4: GASTROINTESTINAL PATHOLOGY

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Oesophageal carcinoma

Squamous carcinoma oesophagus

Definition

Squamous and adenocarcinoma carcinoma, essentially different disease.

Epidemiology/aetiology

Incidence in UK 5/100,000. Incidence stable in the UK.
Highest in China, Japan, northern east Asia.
Predispositions: Smoking, alcohol, achalasia, tylosis, anaemia associated with oesophageal web (Plummer Vinson syndrome), human papilloma virus infection.

Classifications/staging

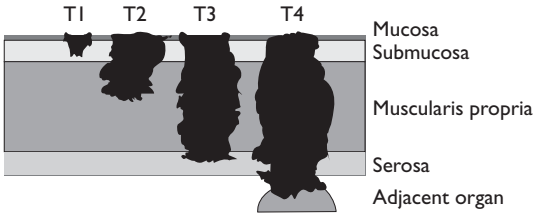


Fig. 18

TNM (UICC)
T stage – see Figure above

N0	No involved nodes	N1	Involved nodes
M0	No metastasis	M1	Distant metastasis

FIGO stages:

I	T1 N0 M0
IIa	T2 or T3 with N0 M0
IIb	T1 or T2/N1/M0
III	T3, N1 or T4 (N0 or N1)
IV	Any T, any N, M1

Macroscopic features
Location: 10% upper third/post-cricoid, 60% middle third, 30% lower third.
Morphology: Polypoid, ulcerating, infiltrative.

Microscopic features
Dysplastic squamous epithelium, dense fibrous stroma. Keratin pearl formation, intercellular bridging.

Stains/special tests

Cytokeratin positive (IHC) (Ck7 positive, cardia; Ck20 positive gastric body immunohisto-chemistry adenocarcinoma).

Adenocarcinoma oesophagus/gastro-oesophageal junction

Epidemiology/aetiology

Incidence in UK 5/100,000 (rapidly increasing in the UK).
Highest in Northern Europe.
Predispositions: Columnar lining to lower oesophagus liable to intestinal metaplasia (Barrett's oesophagus), possible relations to biliary reflux, hypochlorhydria.

Barrett's oesophagus

Definition: Columnar mucosa of at least 2 cm length appearing within the anatomical oesophagus.
Types of columnar mucosa:
- *Fundic*: gastric body type cells with parietal cells.
- *Junctional*: gastric cardiac type cells with mucus glands.
- *Intestinal*: goblet cells.

Dysplasia in Barrett's type columnar mucosa may be low grade, high grade (at least 50% associated with synchronous invasive or *in situ* adenocarcinoma). Indefinite for dysplasia (when tissue malorientated or severely inflamed/regenerative).

Classifications/staging

As per squamous carcinoma.

Macroscopic features
Location: 5% upper third, 20% middle third, 60% lower third, 15% gastro-oesophageal junction.

Microscopic features
Severely dysplastic glandular structures, mucin containing cells (signet ring cells) dense fibrous stroma.

Stains/special tests

Cytokeratin positive IHC (Ck7 positive, cardia; Ck20 positive, gastric body adenocarcinoma).

Peptic ulcer disease and gastritis

Definition

Ulceration of the stomach or duodenum caused by or related to the presence of gastric acid secretion.

Gastric ulcer (body)

Epidemiology/aetiology

Male:female 3:1.
Peak incidence over 55 years.
Predispositions: Smoking, non-steroidal anti-inflammatory drug (NSAID) use, alcohol, biliary reflux, acute 'stress' ulceration – acute severe illness, burns, prolonged mechanical ventilation, *Helicobacter pylori* infection of the gastric antrum.

Macroscopic features
Acute/stress ulcers may be superficial erosions, erosive gastritis or confluent superficial ulceration. Hypervascular, friable base, contact bleeding common.
Chronic ulcers usually deep, pronounced firm edge, necrotic slough in base.

Microscopic features
Acute/stress acute inflammatory infiltrate, granulation tissue, exposed submucosal vessels.
Chronic ulcers: Fibrosis, replacement of muscle fibres with fibrosis, obliterative arteritis in areas of chronic inflammation, chronic inflammatory infiltrate.

Stains/special tests

Urease test ('CloTest'™), ^{13}C breath test, serology – *H. pylori.*

Duodenal and prepyloric gastric ulcer

Epidemiology/aetiology

Male:female 4:1.
Peak incidence 20–45 years.
Predispositions: Increased acid secretion, *H. pylori* infection of the gastric antrum, hypergastrinaemia (Zollinger–Ellison syndrome), NSAID use.

Macroscopic features
As for gastric ulcer.

Microscopic features
As for gastric ulcer.
H. pylori: Curved rod-shaped organisms within the surface mucus, associated mucosal vacuolisation and chronic and acute inflammation.

Stains/special tests

Urease test ('CloTest'™), ^{13}C breath test, serology – *H. pylori.*
Serum gastrin – hypergastrinaemia.
Modified Giemsa stain for *H. pylori.*

H. pylori associated gastritis

Epidemiology/aetiology

Associated with *H. pylori* infestation.

Macroscopic features
Antral gastritis associated with duodenal ulceration, pangastritis associated with multifocal gastric atrophy and risk of malignancy.

Microscopic features
Acute and chronic inflammations, entirely mucosally based.

Reactive/chemical gastritis

Epidemiology/aetiology

Associated with drugs (especially NSAIDs), bile reflux.

Macroscopic features
No characteristic features.

Microscopic features
Mucosal oedema, foveolar hyperplasia, vascular ectasia and no or few inflammatory cells.

Rare types of gastritis

- Lymphocytic gastritis
- Eosinophilic gastritis

Gastric carcinoma

Definition

Adenocarcinoma rising from gastric mucosal glands.

Epidemiology/aetiology

UK incidence 20/100,000 (declining).
Male:female 2:1 (intestinal type).
Male:female 1:1.2 (diffuse type).
Highest incidence Japan, South America, Eastern Europe.
Predispositions: Ingested nitrosamines (raw/smoked fish), atrophic gastritis, intestinal metaplasia, pernicious anaemia, previous gastric surgery (proximal tumours), gastric adenomatous polyps (body tumours), *H. pylori* infection (distal tumours).

Genetics

Associated with abnormalities in K-ras, p53 c-met and DCC (deleted in colon cancer) genes.

Classifications/staging

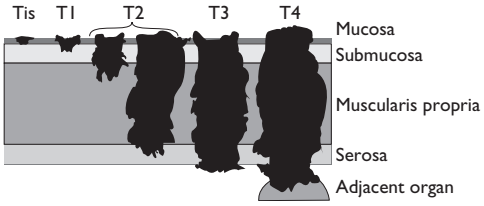


Fig. 19

TNM (UICC)
T stage – see Figure above

N0	No involved nodes	M0	No known mets
N1	1–6 involved nodes	M1	Distant mets
N2	7–15 involved nodes		
N3	16+ involved nodes		

Early gastric cancer (EGCa) = Tis or T1 (N0/N1/N2) (15% in UK).

FIGO stages:

I	T1/N0, T1/N1
II	T1/N2, T2/N0, T2/N1
IIIa	T2/N2, T3/N0, T3/N1
IIIb	T3/N2, T4/N0, T4/N1
IV	T4/N2, Any stage with M1

Macroscopic features

Morphology: Polypoid, infiltrating, ulcerated, stenotic.

Location: 30% proximal (increasing incidence), 40% body, 25% distal (decreasing incidence), 5% diffuse infiltrating.

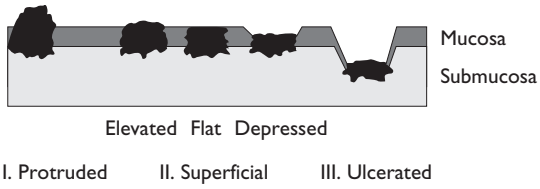


Fig. 20 EGCa: subtypes

Microscopic features

Lauren classification

- Intestinal type: associated with carcinoma of the cardia and distal oesophagus.
- Diffuse type: includes signet ring cell tumours and linitis plastica.

Differentiation grades

- G1: well.
- G2: moderate.
- G3: poor (includes signet ring cell).
- G4 (includes small cell and undifferentiated).

Stains/special tests

Cytokeratin positive IHC (Ck7 positive, cardia type; Ck20 positive, body type).

Crohn's disease

Definition

Idiopathic chronic inflammatory disease of bowel typified by non-caseating B-cell granulomatous.

Epidemiology/aetiology

- Prevalence 5 in 100,000.
- Male:female 1:1.6.
- Two peaks of incidence: 13–29 and 45–60 years.
- Highest in Anglo-Saxon Caucasian populations.
- Definite genetic link but precise candidate genes unknown.
- Definite association between active inflammation and faecal micro-particles.
- No proven cause from myxoviruses or tuberculosis strains.
- Definite association between tobacco smoking and risk of recurrent disease especially in young women.

Classifications

Clinical (but *not* pathologically distinct) phenotypes include:
- Inflammatory features (thickening, mass, bleeding).
- Perforating features (fistulation, abscess, free perforation).
- Stenosing features (strictures).

Location of disease:
- Ileocaecal: 80% have disease within 60 cm of the ileocaecal valve.
- Colonic: 25% of patients (rectum often spared).
- Ileal only: 30% of patients (usually multifocal).
- Anal: usually occurs in association with ileal or colonic disease.

Stains/special tests

None.

Genetics

Familial clustering suggests genetic factor, precise gene(s), unproven but NOD2 (Ch16) implicated.
HLA (human leukocyte antigen) B27 association.

Macroscopic features

External

- Discontinuous disease ('skip lesions').
- Para-enteric/inter-mesenteric abscess formation.
- Mesenteric thickening.
- Increased mesenteric fat.
- Blue discolouration of affect segments (particularly ileum).
- Fine spiral serosal neovascularisation.

Internal

- Transmural thickening.
- 'Cobblestoned' mucosa and 'rake' ulceration.
- Deep serpiginous ulceration in the line of mesenteric vascular entry.

Microscopic features

- Transmural inflammation in the form of lymphoid aggregates.
- Non-caseating B-cell granulomata.
- Subserosal lymphoid aggregates (Crohn's rosary').
- Microscopic crypt abscesses.
- Periarteritis.
- Perineural inflammation in the myenteric plexuses.

Inflammatory small bowel diseases

Coeliac disease

Epidemiology/aetiology

T-cell-mediated chronic allergic reaction to α-gliadin portion of gluten protein (present in wheat flour).

Genetics

HLA B8 DW3 associated.

Macroscopic features
- Pale, velvety mucosal surface.
- Atrophy and flattening of duodenal mucosal folds in severe cases.
- Most prominent in duodenum and proximal jejunum.

Microscopic features
- Increased intraepithelial T-lymphocytes.
- Villous atrophy with crypt hyperplasia.

Stains/special tests

Serum anti-endomysial antibody, serum tissue transglutaminase (TT).

Intestinal lipodystrophy (Whipple's disease)

Epidemiology/aetiology

Bacterial infection (*Trophorema whipplei*).

Macroscopic features
Prominent white distended intramesenteric lymphatics, thickened mucosal.

Microscopic features
Prominent lymphatics and lacteals with mucosal macrophage collections.

Stains/special tests

Periodic acid schiff (PAS) stains organisms positively in lamina propria macrophages.

Radiation enteropathy

Epidemiology/aetiology

Caused by direct or, more usually, transcutaneous exposure of small intestinal tissues to ionising radiation.
Extent of disease directly relates to total tissue dose of radiation per unit volume exposed.

Macroscopic features
Early changes: Hyperaemic, oedematous bowel with mucosal thickening and even sloughing.
Late changes: Thickened, pale and stenosed areas of small bowel, dense adhesions to adjacent bowel loops/structures, subserosal neovascularisation, wall thickening, interenteric fistulation.

Microscopic features
Early changes: Acute submucosal inflammatory infiltration, subintimal inflammation and progressive obliterative endarteritis.
Late changes: Submucosal fibrosis, progressive mural sclerosis and replacement of muscle fibres by collagen and fibrocytes, fine neovascularisation vessels.

Stains/special tests

None.

Colitis

Ulcerative colitis

Definition

Idiopathic acute and chronic inflammatory diseases primarily affecting the colonic mucosa.

Epidemiology/aetiology

- Prevalence 5 in 100,000.
- Male:female 1:1.5.
- Peak age of incidence: 25–45 years.
- Highest in Anglo-Saxon Caucasian and Jewish populations.
- Definite genetic link but precise candidate genes unknown.
- No proven relationship to infectious agents although attacks may be precipitated by infectious episodes.

Classifications

Location of disease:
- Isolated rectal: ulcerative proctitis
- Left-sided colitis (sigmoid and rectum)
- Pancolitis.

Stains/special tests

None.

Genetics

HLA B27 association.

Macroscopic features
External
No diagnostic features.

Internal
Continuous mucosal inflammation.
Focal ulceration progressing to confluent mucosal loss.
Pseudopolyposis.
Wall thinning and secondary muscular wall inflammation in severe disease.

Microscopic features
Diffuse mucosocentric acute and chronic inflammatory infiltrate.
Microscopic crypt abscesses.
Crypt distortion and mucin depletion.

Infectious colitis: typhoid

Aetiology

Salmonella typhi infection.

Macroscopic features
Haemorrhagic mucosal degeneration.

Microscopic features
Neutropenic mucosal inflammation.
Lymphoid aggregates filled with lymphocytes.
Focal muscular necrosis ('Zenker's degeneration').
Lymph node necrosis.

Infectious colitis: pseudomembranous colitis

Aetiology

Clostridium difficile infection.

Macroscopic features
Extensive pale white 'pseudomembranes'.
Extensive mucosal loss.

Microscopic features
Pseudomembranes comprised of fibrin, mucus and neutrophils from intercrypt erosions, crypt withering, oedema and extensive lamina propria neutrophil infiltration.

Infectious colitis: amoebic dysentery

Aetiology

Entamoba histolytica infection.

Macroscopic features
Patchy right colonic ulceration: transverse, pale, haloed ulcers.

Microscopic features
Flask-shaped ulcers, deep intramural abscesses containing lymphocytes and neutrophils and occasional amoebae.

Colorectal neoplasia

Colorectal adenomas

Epidemiology/aetiology

Prevalence.
Highest North America, Europe, Australian, New Zealand.
Abnormalities of adenomatous polyposis coli (APC), DNA mismatch repair (MMR) genes (hMSH2, hMLH1, hPMS1/2) or DNA hypomethylation (somatic or germline) thought to be required for adenoma formation.

Classifications/staging

- Tubular (75%) (Ca risk 5%)
- Tubulovillous (15%) (Ca risk 20%)
- Villous (10%) (Ca risk 40%).

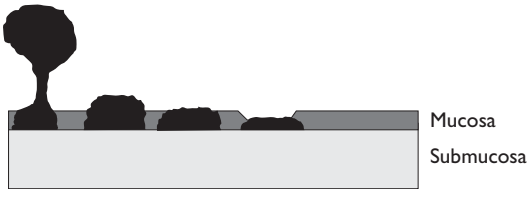


Fig. 21 *Morphology*: Pedunculated or sessile (raised, flat, depressed).

Genetics

Hereditary non-polyposis colorectal cancer (HNPCC): Germline DNA MMR gene abnormalities, polyp formation occurs but with rapid progression to malignancy.
Familial adenomatous polyposis (FAP): Germline abnormality in APC gene, autosomal dominant, multiple adenomata, eventual progression to carcinoma (same as population progression).

Colorectal carcinoma

Epidemiology/aetiology

UK incidence: lifetime risk 1/18.
Highest incidence North America, Europe, Australia, New Zealand.
Predispositions (induced genetic abnormalities commoner): Ulcerative colitis (Crohn's colitis), ureterosigmoidostomy, previous radiotherapy.

Genetics

Underlying adenoma-related gene abnormality + additional gene abnormalities in K-ras, p53 or DCC:
- 85% sporadic: dietary factors + somatic cell gene mutations.
- 10% genetic linkage: unidentified germline abnormalities.
- 5% identifiable germline genetic cause: includes FAP (APC), HNPCC (DNA MMR defects).

Classifications

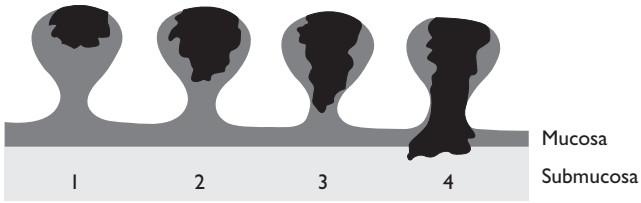
Fig. 22 *T stage classification*: extent of tumour.

TNM (UICC)
T stage – see Figure above

N0	No involved nodes	M0	No mets
N1	1–3 involved nodes	M1	Mets
N2	4 or more involved nodes		

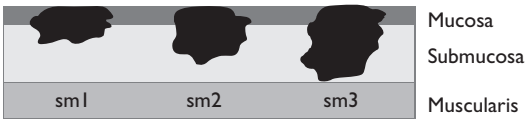
Dukes' classification

A: confined to bowel wall; B: penetration beyond muscularis propria; C: any depth and positive lymph nodes; D: any stage and mets.



1: confined to head; 2: up to stalk; 3: into stalk; 4: into submucosa.

Fig. 23 *Haggitt classification*: stages of polyp carcinoma.



sm1: upper 1/3; sm2: middle 1/3; sm3: deepest 1/3.

Fig. 24 *Kikuchi classification*: substages of early (T1) carcinoma.

Macroscopic features

Morphology: Polypoid, spreading, ulcerated, stenotic.
Location: 45% rectum, 25% sigmoid, 5% left, 5% transverse, 20% right colon (3% have synchronous lesions).

Microscopic features

Differentiation: Anaplastic, poor, moderate, well.
Mucinous, signet ring cell variants (10%): Poor prognosis if sporadic, commoner in HNPCC tumours.
Extratumoural vascular invasion (VI) and lymphatic invasion (LyI): Increased risk of systemic recurrence.

Pancreatitis

Definition

Inflammatory process occurring within the exocrine pancreatic tissue with either acute or chronic inflammatory infiltrates.

Acute pancreatitis

Epidemiology/aetiology

Commonest in Anglo-Saxon Caucasians related to gallstone incidence.
Causative agents: gallstones (especially choledocholithiasis), alcohol, drugs (thiazides, immunosuppressives), viral infections (Coxsackie, mumps, HIV–AIDS), hyperlipidaemia, hypercalcaemia, trauma, post-ERCP (endoscopic retrograde cholangiopancreatography).

Classifications

- Phlegmonous 80%.
- Haemorrhagic 15%.
- Necrotic 5% (usually sterile, may be infected – high mortality).

Macroscopic features
Oedematous pale pancreatic tissue, peripancreatic bleeding, intrapancreatic fluid collections, destruction and saponification of surrounding adipose tissues.

Microscopic features
Exocrine acinar oedema infiltration with leak of exocrine secretions into paracellular tissues, neutrophil and monocyte infiltration. Perilobular thrombosis and vascular injury. Periductal or perilobular necrosis progressing to panlobular necrosis.
With increasing severity, increasing destruction of pancreatic tissue integrity, intraparenchymal bleeding and necrosis (sterile necrosis).

Chronic pancreatitis

Epidemiology/aetiology

Male:female 3:1.
Commonest in northern countries (especially northern Scandinavia).
Related to per capita alcohol consumption (commonest aetiological factor).

Other causative agents: recurrent acute pancreatitis secondary to gallstones, familial hyperlipidaemia, hypercalcaemia.
Secondary obstructive chronic pancreatitis due to congenital malformations, pancreatic head tumours, Crohn's disease, cystic fibrosis, Sjogren's syndrome, haemochromatosis.

Genetics

Familial hyperlipidaemia.
Idiopathic familial pancreatitis possibly related to lipid metabolism, abnormal lithostatin levels.

Macroscopic features
Pale, shrunken, fibrotic glandular tissue.
Ductal dilatation (often multifocal) with multiple ductal stenoses and occasional intraductal pancreatic stones.
Parapancreatic small vessel thrombosis.

Microscopic features
Predominantly exocrine acinar destruction and fibrosis. Chronic inflammatory infiltrate.
Intralobular ductal distortion and eosinophilic infiltration. Intraductal protein deposition. Microcalcific deposits. Secondary acinar dilatation, epithelial destruction and subsequent fibrosis and acinar atrophy.

Pancreatic tumours

Adenocarcinoma of pancreas

Definition

Malignant tumour of exocrine ductal tissue.

Epidemiology/aetiology

Incidence 8/100,000.
Highest in Maoris, pacific island races and Afro-Caribbeans.
Male:female 2:1.
Predispositions: Smoking, high-fat diet, familial pancreatitis, chemical carcinogen exposure, possibly chronic pancreatitis.

Classifications

TNM (UICC)

T1	<2 cm intrapancreatic	N0	No involved nodes
T2	>2 cm intrapancreatic	N1a	1 regional node positive
T3	Peripancreatic/duodenum/ common bile duct	N1b	>1 regional node positive
T4	Extrapancreatic tissue	M0	No mets
		M1	Mets

Stains/special tests

CA19–9 positive IHC.
May be carcinoembryonic antigen (CEA) positive IHC.
Cytokeratin 7, 8, 18 positive IHC.

Genetics

Abnormalities in p53, p16, DPC4 genes implicated.

Macroscopic features
Location: Head 65%, body 30%, tail 5%.
Morphology: Usually sclerotic, cirrhous.

Microscopic features
Mucinous ductal carcinoma with ductal obstruction, acinar atrophy and intense desmoplastic reaction. May exhibit features of peritumoral chronic pancreatitis.

Periampullary adenocarcinoma

Definition

Malignant tumour of the endoampullary biliary epithelium or outer duodenal ampullary epithelium.

Epidemiology/aetiology

Incidence 6/1,000,000.
Male:female 1:1.
Predispositions: Ampullary adenoma, smoking.

Classifications

TNM (UICC)

T1	Ampullary	N0	No positive nodes
T2	Duodenum involved	N1	Positive nodes
T3	<2 cm pancreas involved	M0	No mets
T4	More extensive invasion	M1	Mets

Stains/special tests

CA19–9 negative IHC.

Genetics

Abnormalities in p53, K-ras associated.

Macroscopic features
Often polypoid or pedunculated. May be frank invasive ulceration of periampullary tissues.

Microscopic features
Varies from atypical columnar epithelium to anaplastic cells, typically clear eosinophilic cytoplasm.

Cystadenocarcinoma of pancreas

Definition

Malignant end of a spectrum of cystic tumours of exocrine ductal tissue.

Epidemiology/aetiology

Male:female 1:6.

Stains/special tests

CA19–9 strongly positive IHC.
CEA positive IHC.

Features
Large, multilocular septated cystic tumours. Mucinous, serous papillary variants.

Neuroendocrine tumours of pancreas

Definition

Spectrum of tumours of endocrine (islet) cell tissue varying from benign incidental tumours to frankly malignant invasive tumours.
Commonest insulinomas, gastrinomas.
Rarely vasoactive intestinal peptide (VIP), parathyroid hormone related peptide (PTHrP), glucagon, C-peptide, somatostatin producing cell tumours.
May be polyhormonal in secretion patterns (30%), may be non-secretory (30%).

Epidemiology/aetiology

Incidence wide from 30–60 years peak. Less than 1/100,000.

Stains/special tests

Serum insulin (and C-peptide) – insulinoma.
Generally neurone-specific enolase, chromogranin, synaptophysin positive IHC.
Generally C-100 positive IHC.
IHC positive for respective hormones even if not secretory.

Genetics

Often related to multiple endocrine neoplasia syndromes (MEN1 – insulinoma, gastrinoma).
Gastrinomas often related to Zollinger–Ellison syndrome.

Macroscopic features
Smooth, well defined, tan or beige coloured homogeneous if benign.

Microscopic features
Agyrophilic, chromogranin-positive cytoplasmic granule.

Gallstones and related gallbladder pathologies

Cholecystolithiasis

Definition

The presence of solid material within the gallbladder. Most commonly refers to single or multiple large stones but also includes multiple file particulate material (microlithiasis).

Classifications

- *Cholesterol stones*: Compromise mainly proteinaceous elements and crystalline cholesterol with smaller amounts of bile pigments and calcium salts (<10%). Typically pale green-yellow, large, smooth surfaced, may be faceted if multiple; laminated, crystalline internal surface on cutting. May occur as a single large stone, multiple stones.
- *Dark pigment stones*: Compromise bile pigment polymers with calcium salts and small amounts of cholesterol and organic material (<10%). Typically dark brown/black, multiple small (<0.5 cm) stones. Hard and irregular surface, homogeneous cut surface.
- *Light pigment stones*: Composition similar to dark pigment stones but also contain bacterial deposits. More rapidly and hence loosely formed with soft, amorphous texture, readily crushed or broken apart. Often form in bile ducts primarily.
- *Mixed stones*: Commonest, usually many small multi-faceted stones of mixed cholesterol and pigments composition.

Epidemiology/aetiology

Cholesterol stones
- Female:male 4:1.
- Western diet (high in cholesterol and saturated fats).
- Obesity.
- Family history (related to composition of 'normal' bile).
- Diabetes mellitus.

Pigment stones
- Chronic haemolysis (hereditary or acquired).
- Chronic biliary disease (e.g. strictures).
- Chronic biliary sepsis (light pigment stones especially).

Other than simple acute and chronic infections of the gallbladder or biliary tree, several conditions exist related to cholecystolithiasis.

Cholesterolosis of the gallbladder

Definition

A condition characterised by the deposition of cholesterol esters within the mucosa of the gallbladder.

Macroscopic features
Multiple fine pale yellow spots or lines marking the inner surface of the mucosa 'strawberry gallbladder', occasional larger nodular deposits covered by thin mucosa 'cholesterol polyps'.

Microscopic features
Mucosal collections of macrophages filled with foamy cholesterol filled vacuoles, extracellular cholesterol deposits in the submucosa.

Chronic cholecystitis

Definition

A chronic, unresolving inflammatory condition of the gallbladder wall. Usually associated with the presence of cholecystolithiasis and repeated episodes of acute cholecystitis but may be acalculous and chronic *de novo*.

Macroscopic features
Grossly thickened, fibrotic and often shrunken gallbladder wall. Thickened irregular mucosal lining, often with pseudo-septations due to 'pocketing' of stones, mucopurulent material often present within the lumen.

Microscopic features
Grossly fibrotic and disordered mucosa and submucosa, proliferation and extension of epithelium into the submucosa and between thickened muscle layers of the wall to form cystic sinuses 'Rokitansky–Aschoff sinuses' which, if extensive with a large glandular element in the fundus is referred to as 'adenomyosis'.

Biliary tumours

Biliary adenomas

Definition

Adenomas and papillomas may occur in the gallbladder or bile ducts.
Associated with malignant transformation in sizes >1 cm.
Common asymptomatic, incidental finding.

Carcinoma of gallbladder

Definition

Malignant tumour of gallbladder epithelium.

Epidemiology/Aetiology

UK incidence 2% of all gastrointestinal (GI) tract malignancies.
Highest incidence in populations with highest incidence of cholecystolithiasis (South America, Native Americans).
Associated with chronic biliary typhoid carriage and obesity.
Large adenomas may follow adenoma–carcinoma sequence.

Classifications

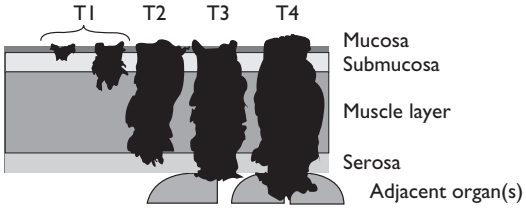


Fig. 25 *T stage classification*: extent of tumour.

TNM (UICC)
T stage – see Figure above

N0 No positive nodes	M0 No mets
N1 Positive cystic/ductal nodes	M1 Mets
N2 Positive regional nodes	

FIGO stages:

I T1/N0/M0	IVa T4/N0–1
II T2/N0/M0	IVb Any T, if N2 or M1
III T1–2/N1, T3/N0–1	

Microscopic features

Adenocarcinoma 80%	Majority papillary (80%)
Squamous 15%	Minority scirrhous (20%)
Squamocolumnar 5%	

Cholangiocarcinoma

Definition

Malignant tumour of the bile duct epithelium.

Epidemiology/aetiology

UK incidence 2/100,000 population.
Male:female 1:1.4.
Peak age incidence 50–70 years.
Associated with chronic biliary parasite infection, sclerosing cholangitis (particularly in association with inflammatory bowel disease (IBD)), chronic biliary typhoid carriage.
Large adenomas may follow adenoma–carcinoma sequence.

Classifications

Location:
- Intrahepatic.
- Proximal (extrahepatic ducts down to confluence)('Klatskin' tumours).
- Middle (common bile duct down to duodenum).
- Distal (retroduodenal or intrapancreatic bile duct).

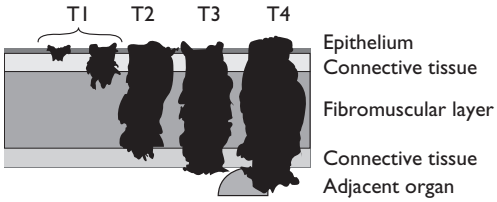


Fig. 26 *T stage classification*: extent of tumour.

TNM (UICC)
T stage – see Figure above.

N0	No positive nodes	M0	No mets
N1	Positive cystic/ductal nodes	M1	Mets
N2	Positive regional nodes		

FIGO stages:

I	T1/N0/M0	IVa	T3/N0–1–2
II	T2/N0/M0	IVb	Any T, any N, M1
IIIa	T1/N1–2, T2/N1–2		

Microscopic features
Adenocarcinoma of the bile duct.

Hepatitis

Acute hepatitis

Definition

A diffuse acute inflammatory process involving the liver parenchyma. Regeneration and restoration of architecture is normal unless death or chronic hepatitis ensues.

Epidemiology/aetiology

Infectious.

- Viral infections: Hep A (picoRNAvirus), Hep B (dsDNA virus), Hep C, Hep D (viral particle), Hep E (RNAvirus), herpes group (CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus), paramyxoviruses (e.g. measles, mumps), arboviruses (e.g. yellow fever), togaviruses (e.g. rubella) and arenaviruses (e.g. Lassa fever).
- Toxic (drugs, poisons, alcohol).
- Inflammatory (IBD associated).

Macroscopic features

Mild/moderate: Mild swelling, oedema and congestion of the affected liver.
Severe: Patchy areas of palour with bile staining and yellow discolouration.
Massive: Initially swollen, extensively yellow discoloured and firm texture becoming, shrunken, red, haemorrhagic and soft as necrosis and intraparenchymal haemorrhage proceeds.

Microscopic features

Mild/moderate: Focal, 'spotty' hepatocyte swelling, granular cytoplasm, ballooning and cell death especially perivenular. Periportal mononuclear cell infiltration.
Severe: Worsening cellular destruction (periportal) with extension between adjacent acini, necrosis leaves empty and collapsed reticulin framework.
Massive: Panacinar necrosis with patchy survival of hepatocytes around portal triads and relatively little inflammatory cell infiltration.

Stains/special tests

Viral inclusion bodies typical of herpes group infections.

Chronic hepatitis

Definition

A diffuse chronic (>6 month) inflammatory or infective process involving the liver parenchyma.

Epidemiology/aetiology

Infectious.
- Viral infections (Hep B, Hep C, Hep D).
- Toxic (drugs, poisons, alcohol).
- Inflammatory (autoimmune, IBD associated).

Classifications

- Chronic active hepatitis
- Chronic persistent hepatitis

Stains/special tests

Hep B surface Ag IHC.
Reticulin, connective tissue; PAS, glycogen and mucin.

Macroscopic features
Mild/moderate: Mild swelling, oedema and congestion of the affected liver.
Severe: Patchy areas of palour with bile staining and yellow discolouration.
Massive: Initially swollen, extensively yellow discoloured and firm texture becoming, shrunken, red, haemorrhagic and soft as necrosis and intraparenchymal haemorrhage proceeds.

Microscopic features
Chronic persistent: Mild to moderate periportal mononuclear cell infiltration with mild to moderate associated hepatocyte necrosis and ongoing active regeneration with preservation of reticulin framework.
Chronic active: Ongoing hepatocyte necrosis in the interface between parenchyma and connective tissue framework with marked lymphocytic infiltrate ('piecemeal necrosis') focused around the portal triads, typical hepatocyte vacuolation and swelling ('feathery degeneration', 'ground glass appearance').

Alcoholic liver disease

Definition

Range of acute and chronic disorders of liver architecture caused by the cellular effects of ethanol.

Epidemiology/aetiology

- Commonest cause of acute and chronic liver dysfunction and chronic liver failure in the UK. Commonest single cause of cirrhosis.
- Male > female (female incidence increasing).
- Weak relationship to latitude especially in Northern hemisphere (e.g. higher incidence in Scandinavian countries, Scotland, northern Russia than southern European countries).
- Population differences in alcohol dehydrogenase (ADH) and hepatocyte enzyme function explain individual variability in susceptibility to alcohol-related injury.

Ethanol converted to ethanal in hepatocytes by ADH.
ADH consumes NAD(P) from cellular stores deficiency of which impairs lipid metabolism and breakdown leading to lipid build up.
$NAD(P)H/H^+$ decreases intracellular pH and affects intracellular enzyme pathways.
Ethanal directly hepatotoxic in large quantities.

Classifications

Acute fatty infiltration (fatty liver):

Macroscopic features
Minimal change, slight palour and swelling.

Microscopic features
Intracellular lipid vacuoles in hepaocytes and hepatocytes swelling. Extracellular lipid deposits in severe episodes. Reversible even if moderately extensive.

Acute alcoholic hepatitis:

Macroscopic features
Pale swollen oedematous liver.

Microscopic features
Acute hepatocyte swelling (ballooning), intracellular deposition of 'Mallory's' hyaline material, acute hepatocyte necrosis (centrilobular necrosis), perilobular lymphohistiocytic infiltration.
Still largely reversible with centrilobular necrosis mostly replaced by regeneration.

Alcoholic fibrosis:

Macroscopic features
Irregular surface, heterogeneous cut surface with areas of pale fibrosis.

Microscopic features
Focal spotty areas of necrosis with fibrosis around portal triads, and centres of lobules (centrilobular sclerosis). Perivascular fibrosis and spurs and laminae of fibrosis extending into the lobules in more extensive cases.
Mostly irreversible result of repeated episodes of acute alcoholic hepatitis.

Alcoholic cirrhosis:

Macroscopic features
Grossly irregular surface with large nodular appearance, heterogeneous cut surface with extensive areas of pale fibrosis often with only islands of normal coloured liver tissue visible.

Microscopic features
Extensive panlobular fibrosis with wide deep septations dividing areas of more structurally normal tissue. Isolated islands of surviving hyperplastic hepatocytes, portal triads encased in fibrosis restricting vascularity of surviving hepatocytes.
Irreversible endpoint of ongoing alcoholic fibrosis.

Non-alcoholic cirrhosis

Definition

A diffuse, chronic, progressive process characterised by the replacement of normal liver architecture with structurally abnormal nodules.

Epidemiology/aetiology

Classifications

- Range of pathologies resulting in chronic or ongoing liver damage with fibrosis including:
  - Chronic active hepatitis
    (a) Infective (Hep B, C, E)
    (b) Autoimmune
    (c) Idiopathic
  - Primary biliary cirrhosis (PBC) (autoimmune – anti-mitochondrial antibody)
  - Secondary (obstructive) biliary cirrhosis
    (a) Biliary strictures/atresia
    (b) Chronic parasitic infestation
    (c) End-stage sclerosing cholangitis
  - Metabolic/enzymatic
    (a) Haemochromatosis
    (b) Wilson's disease
    (c) α1 anti-trypsin deficiency
    (d) Cystic fibrosis
  - Chronic hepatic venous congestion
    (a) Budd Chiari syndrome
    (b) Cardiac failure (especially right ventricular).
- *Macronodular cirrhosis*: nodules >1 cm (typically chronic active hepatitis, chronic venous congestion).
- *Micronodular cirrhosis*: nodules <1 cm (typically PBC, metabolic obstructive causes).

Macroscopic features
Macronodular cirrhosis: Nodular capsular surface of liver, large irregular nodules, often irregularly distributed through the parenchyma, easily visible heterogeneous cut surface.
Micronodular cirrhosis: Many small nodules relatively evenly distributed throughout the parenchyma.

Microscopic features – early
Differ according to aetiology:
Chronic active hepatitis: Cytoplasmic vacuolation and degeneration of hepatocytes, piecemeal patchy, necrosis with plasma cell lymphocytic infiltration, usually periportal but may extend to hepatic veins (bridging necrosis).

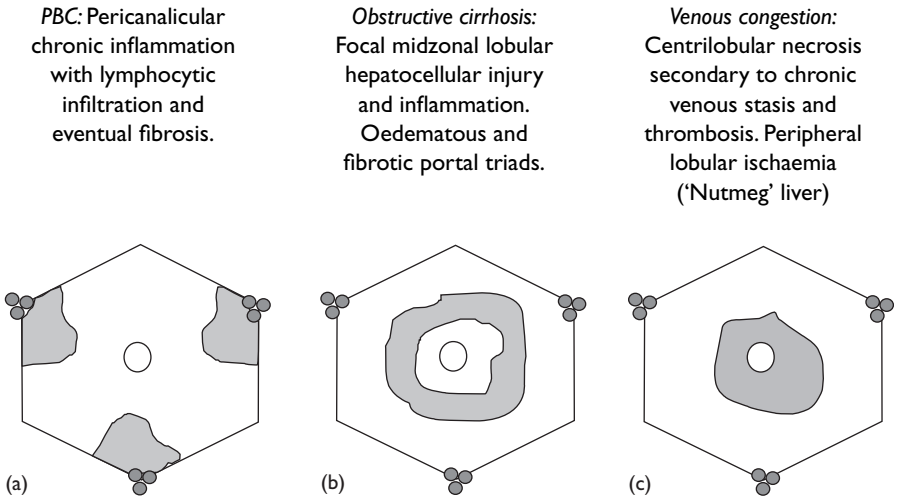


Fig. 27

Microscopic features – late
Relatively similar end-stage appearances:
Extensive panlobular fibrosis with wide deep septations dividing areas of more structurally normal tissue. Isolated islands of surviving hyperplastic hepatocytes, portal triads encased in fibrosis restricting vascularity of surviving hepatocytes.

Stains/special tests

Perls' stain: iron deposits in haemochromatosis.
Serum Cu^{2+}: Wilson's disease.
PCR identification viral DNA (Hep B, C, D).

Liver tumours

Hepatocellular adenoma

Definition

Primary benign tumour arising from hepatocytes.

Epidemiology/aetiology

Associated with oestrogen containing oral contraceptives, glycogen storage disorders.

Macroscopic features
Variable size, tend to be homogenous on cut surface resembling normal liver tissue, well circumscribed.

Microscopic features
Pronounced trabecular and acinar arrangement of cells strongly reminiscent of hepatocytes with biliary canaliculi common. Portal venous branches present but bile ducts absent.

Focal nodular hyperplasia

Definition

A non-neoplastic growth of disordered hepatocytes and connective tissue.

Epidemiology/aetiology

Possibly a local response to vascular or toxic injury.
Often multiple.

Macroscopic features
Similar to a small, focal area of cirrhotic change – firm, white-grey surface, central scaring and fibrosis.

Microscopic features
Prominent connective tissue and septations with regenerated hepatocytes within.

Haemangioma of liver

Definition

Primary benign tumour arising from the vascular tissues of the portal acinus.

Macroscopic features
Tend to be <3 cm diameter, usually subcapsular, dark red-purple on cut surface, soft and almost gelatinous texture.

Microscopic features
Multiple endothelial lined, blood filled spaces with supporting connective tissue.

Hepatocellular carcinoma

Definition

Primary malignant tumour arising from hepatocytes.

Epidemiology/aetiology

Relatively uncommon as spontaneous tumour.
Strong association with pre-existing macronodular cirrhosis (especially alcoholic, Hep B and C virus related).
Weaker associations with Wilson's disease, aflatoxin ingestion, α1 anti-trypsin deficiency.
Commonest in central Africa, East Asia (Hep B and C infection).
Male:female 2.5:1 (higher in relation to cirrhosis).
Two peak ages 35–50 years (related to cirrhosis) and >60 spontaneous.

Classifications

Fibrolamellar variant.

Stains/special tests

Serum α-fetoprotein >100 ng/ml.

Macroscopic features
Large, heterogeneous mass, often difficult to distinguish from surrounding cirrhosis if pre-existing, central necrosis, haemorrhage and bile staining in areas. Often arise within central, deep parenchyma.

Microscopic features
Trabecular arranged cells morphologically similar to hepatocytes with areas of 'sinusoid' and 'canaliculi' formation. Intraportal venous invasion common and intrahepatic satellite lesions sometimes seen.
Fibrolamellar variant – large polygonal cells with pronounced trabeculation and fibrous stroma intervening between lamellae.