### 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 resections, 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 anastomosis formed at a later date
- Elective treatment should be with a right or left hemicolecotomy, 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 (capecitabine/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**
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- **What are the major risk factors for colorectal cancer?**
  - **Demographic risk factors**
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  - **Family history**
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    - 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
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- **What genetic disorders are associated with colorectal cancer?**
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