of ulcerative colitis.

3-Sulindac is antiinflamatory drug, could decrease adenoma in colon polyposis syndrome and this decrease colorectal cancer[9].

4-NSAID and aspirin was found to reduce all forms of colorectal cancer when was taken as prophylaxis[9].

Treatment

In patients with potentially curable colorectal cancer, surgical resection is essential for optimal oncologic and functional result. In majority of such cases en bloc resection of the primary tumor and regional lymph nodes is only needed[1,3,4,10]. But for locally advance disease (transmural or node positive) are benefit from surgery and adjuvant chemoradiation therapy. Clinically tethered or fixed rectal cancer is treated with pre-operative radiation therapy, while small rectal cancer may be cured with local excision alone if they are low grade on post operative pelvic radiation and concurrent chemotherapy if they are high grade[3,4,9,10,11]. The modern surgical approach to colorectal cancer must consider margins free of resection and en bloc resection of draining lymphatic tissue. Almost 90% of patients have tumors that can be resected completely and the mortality rate 2-10%. After good bowel preparation for the patients by mechanical and chemical ways. The anatomical resections are as follow:

1)Caecum and ascending colon.	Right hemicolectomy.
2)Hepatic flexture and proximal transverse colon	Extended right hemicolectomy with omentectomy.
3)Distal transverse colon and splenic flexture.	Either I-extended right hemicolectomy to descending colon. Or II Left hemicolectomy with omentectomy.
4)Descending colon and sigmoid.	Left hemicolectomy with sigmoid colectomy.
5)Upper and middle third rectum.	Upper or lower anterior resection with coloanal anastomosis.
6)Lower third rectum	Abdomino-perineal resection.

Well-differentiated rectal cancer requires distal margin of 2cm as adequate margin clearance, while poorly differentiated rectal cancer requires 5 cm distal margin clearance.

*Since the advent of circular stapling device in 1970s. However, the double-stapled technique developed by Knight and Griffen in 1980s is most frequently used in creating distal anastomosis after resection of low lying rectal cancer[10].

**Some have implemented construction of colon J Pouch to produce neorectal resrvoir in order to reduce the stool frequency[10].

***Local excision of rectal cancer involves removing the tumor in its entirely in addition to margins of surrounding normal tissue. The success of this operation depends on criteria of the tumor as:

1-less than 4 cm in diameter.
2-within 6-8cm from anal verge.
3-less than one quadrant of rectal circumference involved.
4-mobile one.
5-well differentiated and no lympho-vascular or perineural invasion.
6-endo-rectal u/s show that the tumor T1 or T2 No (no lymph nodes involved).
7-CT no metastasis.

This local excision done by one of these procedures:

a-transanal excision.
b-transcoccygeal excision (Kraske).
c-transsphincteric excision (York-Mason).
d-transanal endoscopic micro surgery (TEM)[10,12].

Although a 1 cm margin is ideal but 0.5 cm margin of grossly normal mucosa beyond the edge of the tumor is more realistic. A full thickness rectal wall excision to the level of perirectal fat is required. The wound is irrigated and closed. A transmural extension (T3) are major risk factors for local recurrence, so requires postoperative chemo-radiation therapy. The major advantage of local excision is avoiding laparotomy, avoiding longer period of pain and avoiding urinary, sexual and wound complication of lower anterior resection (LAR)[10,11].

Laparoscopic colectomy[10,14,15,16]

Because of technological advances and the overwhelming success of laparoscopic technology in abdominal operations, laparoscopic colectomy has been used in management of colorectal cancer. Right and left colon, sigmoid colon and upper rectum are the most frequent part to be resected by laparoscope, while other parts of colon are difficult to be resected because of omental attachment. The benefit of laparoscopically assisted colectomy are:

1-reduces postoperative pain and ileus.
2-early tolerance of feeding.
3-shorten hospital stays.
4-less operative blood loss.

5-improve cosmesis.

The disadvantages of these procedures are:

a-longer operative period.

b-expensive equipment.

c-additional surgeons.

d-implication of Co_2 insufflation which may lead to spread of malignancy.

e-there is a danger of local recurrence of malignancy which is due to :

1-contamination of wound by tumor cells.

2-increase exfoliation of tumor cells by laparoscopic technique and manipulation.

3-pneumo-peritonium effect on tumor cells attachment and growth[15].

There is no special criteria for choosing patients to laparoscopic colectomy, but the following points are considered:

I-thin.

II- no previous adbominal surgery.

III-patients with no coagulopathy, liver, respiratory and cardiac disease.

IV-advance colorectal disease such as perforation, obstruction and colo-vesciral fistula.

Laparoscopic colectomy may be converted to laparotomy if there are unclear anatomy, adhesion, abscesses, bleeding and technical difficulties. As we mentioned before right hemi-colectomy, sigmoid colectomy, high anterior resection and stoma formation are the procedures that can be performed by a laparoscope.

Palliative treatment

The poor condition of some patients with acute malignant obstruction of the left colon or irresectable advance pelvic disease make the performance of colo-stomy the only reasonable and un-avoidable technique[17]. But recently one can use the self-expanding metal stent (SEMS) to relieve colorectal malignant obstruction as a palliative measure in patients with advanced colorectal malig-nancies. This can be done through a colonoscope with or without sadation. For low type rectal carcinoma this SEMS must not be used because the patient can not tolerate it and there is a feeling of tenesmus all the time. It is better to do balloon dilatation or laser recanalization[17].

Adjuvant treatment for colorectal cancer[2,3,4]

It is clear now that curative surgery alone is not sufficient for patients with increase risk of recurrence after surgery. Those patients are:

1)stage II colorectal cancer with elevated CEA pre-operatively.

2)stage III colorectal cancer.

So those patients requires adjuvant therapy (chemical, immunological, rad-iotherapy and hormonal therapy).

I-Adjuvant chemical therapy

Those are 5-Fluorouracil (5 FU.), leva-misole, leucovorin, and interferon. They are given alone or in combination, they improve overall and disease free survival (DFS). Levamisole is an antihelmintic agent that enhances 5FU's toxicity to human colon cancer cell lives, but its exact mechanism of action is unknown[2], it may:

a-inhibit tyrosine phosphatases in tumor cells.

b-enhance natural-killer lymphocyte activity.

c-induce expresion of HLA, molecule in cancer cell.

d-claimed immunomodulatory effect (non specific active immunothera-py)[18].

II-Adjuvant immunotherapy[3,4,18,19,20]

These are:

1-tumor targeting monoclonal anti-bodies (MoAb).

2-auto logous tumor vaccine.

3-expanded cytotoxic T.cells with cyto-kines administration.

1-Tumor targeting monoclonal anti-bodies

Two categories of antigen are present on the surface of colorectal cancer cells.

a-tumor associated antigen.(TAA)
b-tumor-specific antigen. (TSA)[20]

The (TAA) includes the following antigens C6-17.1A, TAG 72, CA19-9, CEA, L6, and 28A32. Monoclonal anti-bodies (MoAbs) are developed against these (TAA) and all are of mouse origin except 28A32, which is human IgM. The mechanism of these antibodies-mediated tumor cell cytotoxicties are:

-antibody dependant cellular cytotoxicity (ADCC).
-complement dependent cytotoxicity (CDC).
-antiiodo type response[19].

2-autologous tumor vaccine

Active specific immunization were used in colo-rectal cancer.

a-neurominidase-modified autologous tumor cells and BCG.
b-autologous tumor cells modified by New Castle disease virus.

These produce cell-mediated antitumor immunity[3,18,20].

3-administration of expanded cytotoxic T.cells with cytokenis

IL2 (inter leukin-2) which is lymphokine before.
LAK cell (lymphokine-activated killer cells).

IL2 was found to be solely responsible for generation of LAK cell phenomenon. This phenomenon result in activation of macrophages and tumor killer cells result in regression of tumor cells, and reduction of tumor outgrowth and prolong survival over controls[18]. Injection of IL2 alone or in combination of LAK cells and IL2.

III-Adjuvant radiotherapy

Radiotherapy is limited in colon cancer but it used in rectal cancer.

a-radiation to the bed of colon and rectal cancer to reduce the post operative recurrence.
b-radiation is used in complicated colo-rectal cancer like perforation or obstruction.
c-radiation is used in patients with tumor containing margin in the lymphatics or at the tangential margin of resection.

Radiotherapy may be given pre-operatively, post-operatively and in combination of the two known as sandwich technique. In theory, administration of pre-operative radiation therapy is better than post operative one because undisturbed oxygenated tissue are more susceptible to ionizing radiation than the vascular planes created by operation[9]. In rectal cancer, radiotherapy is used pre-operative either by external radiation or endocavity radiation (through the anus). The following regime is used:

I-suspected transmural invasion. (non fixed, well differentiated cancer)	2000 cGy external radiation for 5 days then surgical resection in the next week.
II-suspected trans-mural invasion (fixed, poor differentiated cancer).	4500 cGy external radiation for 5 weeks 5 days/week), wait for 6-7 week +reevaluation +resection.
III-poor operative risk or extensive metastatic disease.	4500 cGy external radiation for 5 weeks. reevaluation endocavitory radiation 6000 cGy for 2 weeks or surgical resection.

*We wait for 6-7 weeks after external radiation before surgery because:

a-to allow maximum tumor shrinkage.
b-to allow the acute inflammatory changes of radiation to subside.
c-to allow the surgery to be perform before the chronic fibrotic changes of radiation occur[4].

IV -Adjuvant oophorectomy[9]

Bilateral oophorectomy is recommended in all post menopausal women with carcinoma of the colon to decrease the morbidity of neoplastic changes, while in pre-mcnopausal women, this procedure is only done if there is ovarian abnormalities or in the presence of peritoneal implants[9].

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