

Colorectal carcinoma

Colorectal carcinoma is a common malignancy affecting up to 80 per 100 000 people in Western countries and fewer than 15 per 1 000 000 people in developing countries.

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Incidence and aetiology

Up to 95% of cases of colorectal carcinoma (CRC) are sporadic; the remainder are inherited or associated with an underlying abnormality such as inflammatory bowel disease. The condition becomes more common with increasing age. An important aetiological factor is diet. Risk factors include high fat, high protein, increased total calories, processed foods (low fibre), and alcohol and smoking. Exercise is protective, and low-dose NSAIDs may be of value in reducing risk by inhibition of cyclo-oxygenase.¹ Patients should be advised to change to an unprocessed diet rather than supplement a Westernised diet with bran.

There is an increased risk in people with first-degree relatives with CRC. The two commonest hereditary syndromes are familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC). The gene responsible for FAP is the APC gene on chromosome 5. These patients present with multiple (>100: usually > 1 000) polyps of the large bowel. The defect in HNPCC is the mismatch repair gene associated with micro-satellite instability, and has a high lifetime risk of developing CRC (98% in men, 40% in women). There are at least 5 pathways involved in the molecular expression of CRC cancer genes.

Screening

The purpose of screening is to identify and remove adenomatous polyps and thereby decrease the incidence of CRC. The South African Gastroenterological Society (SAGES) recommends 10-yearly colonoscopy from the age of 50, since this is cost effective and has a high sensitivity and specificity.

In patients at higher risk, that is those with affected first-degree relatives, known hereditary syndromes, or inflammatory bowel disease, screening should start earlier – generally 10 years prior to the age at which a first-degree relative was diagnosed with CRC. Prophylactic colectomies are recommended for patients with FAP and HNPCC once the presence of the genotype has been confirmed.

In FAP, the initial procedure (late teens to early twenties) should be total colectomy with ileorectal anastomosis, followed approximately 10 years later by proctocolectomy and ileal pouch construction. Patients with FAP who present for surgery later should have a proctocolectomy and pouch without delay. The role of prophylactic colectomy in HNPCC is controversial, but if these patients present with established malignancy, the initial procedure should always be a total rather than a segmental colectomy (high rate of metachronous tumours). In general the rectum can be kept under surveillance, rather than proceeding routinely to proctectomy and pouch.

Diagnosis

The commonest symptoms with large-bowel cancer are:

- altered bowel habit
- rectal bleeding
- iron deficiency anaemia
- abdominal pain.

All such patients must be fully investigated, in particular with colonoscopy. The staging of colorectal cancer is given in Table I. Duke's classification for staging CRC was developed in the 1930s. The American Joint Committee on Cancer Staging has now adopted the TNM system (see Table). This is based on pathological findings and the final stage can only be determined postoperatively.

Surgical management

Tumours involving the large bowel between the caecum and sigmoid colon, without evidence of metastases, are resected by means of the appropriate segmental colectomy.

Historically, surgery for carcinoma of the rectum included abdominoperineal resection and permanent colostomy. Now that we better understand the nature of local spread in the mesorectum, meticulous dissection, and very low stapling or suturing techniques

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have allowed far more sphincter-sparing procedures, without any increase in local recurrence.

Occasionally, in the frail elderly patient, local (transanal) excision can be considered for superficial lesions in the lower third of the rectum. Tumours lying more than 2 cm above the sphincters may be safely treated with anterior resections with total mesorectal excision (TME).² This procedure should be confined to high-volume units, with surgeons who have been trained in the technique. It involves resection of the tumour with sharp dissection of the pelvic fascia between the perineal and visceral planes to remove the entire mesorectum. Reconstruction is done using a colonic J pouch. Many patients will require a temporary ileostomy, given the risk of leakage with these low anastomoses. Low rectal tumours less than 2 cm from or involving the sphincters require abdominal resection with a permanent colostomy. The use of TME has reduced local recurrence rates from 30 - 50% to 5 - 8%.

Role of radiation in rectal cancer

In the frail elderly patient with superficial lesions in the lower third of the rectum endocavity radiation with orthovoltage applicators or high-dose-rate brachytherapy give equivalent results to local excision (96% for T1 tumours, 86% for T2). Additional external radiation is recommended for T2 tumours.

For tumours of doubtful resectability radiation to the pelvis to a dose of 45 - 50 Gy over 5 - 6 weeks with concurrent 5-fluorouracil (5FU)-based chemotherapy should be administered preoperatively. Surgery should then be performed between 1 - 2 months post-radiation (after inflammation has settled and before fibrosis sets in). For locally advanced colorectal cancers intraoperative radiation may be used to control residual disease. Local control rates of 75% for gross residual disease and 95% for microscopic residual disease can be achieved. Intraoperative radiation can also be used in conjunction with surgery for locally recurrent disease in previously irradiated patients.

For lesions that are clearly resectable radiation is indicated for high-risk cases. Prior to the introduction of TME, the rate of local recurrence was high, because the technique used to remove the rectum fractured the mesorectum precisely where it was most friable, over the cancer, and implanted malignant cells in the pelvis. Radiation given pre- or postoperatively was found to reduce the recurrence rate by a factor of 2 - 3. A German collaborative study³ compared preoperative with postoperative radiation and found local recurrences were halved from 12% to 6% ($p = 0.006$) in the preoperative group. 20% of patients who would have required abdominoperineal resections were able to have sphincter-preserving operations. There was no difference in survival between the two groups.

A Dutch randomised trial⁴ has compared short-course preoperative radiotherapy and TME with TME alone and found that the rate of local recurrence was reduced in the combined arm from 8.2% to 2.4% at 2 years ($p < 0.001$) This trial was not stratified according to the level of the tumour. It has been shown that local recurrence varies with the level of the tumour in the rectum. Lesions in the upper 1/3 have a low recurrence rate (1 - 2%), comparable with that of sigmoid cancers. Middle-third lesions have a recurrence rate of 4 - 6%, while the lower-third lesions (where sphincter salvage is possible) recur slightly more frequently. Local recurrence is highest in distal cancers (12 - 20%) where abdominoperineal resection is necessary. This is possibly due to the absence of a mesorectum in the distal 2 cm of the rectum, allowing malignant cells to breach the capsule instead of being filtered into the mesorectum. For this reason our policy is to give all lower-third clearly resectable lesions short course (25 Gy in 5 days) preoperative radiation. Surgery must be performed within 7 days to minimise complications.

In the postoperative setting radiation is indicated for all T4 tumours or those with positive circumferential margins. The dose is 45 - 54 Gy given concurrently with 5FU-based chemotherapy over 5 - 6 weeks. If the surgery was not a TME, and preoperative radiation was not given, postoperative chemoradiation is also indicated to T3 and node-positive tumours.

The use of radiation does increase the risk of bowel dysfunction and impaired sexual function. The German study has shown decreased toxicity with preoperative as compared with postoperative radiation.

Palliative radiation plays an important role in the control of bleeding and pain in locally advanced irresectable disease, as well as in pain control for metastatic disease.

Table I. Staging of colorectal cancer

Stage	T stage	N stage	M stage	5-year survival
I	T1 or T2	N0	M0	93.2*
IIa	T3	N0	M0	84.7*
IIb	T4	N0	M0	72.2*
IIIa	T1 or T2	N1	M0	83.4* 59.8*
IIIb	T3 or T4	N1	M0	64.1* 42.0*
IIIc	Any T	N2	M0	44.3* 27.3*
IV	Any T	Any N	M1	8.1*

T1 = tumour invades submucosa; T2 = tumour invades muscularis propria; T3 = tumour invades through the muscularis propria into the subserosa nonperitonealised pericolic tissues; T4 = tumour directly invades other organs or structures and/or perforates visceral peritoneum; N0 = no regional lymph node metastasis; N1 = metastasis to one to three regional lymph nodes; N2 = metastasis to four or more regional lymph nodes; M0 = no distant metastasis; M1 = distant metastasis.

Tumours involving the large bowel between the caecum and sigmoid colon, without evidence of metastases, are resected by means of the appropriate segmental colectomy.

Chemotherapy in colorectal cancer

Trials in the 1980s and early 1990s showed a small (5 - 6%) survival benefit for patients with resected node-positive (i.e. stage III) colon cancer with the use of adjuvant 5FU-based chemotherapy. A recent trial has shown improved disease-free survival in these patients using the combination of oxaliplatin with 5FU and leucovorin.

Chemotherapy for metastatic disease has developed dramatically over the last 10 years. Prior to the late 1990s the only agent to show any significant effect was 5FU, with response rates of 20 - 30% and median survivals of 10 months. More recently the addition of the newer agents oxaliplatin or irinotecan to 5FU has increased response rates to 60% and median survival to 15 months. Development of targeted agents, such as cetuximab and bevacizumab, is expected to further increase survival to 2 years. The availability of numerous drugs has allowed the use of second- and third-line regimens. All the agents are well tolerated and treatment does not compromise quality of life for improved survival.

Isolated liver or lung metastases should be resected. Another exciting development is the use of combination chemotherapy to downstage liver metastases and allow for resection. Localised irresectable liver

metastases can be treated with radiofrequency ablation, cryotherapy, body radiosurgery or high-dose-rate brachytherapy delivered intraoperatively or percutaneously. Long-term survival is possible and 5-year survival rates of 50 - 60% have been reported.^{5,6}

Conclusion

Large-bowel cancer is a common disease. Screening is critical in order to reduce the incidence of the disease. In symptomatic patients, clinicians should have a high index of suspicion and refer them for investigation. There is good long-term survival after treatment of early lesions. Advances in surgical techniques have resulted in lower recurrence rates, better overall survival and better functional outcomes. Improvements in the timing and delivery of radiation have resulted

in lower local recurrence and complication rates. Recent developments in chemotherapy and targeted agents have produced a marked improvement in survival of patients with metastases. Multidisciplinary management improves outcomes of treatment by optimal co-ordination of all treatment modalities.

References

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In a nutshell

- Large-bowel cancer is a common disease, especially in ageing Western populations.
- Diet is an important aetiological factor.
- Screening is critical in order to reduce the incidence of the disease. In symptomatic patients (change of bowel habit, rectal bleeding), clinicians should have a high index of suspicion and refer patients for investigation.
- There is good long-term survival after treatment of early lesions.
- Advances in surgical techniques, especially the introduction of total mesorectal excision, have resulted in lower recurrence rates.
- Improvements in the timing, and delivery of radiation have resulted in lower local recurrence rates and complication rates.
- Recent developments in chemotherapy and targeted agents have produced a marked improvement in survival of patients with metastases, allowing patients with metastases to survive 2 years and more.
- Multidisciplinary management improves outcomes of treatment by optimal co-ordination of all treatment modalities.