COLORECTAL CANCER

Colon cancer 70%:
Rectal cancer 30%: tumour with lower edge at/below 15cm from anal verge (low if at/below levator origin ie 6cm)

Epidemiology:
Age: Gender: Incidence: Prevalence 3rd commonest cause of cancer death
Distribution:

Aetiology:
1. GENETICS (a)Germline(inherited bowel cancer syndromes) (b)Sporadic:APC (60%)/k-ras oncogene/p53 TS gene: rare in adenomas, common in invasive cancer/DCC
2. DIET & LIFESTYLE: *2007 WCRF Report on Food, Nutrition, Physical Activity and the Prevention of Cancer*
Decreased risk: exercise/fibre/calcium/garlic/non-starch veg/pulses
Increased risk: obesity/red meat/processed meat/alcohol/animal fat/smoking
3. PREDISPOSING CONDITIONS: IBD/ureterosigmoidostomy/gastric surgery incl. vagotomy →altered bile acid metabolism

Pathology:
Most arise from **adenomas**
KRAS/HRAS/NRAS= mutation in 40% CRCs (10% <1cms, 40% >1cms)
p53= regulates cell-cycle checkpoints at G1/S and G2/M boundaries

Pathogenesis:
Adenoma-Carcinoma Sequence: sequential progression of **mucosa→adenoma→adenocarcinoma**
multiple hit hypothesis in sporadics vs germline mechanisms in familial

Polyp
Epithelial elevation above mucosal surface
Micro: adenoma
Macro: characterised by **size/number/architecture**(tubular/tubulovillous/villous)**/morphology**(sessile/pedunculated)
Site:
Clinical features: bleeding/mucous/mass effect/hypokalaemia
Investigations: LGI endoscopy +/- CT
Management: polypectomy/resect(1mm margin/high grade/poor diff/EMVI)/TEMS(rectal)
Resection: (i)Polyp cancer if size >2.5cm/<1mm margin/incomplete excision/high grade/poor diff/EMVI (iii)T2 (H4/Ksm1+)
20%LNs/30% LNs

Haggitt levels (pedunculated): 1-head 2-head/stalk junction 3-stalk 4-invading submucosa (or all sessiles by definition)
Kikuchi levels (sessile): Sm1,2,3 depending on depth of submucosal invasion by thirds
Kudo levels (pit pattern): 1=normal rounded 5=irregular, amorphous

Polyp surveillance
Low risk: one or two adenomas <10mm
Intermediate risk: three or four adenomas <10mm OR one or two adenomas if one >10mm
High risk: five adenomas <10mm OR three of four adenomas if one >10mm

Low risk → colonoscopy 5yrs → discharge if negative

Intermediate risk → colonoscopy 3 yrs → negative: colonoscopy 3yrs → discharge if two consecutive normal scopes
→ low/int risk: colonoscopy 3yrs → colonoscopy 3yrs as per intermediate risk
→ colonoscopy 1yr if high risk and follow high risk pathway

High risk → colonoscopy 1 yr → negative/low/int risk: colonoscopy 3yrs and follow intermediate pathway
→high risk: colonoscopy 1 yr

Spread:

Direct: colon=longitudinally$_{\text{in intramural lymphatics (rarely >2cm → 5cm resection margins)}}$; transversely; radially
rectal= 1cm (2cm margin sufficient); 4cm if poorly-differentiated (5cm margin)
Lymphatic: paracolic/peri-rectal nodes along arterial pedicle → para-aortic nodes (30% nodal spread skips this)
(colon: not likely if not breached MP, unlike rectal)
Blood: Liver$_{(50\%)}$, Lung $_{(10\%)}$, Other: bone, brain, ovary, adrenal, kidney
Transcoelomic: through peritoneum (subperitoneal lymphatics) + tumour cell-shedding

CLINICAL FEATURES

Symptoms:

CIBH (constipation/diarrhoea/alternating) → obstruction (20% present as emergency, including perforation)
Pain/bloating/discomfort
PR bleeding (bright/dark)
Mucoid stools (polyps/cancers have columnar epithelium)
Constitutional symptoms
Anaemia
Tenesmus/incomplete evacuation in rectal

Signs:

Inspection/Palpation/Percussion/Ausculation
DRE

*Right-sided: wide, liquid faeces, polypoid tumours → non-obstructive
*Left-sided: narrower, solid faeces, stenosing tumours → obstructive

SUSPECTED CANCER PATHWAY REFERRAL

Colorectal clinic appointment within 2 weeks
40+: unexplained weight loss + abdo pain
<50: unexplained rectal bleeding PLUS any of abdo pain/weight loss/CIBH/IDA
50+: unexplained rectal bleeding
60+: IDA/CIBH to loose for 6 wks
Positive FOB
Mass in rectum/abdomen

INVESTIGATIONS

CRC 3rd commonest cancer (incidence: 40,000/year) w/ 16000 deaths/yr
21% present as emergency + later stage (3x more likely than screened cancers) → poorer outcome
Stage correlates with overall outcome

1. Guaiac-faecal occult blood testing (gFOBt):

Normal blood loss 1ml/day; polyps/cancers produce more
Haem contains psueoperoxidase; when PP exposed to H202, releases O2 which turns guaiac blue
Sensitivity: 92-94% from 3 samples over 2 weeks (25-38% from single sample)

NHSBCSP: All 60-74yo every two years in England/Wales/NI (earlier in ighi risk groups)
Positive test (20/1000) → colonoscopy (16) or OPD in 14d → 2 cancers/6 polyps/8 normal

2. National Bowel Scope Programme:

Flexible sigmoidoscopy to all at 55yo (can opt in up to 60)
Reduces CRC incidence 23%/mortality 31% (Atkin et al 2010)

Colon:

Bloods: **CEA**/Hb/LFTs/U&Es for bowel prep

Endoscopy: **Colonoscopy** (visualise/biopsy/excision eg EMR or ESmR/stent)

Imaging: **CT TAP**(staging in all); **CT colon** (polyps 6mm+)

NICE: offer colonoscopy to all unless comorbid; flexi then CT colon if majorly comorbid; biopsy suspicious lesions

Rectal:

Histological diagnosis essential before treatment when surgery might result in permanent stoma; cf optimal in colon cancer

1. **MRI**: assess risk of local recurrence (CRM most important predictor; T stage also but less so)

MERCURY: MRI accurately predicts pT stage/CRM to 1mm/extramural (T3) spread to 0.5mm/LN status(less accurate)/EMVI

2.**ERUS**: (i)all rectal cancer if MRI contraindicated (ii)assess amenability to local resection ie early rectal cancers

Accurate predicts T stage but poor at N stage and CRM

Risk of local recurrence in rectal cancer:

NICE: rectal cancer categorised according to recurrence risk based on MRI

Main determinant of LR(2.6-32%) is CRM ||other: T stage/<4cm from verge/size/grade/extent of spread/incomplete excision

1. High: (i)threatened (within 1mm) or breached CRM (ii)low tumour involving levators/intersphincteric plane

2.Moderate: (i)cT3b with non-threatened CRM (ii)LN not threatening margin (iii)EMVI

3. Low: up to T3a + N0

STAGING

Microscopic: type/differentiation/invasion depth(T)/LN's inc. apical node/EMVI/completeness of excision/margins

Macroscopic: morphological classification: annular/papilliferous/tubular/ulcer

T(similar to gastric ca)	N	M	DUKES	STAGES
Tis: in situ	N1a: 1	M1a: 1 organ		0
T1: mucosa(E/LP/MM)/submucosa	N1b: 2-3	M1b >1 organ	A: T1/2 N0M0	I: T1/2 N0M0
T2: muscularis propria	N2a: 4-6		B: T3/4 N0M0	II: T3/4 N0M0
T3a: subserosa	N2b: 7+		C1/2: any T N1/2	III: any T N1/2
T3b: pericolic/perirectal tissues			D: mets	IV: mets
T4a: visceral peritoneum				
T4b: other organs				

MANAGEMENT OF COLON CANCER

Stage O:

Stage I: A=consider if involved resection margins

Stage II: A=high risk T4/poor differentiation/EMVI

Stage III: A=FOLFOX/cap monotx (+/-cetuximab for wild-type k-ras)

Stage IV: (i)site specific MDT ?resect mets

(ii) FOLFOX then irinotecan/FOLFOX then FOLFIRI/XELOX then FOLFIRI/TEGAFUR+URACIL+FOLINIC ACID

(cetuximab +/- irinotecan for wild-type k-ras)

ELECTIVE COLECTOMY

Principle: remove **tumour** + vascular pedicle w/ associated **lymphatic** drainage

Segmental resections: **Right hemi:** IC+RC||**Transverse:** MC (largely abandoned)||**Left hemi:** LC||**Sigmoid:** IMA||**Rectum:** IMA

Splenic flexure: left hemi vs extended right hemi; need to ligate LC/RC/MC left branch → extended right hemi makes sense

Variations in splenic flexure blood supply: 6% have no left colic, 22% have no middle colic

Pre-op:

Transfusion: only if anaemia

Prep: most leaks late after full diet so prep won't affect these → not routinely recommended

Thromboprophlyaxis: no disease specific studies but higher risk → extended thrombrophylaxis 28 days

Antibiotics: one dose on induction vs wound infection (RCT evidence); no difference between single and triple dose

Pre-op carbohydrate: 800mls at midnight, 400mls 2-3 hrs before surgery reduces post-op insulin resistance/reduces protein cat

Operative:

Anastomoses: no difference between staples and suturing for leak rates
Rectal washout: cytocidal wash recommended vs viable tumour cells in colonic lumen
Drain: not routine except low AR
Defunctioning ileostomy: low AR (DFI vs loop colo: less prolapse, SB less damaged by DXT so leak less, less wound sepsis on closure)

Post-op:
Drain: no evidence for routine insertion; may have role in low anterior rectal resections
Enhanced Recovery Programme: NG out,, TWOC early etc

Complications:
Leak: risk increased if male/old age/obese/low anastomosis (within 5cm of anorectal junction)
Stricture:
Sexual/urinary dysfunction: nervi erigentes
Bowel dysfunction: urgency/frequency after anterior resection esp if DXT
Other: as predictable for laparoscopic/open colorectal surgery

MANAGEMENT OF RECTAL CANCER
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Stage IV: (i)site specific MDT ?resect mets
(ii) FOLFOX then irinotecan/FOLFOX then FOLFIRI/XELOX then FOLFIRI/TEGAFUR+URACIL+FOLINIC ACID

(cetuximab +/- irinotecan for wild-type k-ras)

NA therapy: (i)Resectable – high risk → NA-CRT then surgery (ii)Unresectable – high risk = NA-CRT then interval surgery
-moderate risk → SPRT then surgery
-low risk → straight to surgery

NA-DXT: proctitis/perineal wound problems/impairs anal function/threatens anastomosis

A. Anterior resection of rectum
TME: optimal therapy for low/mid rectal cancers (may not be necessary in some uppers)
Mesorectal spread up to 4cm if poorly differentiated → 5cm distal margin; others rarely >1cm so 2cm sufficient
IMA: high (1-2cm distal to aortic wall) or low (distal to L colic); low anast needs high ligation; no difference in overall survival
Lateral pelvic nodes: risk with female/high T/high grade/low cancer/LVI → LPLD vs chemo

B. Low rectal cancers:
No TME here so priority is distal muscle tube excision; 1cm distal margin sufficient if low-grade

1. Low anterior resection:
TME + colo-anal anastomosis$_{(side\text{-}to\text{-}side>end\text{-}to\text{-}end)}$ if above sphincter complex and MRF not threatened
Colo-anal after TME has poor outcome → neorectum with 5-6cm J pouch better for early function/leak rate
Defunctioning proximal stoma recommended (25% permanent)
Rectal function: urgency/frequency

2. APER
Low rectal cancer involving sphincter/too close to preserve it
Restorative surgery likely to have poor outcome (esp if poor pre-op anal function eg obstetric injury)
Prohibitive anastomotic complications predicted

3. ELAPE
Advanced low rectal cancers (threatening or involving levators/sphincter complexes)
Prone: better access/haemostasis

Early rectal cancer

Significant rectal neoplasm (SPECC lesion): sessile polyp>20mm; morpho aberrant; polypectomy unsafe/likely to be complete
Investigations: (i)Endoscopy + Bx (ii)MRI before excision(40% of benign biopsies are cancers) (iii)ERUS most accurate T1/2 discriminant
Local excision: TEMS preserves rectum/low M&M/excellent cure rate (vs surgery's 5%mort/50% morbidity)
ACP criteria: T1/<3cm/well or moderately-differentiated/LVI –ive/ → <10% LR
Neo-adjuvant therapy: facilitates complete excision/reduces tumour implantation/treats LNs
Adjuvant therapy: residual disease in high risk pts unwilling/unable to undergo TME
Follow-up: surveillance if excision alone (i)flexi/CEA/MRI 3-6mthly and (ii)CTTAP 12 mthly for 3-5yrs

Emergency presentations
LBO: 60% malignant, 20% diverticular, 5% volvulus, 15% others
20% CRC: obstruction>bleeding >perforation
(a) Laparotomy
Right colon: right hemi + PA(10% leak)/both ends exteriorized/ileotransverse bypass/trephine ileostomy
TV colon: extended right hemi + PA/end ileostomy
Left colon: STC+PA/left hemi + on-table lavage + PA/EI
Rectum: loop colostomy and NA therapy if unresectable/Hartmann's if obstructed(40% permanent stoma)

PRA vs HP: PRA= no stoma, shorter LOS, less M&M BUT leak rate 4%, mortality 10% for segmental resections
On table lavage in left-sided obstn: semental resection + PA w/ lavage → equivalent leak/mortality to right-sided resection
SCOTIA: *91pts L-sided obstn STC+PA/segmenta + lavagel with no diff in mort/leak; STC had more bowel freq/permanent stoma*
(b)SEMS: short left-sided near-complete obstruction(not if right-sided/low rectal/perforation or peritonitis) → palliative/bridge to elective surgery
Complications: perforation/migration/tenesmus Failure: cannot traverse obstruction/re-obstructs

OUTCOMES
Operative standards: mortality <5% elective,<20% emergency||wound infection <10%||leak rate <4% overall||R0 in >90%
Leak rates by site: elective RH 3-5%; AR 10-20%, ICA 1-3%; CCCA 10-20%
5 year survival by Dukes stage: A-87% B-67% C-33%
Locoregional recurrence:
(i)Colonic:
(ii)Rectal: CRM most important predictor; others=T stage || 80% within 2 yrs of surgery; 90% within 5 yrs

METASTATIC DISEASE
Hepatic: resection carries 33% 5 yr survival; 1-3 mets in one lobe suitable
Pulmonary: 5yr 43% survival after lung metastectomy (Zampino el al); better if CEA normal, LN-ive, more time after 1° op
Brain: MRI Head → MDT
NICE: (a)FOLFOX then irinotecan or FOLFIRI (b)XELOX then FOLFIRI

FOLLOW-UP
Rationale:
(i)detect recurrence80% within 2 yrs, 90% within 5yrs (ii) metachronous disease(4%) (iii) synchronous disease4% tumours; 20% benign pathology

Schedule:
(i) 4-6 weeks post-op check (ii)CTTAP: at least 2 in first 3 years (iii)CEA: 6mthly in first 3 years
Colonoscopy: (i)6mths (ii)1/3/5 years (iii)5 yearly until 75 (covers patient until 80)
Stop when surveillance risks>benefits (usually 75 years in practice)
Additional riskers: Dukes B T4b and Dukes C get additional CT at 3yrs; after liver resection, 6mthly CT for 2yrs