LYNCH SYNDROME (HNPCC)

Commonest inherited CRC syndrome; 2% of CRCs; lifetime risk= 50%+; 45yo CRC onset

Right-sided mucinous CR tumours

Also uterine/renal/CNS tumours

Genetics:

Autosomal dominant ie 50% inheritance; expressed when solitary normal gene lost/mutated

(a)**MMR germline** mutations *hMLH1/hMSH2/hMSH6/hPMS2*in 70% *(*b)**Sporadic *EPCAM***

Microsatellite: short(~5 nucleotide) DNA seq repeats in region ||MSI: MS mut. changes # of repeats/length of region (hallmark 50% and 15% sporadic cancers)

MMR= **TS gene** by DNA mismatch repair (i)**repairs** base pair-matching errors in DNA rep (ii)**apoptosis** if damage beyond repair

Defective TS gene → DNA mismatch repair + apoptosis lost → tumorigenesis

Diagnosis:

1.**Pedigree** (Amsterdam II criteria)

3+relatives w/ Lynch-associated cancer (1FDR of other two)/2+ successive generations/1+ diagnosed <50y + exclude FAP

50% families meeting criteria have Lynch; 50% of Lynch individuals from families not meeting criteria **FHx insufficient for Dx**

Amsterdam +ive but MMR i-ve= Familial CRC syndrome X → 3-5yrly scope

2. **Analysis of tumour tissue** 5 MS markers to detect MSI: 2+=MSI high (IHC and genetic testing detect 90% Lynch individuals)

3. **Genetic testing** (refer all): Identify at risk family members for surveillance/discharge non-carriers from surveillance

Surveillance:

1. Colonoscopy 1-2yrly from 25-75(or 5yrs younger than youngest relative) *63% CRC reduction*

2. OGD 2yrly from 50

3. Extracolonic surveillance if FHx of cancer at that site (uterine/renal/CNS)

Intervention: ***REFER TO GENETICS***

1. **SURGERY** (i)Prophylactic colectomy (STC+IRA/RPC+pouch) ||TAHBSO

(ii)Curative colectomy in Ca (segmental/STC+IRA/RPC+pouch for rectal ca)

RPC: two-stage; higher ejaculatory/fertility/defecatory dysfunction; 10% pouch failure -> permanent EI;

STC+IRA: one-stage; better sexual/reproductive/defecatory morbidity; ***rectal cancer 12%@12yrs--> annual anoscopy***

2**. REFER TO GENETICS**

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

Less common than Lynch; 0.5% of CRCs; 100% lifetime risk of CRC

Left-sided tumours and younger

Features:

1. Colorectal: (i)Severe >100 adenomas (ii) Attentuated <100 adenomas

2. Extracolonic: Ectoderm - epidermoid cysts, pilomatrixioma, CNS tumours, cong. retinal pig hypertrophy

Mesoderm **- desmoid tumours**, adhesions, osteoma, exostosis, dental cysts

Endoderm - 80% fundic gland polyps, **90% duodenal adenomas**, SI, biliary tract, thyroid, adrenal adenomas

(non-adenomatous) (5% malignant change)

Genetics:

GERMLINE: **APC C5q**(TS gene regulates B-catenin in Wnt signalling pathway) mutation identified in **80%**

SPORADIC: de novo mututation in 20%

Autosomal dominant (50% inheritance) → expressed when normal APC gene lost/mutated

Diagnosis:

**1. Adenomas ***FAP v Lynch: (i) Microadenomas in FAP/MAP, not Lynch (ii)MSI in 50% lynch but not in FAP/MAP*

2. Predictive genetic test: affected family member → 80% gene detection → at risk members blood test from age 12

Surveillance:

Colon: Alternating flexi/colonoscopy annually from 13-15 → offer surgery from 16

UGI: 3yrly OGD from 30

after surgery: 30% rectal Ca by 60 → 12mthly DRE+ flexi if pouch; UGI surveillance ongoing

Management:

LARGE BOWEL

(a)Prophylactic (STC+IRA/RPC+pouch/PPC+EI)

(b)Therapeutic: same but (i)v. low cancer→PPC+EI (ii)APC codon 1309 mutation/rectal ca/rectal polyposis→RPC

Surveillance after surgery in all (12 monthly DRE + flexisig)

main M&M after surgery is duodenal/dermoid lesions

UPPER GI

Duodenal adenomas in 90% → malignant transformation in 5%

Surveillance: 6mth-5yrly OGD from 20 years (Spiegelman Stage)

Management: no chemoprevention/endotx in stage 4/surgery by PPPD or PD in stage 5

**high rate of progression/invasive cancer has poor prognosis → consider surgery early despite high morbidity*

SCORE	**1**	**2**	**3**
No. of polyps	1-4	5-20	>20
Size (mm)	1-4	5-10	>10
Architecture	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	High

0: 5yrly/1-4: 5yrly/5-6:3yrly/7-8:1yrly +endo therapy/9+:surgery

DESMOID TUMOURS:

Fibromatous tumours composed of clonal proliferation of **myofibroblasts** ->**growth/resolution cycles**

15% of FAP; 10% mortality

Histo: benign

Features: **obstruction/ischaemia** of small bowel/ureter

Management: (i)only rapidly progressive+ relentless → surgery (otherwise anti-E2/cytotoxic chemo)

(ii)surgery for abdominal wall/extra-abdominal desmoids

Outcomes: high recurrence rates

MAP: MYH-ASSOCIATED POLYPOSIS

FAP phenotype but no APC gene mutation identified; lifetime CRC risk 100% by age 60

Genetics: **MYH C1p biallelic** mutation; **autosomal recessive** (hets only marginally increased CRC risk) **AR, FAP is AD**

May have no family history as AR

Features:

LARGE BOWEL: colonic adenomas/carcinomas **tend to be right-sided and older; FAP left/younger**

UGI: gastric fundic polyps/duodenoal adenomas (30%) **fewer duodenal adenomas**

OTHER: breast cancer/osteomas/dental cysts **no desmoids**

Management: as for FAP → annual colonoscopy/OGD from 25 in homozygotes but not for heterozygotes

PEUTZ-JEGHERS

Autosomal dominant (STK11/LKB1 C19p13); not identified in all families

Features: (i)SBO (intussusception from hamartomas) (ii)muco-cutaneous pgimentation

Cancers: SB/breast/ovaries/cervix/testes/pancreas

Surveillance: U+L endoscopy 2-3yrly + capsule/MRI enterography from age 8

Breast: annual MRI 25-50 → enter NHSBSP

Cervix: routine screening

Testes: self-exam *no evidence for ovarian/pancreatic surveillance*

Management: Laparotomy + intraop enteroscopy + comprehensive polypectomy

JUVENILE POLYPOSIS

Autosomal dominant (germline **SMAD4/BMPR1A**)→ Multiple **hamartomas** (colon w/40% CRC risk + UGI)

Surveillance: regular **U+L endoscopy** from **age 15-18 → 70**

Management: prophylactic **surgery**

COWDEN DISEASE

PTEN C10q22 → GI hamartomas/cancers + other Ca (breast/thyroid/uterus/cervix) 50% + benign (breast/thyroid/mucocutaenous lesions ie oral papilloma/acral keratosis) 75%/75%

OTHER POLYPOSIS SYNDROMES

APC variant C5q E1317Q → CRC risk

C15q gene for CRC susceptibility (esp Ashkenazis so don't discharge after negative genetic testing for above conditions)

COLONOSCOPIC SURVEILLANCE OF INHERITED BOWEL CANCER

NO RISK

1 FDR>60

LOW RISK

No personal CRC hx/no FHx CRX/no FDR with CRC/1 FDR>50

2x average risk but not >colonoscopy

Mx: BCS

MODERATE RISK

Low moderate: **1 FDR <50/2FDR >60 → 3x average risk** → one off colonoscopy at 55 + genetics referral

High moderate: **3FDR >50/2 FDR <60 → 6x average risk** → 5yr colonoscopy from 50-75 + genetics referral

HIGH RISK

1. Member of known FAP family
2. Member of known Lynch family
3. Pedigree suggests MYH-associated polyposis
4. Pedigree suggests autosomal dominant cancer

50% chance of inheriting 50% CRC risk → genetics referral and phenotypic diagnosis → surveillance/prophylactic treatment