Colorectal cancer

Definition of colorectal cancer

- A malignant neoplasm arising from epithelium anywhere in the large bowel (caecum, ascending, transverse, descending or sigmoid colon, rectum), excluding the appendix and the anus
- The vast majority are adenocarcinoma
    - Squamous and adenosquamous carcinoma can occur in the distal rectum

Epidemiology of colorectal cancer

- In the UK, colorectal cancer is the 3rd most common cancer at 12% of all cancers, after breast and prostate
- Worldwide incidence (age-standardised) is 17 per 100,000, but varies markedly with geography:
    - 4 per 100,000 in Western Africa to 38 per 100,000 in Australia/New Zealand
- Generally more common in more economically developed countries
- 59% of cases occur in men
- The median age at diagnosis is approximately 70 in the UK

Risk factors for colorectal cancer

- **Demographic risk factors**
    - Age (colorectal cancer is uncommon below the age of 40)
    - Male sex
    - Ethnicity (in the US, black people have a higher risk but this may be due to confounding variables)
- **Family history of colorectal cancer**
- **Previous history**
    - Previous colorectal cancer
    - Previous polyps >1cm, exhibiting high grade dysplasia or with villous/tubulovillous histology
- **Comorbidities**
    - Ulcerative colitis and Crohn's colitis (risk increases with extent and duration of colitis)
    - Abdominal radiation
    - Immunosuppression (e.g. in renal transplant recipients)
    - Diabetes mellitus
- **Modifiable risk factors**
    - Smoking
    - Obesity
    - Processed meat (and possibly also red meat)
    - Alcohol
- **Genetic disorders**
    - **Hereditary non-polyposis colorectal cancer (HNPCC)**
        - Autosomal dominant, due to mutations in various mismatch repair genes
        - Responsible for 3% of colorectal cancers
        - It also increases the risk of endometrial cancer, other GI tract cancers and ovarian cancer
    - **Familial adenomatous polyposis (FAP)**
        - Autosomal dominant defect in *APC* gene
        - Causes numerous colonic polyps in childhood and colorectal cancer by the age of 45 in 90% of patients
    - ***MUTYH*-associated polyposis**
        - Autosomal recessive condition which may cause polyposis and confers increased colorectal cancer risk

Protective factors for colorectal cancer

- Vegetarian and high fibre diet
- Daily aspirin use
- Difluoromethylornithine (DFMO) plus sulindac (an NSAID) reduce recurrence in those with prior adenomata

Presentations of colorectal cancer

- Variable, depending heavily on site of tumour
- **Symptoms from primary tumour**
    - Iron-deficiency anaemia (commonly caecal, ascending colon)
    - Altered bowel habit (anywhere) to more loose stool ± mucous
    - Abdominal pain (from partial obstruction, or perforation causing acute peritonitis, or a localised abscess)
    - Bowel obstruction (pain, bowels not open, abdomen distension, vomiting)
    - Fresh blood per rectum (descending, sigmoid, rectum)
    - Tenesmus (sensation of incomplete defecation; rectum)
    - Rarely, *Streptococcus bovis* and *Clostridium septicum* infections are the first manifestation of a colorectal cancer, and may present as infective endocarditis.
- **Symptoms from metastatic spread (20% have metastatic disease at presentation)**
    - Jaundice, RUQ pain, early satiety, from hepatic metastases
    - Ascites or pain, from peritoneal metastases
    - Pneumaturia or recurrent UTI, due to a colovesical fistula
    - Weight loss
- **Incidental diagnosis**
    - Clinical findings (abdominal or rectal mass)
    - Incidental imaging of large bowel or liver
- **In a screening programme**
    - Positive faecal occult blood test / colonoscopy

Screening for colorectal cancer

- Frequent screening with colonoscopy should be undertaken in those with a known hereditary syndrome (FAP, HNPCC, *MUTYH*-associated polyposis)
- Screening strategies for average-risk populations include colonoscopy, CT colongraphy, and faecal occult blood (FOB) testing
- National guidelines vary; in the UK an FOB test is done every 2 years between the ages of 50 and 74, and a single flexible sigmoidoscopy is performed at age 55.
- In the event of a positive FOB test a colonoscopy is undertaken.

Differential diagnosis for a colorectal mass

- Other rare colonic cancers: lymphoma, carcinoid tumours, Kaposi's sarcoma, invasive prostate cancer
- Benign polyps
- Pseudopolyps in colitis
- Endometriosis
- Lipoma
- Tuberculosis

Investigation of colorectal cancer

- Blood tests
  - FBC, U&E, LFT, Calcium
  - Clotting, group and save
- Colonoscopy is the best first line test, to identify cancers and co-incident second cancers (synchronous lesions), and obtain tissue for histology: brushings, biopsy or resection
  - Note that flexible sigmoidoscopy is inadequate, even with distal tumours, due to the risk of synchronous lesions
- CT colonography may be used in those unlikely to tolerate colonoscopy
- Barium enema should not be used unless the above are not available
- If cancer is confirmed, further imaging for staging should be undertaken
  - CT abdomen-pelvis to assess local invasion of the primary, lymphadenopathy, and hepatic metastases
  - CT chest is usually undertaken, though only 10% of nodules seen are colorectal metastases

Staging of colorectal cancer

- Tumour node metastasis (TNM) last revised in 2010. Briefly:
  - T1 invades through the submucosa, and T4 invades through visceral peritoneum
  - N0-N2 depends on number of regional lymph nodes
  - M0-M1 depends on distant metastases
  - The TNM status is combined to give a stage from I to IV, where III is defined by nodal disease, and IV by metastatic disease
- Dukes staging (A-C, based on invasion of primary and node status) is no longer used

Histology and genetics of colorectal cancer

- Histological grade is divided into low or high, based on gland formation in the tissue
- Mucinous, signet ring and medullary adenocarcinomas carry a worse prognosis
- High microsatellite instability, due to mutated mismatch repair genes, occurs in 15-20% of cancers and is associated with a better prognosis, if the cancer is localised
- Mutations in RAS or NRAS confer resistance to anti-EGFR therapy

Initial surgical management of localised colorectal cancer

- For dysplastic polyps and carcinoma in situ, colonoscopic excision is curative if the margins are clear
- For stage I-III adenocarcinoma, surgical excision is the mainstay of treatment, provided the patient is fit enough for surgery (considering comorbidities and performance status)
- The approach may be determined by urgent complications such as perforation or obstruction; in these instances it may be necessary to create a proximal defunctioning stoma, or an end stoma with an anastamosis formed at a later date
- Elective treatment should be with a right or left hemicolectomy, or sigmoid colectomy, as determined by the site of the primary
- Complete mesocolic excision should be performed, to include the mesentery and regional lymph nodes from the primary site
- In experienced hands, a laparoscopic approach is preferred to an open operation, but with a low threshold for conversion to open in the case of complications
- Patients with FAP, HNPCC or synchronous cancers in the left and right should be managed with a total colectomy
- Locally invasive primary cancer should be resected *en bloc* to achieve clear margins. If this is not possible neoadjuvant (preoperative) chemotherapy can be considered

Adjuvant treatment for localised colorectal cancer

- 6 months of adjuvant oxaliplatin-based chemotherapy should be given in stage III (node positive) disease e.g. oxaliplatin plus 5-FU, or oxaliplatin plus capecitabine
- Rectal cancer should be treated with neoadjuvant chemoradiotherapy if locally invasive or node positive; all other rectal cancer of stage II or higher should be treated with chemoradiotherapy post-operatively

Management of metastatic colorectal cancer

- Limited metastases in liver or lung may be amenable to resection, which may bring long-term cure
- First line chemotherapy for patients unsuitable for curative treatment should be either:
    - FOLFOX (5-FU/leucovorin/oxaliplatin)
    - XELOX (capecitabline/oxaliplatin)
    - FOLFIRI (5-FU/leucovorin/irinotecan)
- Bevacizumab (monoclonal antibody against VEGF) may be added, though it has a poor cost-benefit profile
- Monoclonal antibodies against EGFR (cetuximab; panitumumab) can be added in those with wild-type *KRAS*

Complications of colorectal cancer

- Metastasis
- Obstruction
- Iron deficiency anaemia
- Bleeding
- Colovesical fistula

Prognosis of colorectal cancer

- Mortality overall is 50% worldwide
- Over 90% of stage I patients are alive, whereas only 8% of stage IV are, at 5 years after diagnosis.
- The major determinant of prognosis is TNM staging
- Other poor prognosticators include:
    - Perivascular or perineural invasion
    - High carcinoembryonic antigen (CEA) levels
    - Intestinal obstruction at presentation
    - Macroscopic perforation at presentation

Questions about colon or rectal cancer

- **What are complications of colon cancer?**
    - Local
        - Obstruction
        - Perforation
        - Bleeding (and/or iron deficiency anaemia)
        - Colovesical fistula
    - Distant
        - Metastasis
- **Other than surgery, what treatment would you consider for local colorectal cancer?**
    - Adjuvant oxaliplatin-based chemotherapy should be given in stage III (node positive) disease, for six months.
        - e.g. oxaliplatin plus 5-FU, or oxaliplatin plus capecitabine

- Rectal cancer should be treated with neoadjuvant chemoradiotherapy if locally invasive or node positive
- All other rectal cancer of stage II or higher should be treated with chemoradiotherapy post-operatively

- **What are the initial investigations used to diagnose colon cancer?**
  - Bloods
    - FBC, U&E, LFT, Calcium
    - Clotting, group and save
  - Colonoscopy
    - Identifies cancers and co-incident second cancers (synchronous lesions), and obtain tissue for histology: brushings, biopsy or resection
    - CT colonography may be used in those unlikely to tolerate colonoscopy
  - If cancer is confirmed, further imaging for staging should be undertaken
    - CT abdomen-pelvis to assess local invasion of the primary, lymphadenopathy, and hepatic metastases
    - CT chest is usually undertaken, though only 10% of nodules seen are colorectal metastases
- **What are the major risk factors for colorectal cancer?**
  - Demographic risk factors
    - Age
    - Male sex
    - Ethnicity (black people have a higher risk but this may be due to confounding variables)
  - Family history
  - Previous history
    - Previous colorectal cancer or previous polyps >1cm exhibiting high grade dysplasia or with villous/tubulovillous histology
  - Comorbidities
    - Inflammatory bowel disease (risk increases with extent and duration of colitis)
    - Abdominal radiation
    - Immunosuppression
    - Diabetes
  - Modifiable risk factors
    - Smoking
    - Obesity
    - Processed meat
    - Alcohol
- **What genetic disorders are associated with colorectal cancer?**
  - Hereditary non-polyposis colorectal cancer (HNPCC)
    - Autosomal dominant, due to mutations in various mismatch repair genes and responsible for 3% of colorectal cancers
    - Also increases the risk of endometrial cancer, other GI tract cancers and ovarian cancer
  - Familial adenomatous polyposis (FAP)
    - Autosomal dominant defect in *APC* gene
    - Causes numerous colonic polyps in childhood and colorectal cancer by the age of 45 in 90% of patients
  - *MUTYH*-associated polyposis
    - *A*utosomal recessive condition which may cause polyposis and confers increased colorectal cancer risk