

COLORECTAL CARCINOMA

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The estimated incidence of colorectal cancer in Canada for 2007 is 20,800 with 11,400 occurring in men and 9,400 in women. This makes colorectal cancer the third leading type of cancer in the population tied with prostate cancer and excluding non-melanoma skin cancer. Among men, colorectal cancer is the third leading cancer in incidence after prostate and lung cancer. It is also the third leading cancer in incidence amongst women after breast and lung cancer.

Colorectal cancer is the second leading cause of cancer death after lung cancer accounting for an estimated 8,700 cancer deaths in 2007. Among men, it is the second leading cause of cancer death after lung (prostate a close third) cancer. Among women, it is the third leading cause of cancer death after lung and breast cancer.

Over 50% of colorectal cancer occur in men and women aged 70 and older and over 50% of colorectal cancer deaths occur in this same age group. The lifetime probability of developing colorectal cancer is one in 15.5 for males and one in 17.5 for females. The lifetime probability of dying from colorectal cancer is one in 35.5 for males and one in 38.6 for females.

In 2006, approximately 325 patients with colon cancer and 179 patients with rectal cancer were seen at the London Regional Cancer Centre.

Genetics and Risk Factors

Colon cancer risk factors are summarised in Table 1. The majority of colorectal cancer is sporadic. Allelic loss in chromosome 17p has been observed in 70-80% of sporadic colon cancers. This region encompasses the gene coding for p53. Another common site of allelic loss in sporadic colon cancer is on chromosome 18q where the DCC (deleted in colon cancer) gene resides. Alterations in chromosome 5q are much less common in sporadic colon cancer and may lead to deregulated c-myc expression. Ras gene mutations have been found in 40-50% of colorectal cancers with ki-ras being the most likely mutation.

Familial adenomatous polyposis is usually inherited in the autosomal dominant pattern with almost complete penetrance. A newly discovered genetic mutation of the gene MYH is responsible for an autosomal recessive variant. The polyposis syndromes frequently result from gene mutation on chromosome 5q where the apc (adenomatous polyposis coli) gene resides. There are a large number of different possible mutations of the APC gene, and phenotypic:genotypic correlations with various cluster areas of mutation are seen. These groupings

may be responsible for the syndromes described in the past, such as Turcot's and Muir-Torre, causing different extra-colonic manifestations.

The hereditary nonpolyposis syndromes are characterised by fewer polyps than in the familial adenomatous polyposis syndromes. Patients typically have mutations in MLH1(69%), MSH2 (38%), or MSH6 (1.3%) and rarely others. All these genes are involved in mismatch repair mechanisms of DNA; failure of mismatch repair can result in increased repeats of doublet bases (or occasionally single bases in MSH6 mutations) called microsatellite instability (MSI). Patients with Lynch syndrome also have a tendency to develop extracolonic tumours including breast, stomach, pancreatic, ovarian and uterine cancers (cancer of the uterus in particular has a lifetime incidence of ~70% among that small group with the MSH6 mutations). Various phenotypic variations of FAP and HNPCC may be related to the position of the various mutations in the respective genes.

Dietary fibre is felt to play a role in the etiology and development of colorectal cancer. Bile acids and their products may also play a role. Whether people who have had a cholecystectomy have an increased risk of colorectal cancer is not clear. There has also been an association between fat intake and colorectal cancer development. Finally, selenium appears to inhibit carcinogenesis.

Table 1 Colon Cancer Risk Factors

Sporadic

- Adenomatous polyp
- Personal history of colon cancer
- Inflammatory bowel disease
- History of breast, ovarian, or endometrial cancer

Hereditary polyposis syndromes

Adenomatous polyps

- Familial adenomatous polyposis
- Gardner's syndrome (+ osteomas, dermoid cysts, fibromas)
- Turcot's syndrome (+ adenomas and glioblastoma)
- Muir-Torre syndrome (+ sebaceous gland and skin tumours)

Hamartomatous polyps

- Peutz-Jegher (distinctive muco-cutaneous pigment)
- Juvenile polyposis
- Cowden (tricholemmomas – skin coloured warty papules)
- Basal Cell Nevus Syndrome
- Neurofibromatosis

Hereditary Nonpolyposis Syndromes

- Lynch I
- Lynch II
- Flat Adenoma

Anatomy and Patterns of Spread

The ascending and descending colon, splenic and hepatic flexures have a retroperitoneal location and lack mesentery. Although the cecum lacks a true mesentery, it may have short folds of peritoneum that give it some mobility. Colonic cancers that invade the posterior bowel in these locations may be more difficult to resect and are more likely to compromise the posterior radial surgical margins. The left colon drains to the inferior mesenteric vessels and the right colon to the superior mesenteric vessels.

The rectum begins where the colon loses its mesentery. This is generally at the level of the body of the third sacral vertebra posteriorly. Anterolaterally, the peritoneum covers the rectum until the reflection onto the seminal vesicles and bladder in the male and upper vagina and uterus in the female. This anterolateral dip in the peritoneal reflection is a significant consideration for patients undergoing sphincter preservation as local excision of tumours in the anterior rectum above the peritoneal reflection carries an increased risk of perforation. The rectum has three transverse folds, two to the left and one to the right with the middle transverse fold lying approximately 11 cm from the anal verge.

Spread of colorectal cancer occurs by peritoneal seeding, lymphatic spread, hematogenous spread and surgical implantation. Cancers that occur below the peritoneal reflections are much less likely to lead to peritoneal seeding. Almost 50% of patients have lymph node involvement at diagnosis. The commonest site of distant metastasis is the liver, although pulmonary and bony metastases occur frequently.

Diagnostic Workup

Change in bowel habit and abdominal pain are the most common presenting features with colon cancer. Patients with left sided colorectal cancer more commonly present with rectal bleeding and melena. Large bowel cancer should be considered as a possibility in patients with microcytic anemia.

Consideration is being given to the implementation of colorectal cancer screening of men and women 50 years of age or over using the fecal occult blood test in Ontario. Digital rectal exam is a simple procedure and should be part of the routine physical exam of patients reporting lower GI symptoms, especially bleeding. Screening colonoscopy is gaining popularity, since it can be therapeutic as well as a screening tool. The sensitivity of FOBT is only about 15 to 20% while the sensitivity of colonoscopy is closer to 95% in experienced hands. The risk of perforation is about 1 in 2000. Resources preclude widespread screening with colonoscopy, although with increasing costs of treating colon cancer, such a program would be cost saving.

The initial diagnostic tests to document colorectal cancer are usually a barium enema, colonoscopy and or proctosigmoidoscopy. Approximately 5% of patients with one tumour will harbour a synchronous cancer. Also, approximately 15-20% of patients with colorectal cancer will have synchronous polyps.

Initial staging investigations in addition to history and physical exam include CXR, and US or CT of the abdomen/pelvis. Carcino Embryonic Antigen (CEA) testing can be useful to establish a baseline for subsequent surveillance after treatment.

Colonoscopy follow-up is usually performed to assess the development of polyps or new colonic tumours as well as to assess the anastomosis in patients who have had resection. Sometimes a colonoscopy cannot be done before surgery (or is done, but incompletely because of obstruction by the tumour), and should be done within six months after if that is the case. An annual colonoscopy is performed in patients who continue to demonstrate polyp formation. Otherwise, the frequency of follow-up colonoscopy is often reduced to every 2-3 years.

In patients with previous rectal cancer, even mild persistent discomfort in the area of the sacrum or coccyx or deep rectal discomfort carries a high index of suspicion for recurrence.

Staging

Dukes described the staging of colorectal cancer based on the depth of penetration of the primary tumour through the bowel wall and the presence or absence of lymph node metastasis. This staging system has been further refined in the TNM staging system as well as the modified Astler-Coller staging system (see Table 2).

Table 2: Staging Systems for Colorectal Carcinoma

Stage	Dukes	Astler-Coller	Modified Astler-Coller	TNM	Description
I	A	A	A	T1N0	Nodes negative; limited to submucosa
		B1	B1	T2N0	Nodes negative; penetration into muscularis propria but not through
IIA	B	B2	B2	T3N0	Nodes negative; penetration through muscularis propria
IIB			B3	T4N0	Nodes negative; invasion or adherence to surrounding organs/structures

IIIA	C	C1	C1	T0-2N1	Nodes positive; limited to bowel wall
IIIB		C1-2	C2-3	T3-4N1	Nodes positive; penetration through muscularis propria, (in T4 see below)
IIIC			C3	T4N2	Nodes positive; invasion or adherence to surrounding organs/structures
IV			D	M1	Any metastatic disease

*In the TNM system, T4 lesions also include those lesions with visceral peritoneal involvement. N1 designates involvement of 1-3 nodes; N2, 4 or more nodes; and N3, involvement of nodes adjacent to a named blood vessel.

The T4 group of tumours can be subclassified by our pathologists into T4a and b. T4a tumours invade other local organs directly, while T4b tumours are simply through the serosa, and the raw surface of the tumour is then open to the peritoneal side of the bowel. Often, the T4a tumours can be removed *en bloc* with the organ structures which contain them, perhaps thereby protecting to some extent the inabdominal cavity. T4 tumours which are completely resected, even with a free surface of tumour such as the T4b type, are NOT considered to have a 'positive radial margin' even though there may be no normal tissue at the free edge of the specimen. That designation is reserved for tumours where the mesenteric resection margin is involved.

These staging systems group patients into different prognostic groups for whom there may be different treatment options. Patients with either complete penetration of the primary tumour through the bowel wall, obstruction, perforation and/or lymph node involvement are at increased risk of recurrence. The absolute number and proportion of lymph nodes involved are also important factors affecting outcome (fewer lymph nodes than 12 resected represents an increased risk). Approximately 20-35% of patients with T3 tumours will experience recurrence. The risk of recurrence increased to as high as 50-70% with the presence of both T3 tumour and lymph node involvement.

Local Spread

Local recurrence is especially significant in rectal cancer. In the University of Minnesota reoperation series, local failure occurred as a component of failure in over 90% of patients who had recurrence after surgery only. The high local failure rate in patients with rectal cancer may, in part, be explained by the close apposition of the rectum to the sacrum, making it difficult to obtain wide lateral (radial) margins. It is generally felt that a two centimetre margin above and below the primary tumour is adequate. Radial margins, which are determined by the pathologist examining an inked specimen, are often less than two centimetres while lymphatic spread within the bowel wall is seldom more than two centimetres longitudinally. This feature had led some surgeons to advocate

total mesorectal excision. Obtaining good lateral and radial margins often requires sharp dissection and the suturing of cut vessels rather than the commonly used method of clamping and tying.

Prognostic Features

Other than stage, colloid (mucinous) carcinomas appear to carry a worse prognosis. Tumours with p53 over-expression and with thymidylate synthase over-expression appear to have a worse prognosis as do tumours with lymphatic vessel or vascular invasion. Aneuploid tumours may also have a worse outlook.

Management

Surgery

The primary treatment for colorectal cancer is complete surgical resection. For colon cancer, this is usually a hemicolectomy. For rectal cancer the two most common operations are an anterior resection or an abdominoperineal resection. The latter operation is usually done for low lying rectal cancers when the surgeon would not be able to reanastomose the rectum.

Sphincter (anal) preservation is a consideration for selected patients with rectal cancer. Surgical options here may include transanal or transsacral local excisions or anterior resection with coloanal anastomosis. For local excision, tumours have to be often smaller than four centimetres in size, well to moderately differentiated, fully mobile, and confined to the rectal wall. Transrectal Ultrasound is increasingly being used to assess the depth of penetration into the bowel wall.

Generally patients can be categorised as having early, high risk, locally advanced, recurrent, metastatic, or medically inoperable colorectal cancer for management purposes.

Adjuvant Therapy

Patients with colon cancer who are presently considered for additional treatment after complete resection of their tumour (adjuvant) are those whose primary tumours exhibit lymph node metastasis (stage III). In these patients, the adjuvant treatment is currently chemotherapy given over approximately six months (5-FU/leukovorin). Selected patients who do not exhibit lymph node metastases but whose primary tumour completely penetrated through the bowel wall, caused obstruction or perforation, and/or have lymphatic or vascular invasion or a high degree of aneuploidy may be offered adjuvant chemotherapy (stage II).

The value of radiation in the treatment of colon cancer is not as clear. Radiation may be useful for patients whose tumours exhibit both complete penetration

through the bowel wall and lymph node involvement or whose tumours extend to retroperitoneal structures.

The benefit of adjuvant chemotherapy in colon cancer can be obtained by multiplying the relative risk reduction by the predicted risk. For 5-FU/leukovorin treatment or equivalents such as continuous infusion 5-FU or Capecitabine (oral 5-FU pro-drug), the relative risk reduction is about 25 to 30%. Thus, if the calculated risk of relapse is 50% in 5 years, the absolute benefit of adjuvant chemotherapy is about 15% overall. The risk of relapse is established by the stage of the cancer and other parameters. A commonly used Web based program, AdjuvantOnline!, (<http://www.adjuvantonline.com/online.jsp>), can be used to establish such a risk, although Stage II disease has a survival of over 85%, while stage III disease can be as low as 25%.

Physicians have gradually shifted from the older Mayo Clinic regimen of bolus 5FU and leukovorin given for five days a week once a month, to infusional 5FU over 48 hours every two weeks, having found the latter equal in efficacy, but less toxic.

While the treatment of stage II disease with adjuvant therapy remains controversial, the recent QUASAR study suggests between a 1 and 5% overall benefit for adjuvant 5-FU based chemotherapy. For young healthy patients with other risk factors, this may be enough for them to decide to be treated.

The MOSAIC trial, first reported in 2004, and recently updated, continues to show about a 20% relative risk reduction of death in stage III patients for the addition of Oxaliplatin, as compared to 5FU based adjuvant therapy. While the reports only show trends for stage II patients, many oncologists will use Oxaliplatin based chemotherapy in those high risk patients with stage II disease who elect to proceed with chemotherapy even though the supporting data may be equivocal.

In rectal cancer patients whose tumours have been completely resected by surgery, patients with T3 tumours and/or with positive lymph nodes are considered for adjuvant treatment, which consists of a combination of chemotherapy and pelvic radiation given over 6 months. The radiation component is directed at the pelvis and operative bed and is given daily, five days a week for six weeks. During the pelvic radiation, the patient is given continuous infusion 5-FU chemotherapy (this runs day and night through a central line using a pump).

A recent German study has demonstrated improved toxicity including an improvement in sphincter sparing surgery, by giving the chemo-radiotherapy prior to the surgery, rather than after. This is referred to as neoadjuvant therapy. About 20% of patients treated in this manner will have no sign of the cancer at the time

of surgery, or in the pathology specimen. Preoperative treatment has the advantage of down-staging the cancer, thus increasing the chances of clear margins and of sphincter preservation (avoiding a colostomy). It has the disadvantage of exposing a small number of patients to more treatment if they would have required surgery only. Additional advantages to preoperative chemoradiation seen in the German study were improved local control and better rectal function with no obvious increase in postoperative complications. In addition, there is some evidence now that the chemotherapy component may add to the prevention of local recurrence (in the past, it was felt tht it only affected systemic relapse rates).

At LRCP, neoadjuvant chemoradiotherapy is employed for patients who are suspected of having T3 or N+ disease. The chemotherapy is delivered by a low dose continuous infusion through a percutaneous intravenous catheter (PICC line) during the radiation treatment, which takes about 5½weeks. Surgery is then scheduled to occur within a optimal window of 6 to 8 weeks (before this the tissues are hard to discriminate, afterward they become too fibrotic).

When neoadjuvant therapy is employed, the pathology staging does not truly reflect the pre-treatment staging, as patients' stage may change during neo-adjuvant therapy (hopefully down). When we report pathological staging it is often preceded by the prefix 'p', as in pT4 for example. When the pathology is only available after some form of treatment (radiation or systemic therapy) the prefix 'y' is added, as in ypT2. The pathologic stage after treatment correlates with Disease Free Survival, as shown below. The continued presence of tumour without downstaging is a porr prognostic indicator.

	ypT0	ypT1	ypT2	ypT3	ypT4
5yrDFS	86%	95%	81%	65%	42%
	ypN0	ypN+			
5yrDFS	85%	46%			

Some cancer centres employ a very brief course of preoperative radiation alone (25 Gy in 5 fractions in one week followed by surgery within 2-3 weeks) for rectal cancer, which is not accompanied by chemotherapy. The two approaches have not been compared in randomized trials. The chemoradiation option has the advantage of the early initiation of systemic therapy.

Adjuvant chemotherapy after the neoadjuvant treatment and surgery, is often offered for four months (instead of the usual 6 months in colon cancer, because the continuous infusion provides almost two months of chemotherapy coverage), and treatment protocols are extrapolated from the colon data. There is a tendency however, to use adjuvant post operative chemotherapy in stage II rectal cancer because of the differences in anatomy (no containment by serosa) and

because the original clinical staging is used to determine this therapy (that is, patients with downstaged tumours, even to ypT0N0, would still usually go on to post-operative adjuvant chemotherapy).

Side Effects

For chemotherapy, these include: increased sun sensitivity, mucositis, diarrhoea, lowered blood counts, neutropenic sepsis, and moderate to marked hair loss. Continuous infusion 5-FU has a different side effect profile with less haematologic toxicity, but an increased risk of hand-foot syndrome. Occasionally, 5-FU causes angina or cerebellar ataxia.

An odd complication of Oxaliplatin is laryngopharyngeal dysesthesia, a sensation of the inability to breathe, which can be aggravated by exposure to the cold. Other neuropathies are commonly associated with the platinum agents, but fortunately, almost all grade 3 or higher toxicity is gone within one year.

Common side effects of pelvic radiation include skin reaction, diarrhoea, abdominal cramping, urinary frequency or burning, and proctitis. In men, pelvic irradiation may lead to impotence, sterility and retrograde ejaculation. In women, pelvic radiation causes radiation induced menopause and vaginal stenosis, which may induce dyspareunia.

The small bowel is the dose limiting organ for pelvic radiotherapy. There are surgical manoeuvres to help reduce the incidence of small bowel complications. These include omentoplasty and replacement of and absorbable mesh to lift the small bowel off the posterior pelvis. The use of surgical clips to mark the periphery of an area of suspected residual tumour is of great value in subsequent radiation treatment planning. The placement of these clips should be done in three dimensions if possible in order to define the volume at risk. Neoadjuvant therapy in rectal cancer helps to spare the bowel, because the bowel has not fallen down into the pelvis to replacement the resected rectum.

Clinical Trials

Treatment approaches for colorectal cancer have developed because of a series of randomised clinical trials. Several new chemotherapy drugs are now being tested for their potential value in colorectal cancer including Capecitabine, Irinotecan, and antibodies such as Cetuximab and Bevacizumab.. Laparoscopic surgery for resection of colon cancer is also being investigated in a few centres.

Metastatic or Stage IV Disease

When colon or rectal cancer becomes metastatic, it is often largely palliative. The one exception occurs when metastatic disease is localized to the liver, and can be resected. Survival ranges between 20% and 40% over five years, depending on a number of factors (number of metastatic deposits, duration of disease free interval, CEA level, number of lymph nodes in original surgery).

Appart from those cases where metastatectomy may be performed, survival of patients is severely limited. Before any 'new' treatment programs were available, survival was often at best only 8 months. With newer agents such as Oxaliplatin, Irinotecan, and targeted therapy agents such as Bevacuzimab and Cetuximab (monoclonal antibodies against VEGF and EGFR respectively), patients may be able to live out to 22+ months with metastatic disease. Unfortunately, the prohibitive cost of some of these agents (primarily the targeted therapies) makes them unavailable to most patients in Canada. Using colonoscopy to screen and treat patients before they become advanced stage seems to be the best way to avoid these costs, not to mention avoid human suffering, but again resources restrict the ability to screen all the population at risk.