CHAPTER 4

Tumours of the Small Intestine

The small intestine has a remarkably low incidence of primary carcinomas, especially considering its size. Those that do occur are often related to genetic syndromes, especially familial adenomatous polyposis.

Lymphomas and endocrine tumours are as frequent as carcinomas and have important associations with precursor conditions such as coeliac sprue, multiple endocrine neoplasia and Von Recklinghausen Syndrome.

The small intestine is the main site for metastatic tumours in the gastrointestinal tract.
### WHO histological classification of tumours of the small intestine

#### Epithelial tumours

<table>
<thead>
<tr>
<th>Type</th>
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<tbody>
<tr>
<td>Adenoma</td>
<td>8140/0</td>
</tr>
<tr>
<td>Tubular</td>
<td>8211/0</td>
</tr>
<tr>
<td>Villous</td>
<td>8261/0</td>
</tr>
<tr>
<td>Tubulovillous</td>
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Intraepithelial neoplasia (dysplasia) associated with chronic inflammatory diseases

- Low-grade glandular intraepithelial neoplasia
- High-grade glandular intraepithelial neoplasia

#### Carcinoma

<table>
<thead>
<tr>
<th>Type</th>
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<tbody>
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<tr>
<td>Mucinous adenocarcinoma</td>
<td>8480/3</td>
</tr>
<tr>
<td>Signet-ring cell carcinoma</td>
<td>8490/3</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>8041/3</td>
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<tr>
<td>Squamous cell carcinoma</td>
<td>8070/3</td>
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<tr>
<td>Adenosquamous carcinoma</td>
<td>8560/3</td>
</tr>
<tr>
<td>Medullary carcinoma</td>
<td>8510/3</td>
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<tr>
<td>Undifferentiated carcinoma</td>
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Carcinoid (well differentiated endocrine neoplasm)

- Gastrin cell tumour, functioning (gastrinoma) or non-functioning
- Somatostatin cell tumour
- EC-cell, serotonin-producing neoplasm
- L-cell, glucagon-like peptide and PP/PYY producing tumour

Mixed carcinoid-adenocarcinoma

Gangliocytic parangangioma

Others

#### Non-epithelial tumours

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<td>8890/0</td>
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<tr>
<td>Kaposis sarcoma</td>
<td>9140/3</td>
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<tr>
<td>Others</td>
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</table>

### Malignant lymphomas

- Immunoproliferative small intestinal disease (includes α-heavy chain disease)
- Western type B-cell lymphoma of MALT
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Burkitt lymphoma
- Burkitt-like /atypical Burkitt-lymphoma
- T-cell lymphoma
- Enteropathy associated unspecified

### Secondary tumours

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<tr>
<td>Peutz-Jeghers</td>
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<tr>
<td>Juvenile</td>
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### TNM classification of tumours of the small intestine

#### TNM classification

- **T** – Primary Tumour
  - TX: Primary tumour cannot be assessed
  - T0: No evidence of primary tumour
  - Tis: Carcinoma in situ

- **T1**: Tumour invades lamina propria or submucosa
- **T2**: Tumour invades muscularis propria
- **T3**: Tumour invades through muscularis propria into subserosa or into non-peritonealized perimuscular tissue (mesentery or retroperitoneum) with extension 2 cm or less
- **T4**: Tumour perforates visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery, or retroperitoneum more than 2 cm and abdominal wall by way of serosa; for duodenal only, invasion of pancreas)

- **N** – Regional Lymph Nodes
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis

- **M** – Distant Metastasis
  - MX: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

#### Stage Grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
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<td>M1</td>
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</table>
Carcinoma of the small intestine

Definition
A malignant epithelial tumour of the small intestine. Neoplasms of the periam-
ipple region include those of the du-
denal mucosa, ampulla of Vater, common bile duct and pancreatic ducts.

ICD-O codes
Adenocarcinoma 8140/3
Mucinous adenocarcinoma 8480/3
Signet-ring cell carcinoma 8490/3

Epidemiology
Relative to the length and surface area of the small intestine, adenocarcinomas of
the duodenum, jejunum and ileum are remarkably rare. Data from the United
States SEER program [1928] for 1973 to 1987 show an age-adjusted incidence
rate for adenocarcinoma of the small intestine of 0.4 per 100,000 per year.
Although some reports suggest an increasing incidence of adenocarcinoma
of the small intestine [1339, 1715], this is not reflected in the SEER data base. The
median age at manifestation is approximately 67 years for non-mucinous ade-
nocarcinoma, mucinous carcinoma and carcinoids.

Aetiology
A major factor in the development of small bowel adenocarcinoma is chronic
inflammation. In particular, long-standing Crohn's disease with multiple strictures
is associated with small bowel carcinoma [1016, 1223, 582, 1578]. One study
showed that individuals with Crohn's disease have an 86-fold increased risk of
adenocarcinoma of the small intestine [623]. Coeliac disease is another well
recognized aetiological factor for small bowel carcinoma [116, 1354, 2141].
There is some epidemiological evidence that cigarette use and alcohol consump-
tion are also risk factors [1339]. Carcinoma can develop in ileostomies in
patients with ulcerative colitis or familial adenomatous polyposis (FAP) subse-
quent to colonic metaplasia and intraepi-
thelial neoplasia in the ileostomy mucosa
[1599, 558]. Carcinoma can also arise in
ileal conduits [1965] and in ileal reservoirs, both continent abdominal (Kock)
[347] and pelvic [2013, 1730]. The occurrence of adenocarcinomas in
Meckel's diverticulum [985] and in small bowel duplications [496] has been
reported.

Localisation
The duodenum is the main site, contain-
ing more adenocarcinomas than the jejunum and ileum combined [1928]. In
the duodenum, carcinomas are most common around the ampulla of Vater
[1657, 2123], possibly due to biliary or pancreatic effluents.

Clinical features
Symptoms and signs
The symptoms of small bowel adenocar-
cinoma are related to the size and loca-
tion of the tumour. In the jejunum and ileum, early symp-
toms are often non-specific, with vague periumbilical abdominal pain and rum-
bbling. Later, cramp-like pain is present in up to 80% of cases, and this may be
accompanied by nausea, vomiting, weight loss, asthenia, and intermittent
obstructive episodes. Massive bleeding is rare (8%), but an important clinical
finding is chronic bleeding with second-
ary iron-deficiency anaemia, which may
be found in the early stages of develop-
ment of the tumour. Other clinical signs
are bloating of the loops of the bowel,
meteorism, and the presence of a palpable
mass [20]. Perforation is a possible
complication of small intestinal carcino-
mas [681].

Duodenal carcinomas present in a differ-
ent manner, because of the larger cir-
cumference of the duodenum compared
with the more distal parts of the small
intestine, and because of the relative
accessibility of the duodenum to endo-
scopy [498, 1657]. Unlike jejunal and
ileal carcinomas, carcinomas of the duo-
denum, especially those of the proximal
duodenum, do not present with bowel
obstruction. Biliary obstruction, frank
or occult blood loss and abdominal pain
are the commonest presentations [2123].
Some tumours are largely asymptomatic
and may be discovered by endoscopy
[1809].

Imaging
The radiological methods that have the highest diagnostic accuracy are spiral
CT scan with contrast medium and enter-
oclysis; the two methods can be com-
plementary. With enteroclysis, a filling
defect, an irregular and circumscribed
thickening of the folds with wall rigidity, slowed motility, eccentric passage of
the contrast medium, or a clear stenosis may be observed [199]. Small bowel ade-
nocarcinoma may appear on CT scan as an
annular lesion, a discrete nodular mass,
or an ulcerative lesion. CT scan, with
global vision of the abdomen, can con-
tribute to staging the tumour [1145].
With push enteroscopy, it is possible to
visualize endoscopically the entire
jejenum. Expansion or infiltrative growth
of the tumour causes at a relatively early
phase, an alteration of the endoluminal
surface; via push enteroscopy it is thus
possible to identify small lesions and to
take biopsies. Push enteroscopy is also a
good diagnostic method to diagnose
tumours causing occult bleeding [1495,
1619].

Exploration of the ampulla of Vater
requires a lateral viewing fibroscope,
adapted to tissue sampling and endo-
scopic sphincterotomy. The terminal
ileum may be visualized through retro-
grade ileoscopy during colonoscopy.
Sonde enteroscopy can identify tumours
throughout the small bowel, but it is ham-
pered by the inability to take biopsies
[1064].

Macroscopy
The macroscopic pathology of small
bowel carcinomas is determined by a
number of factors, of which stage and site
are the most significant. Many carcinomas
of the jejunum and ileum are detected at
an advanced stage [498, 189]. A further
determinant of the macroscopic features
is the presence or absence of predispos-

Squamous cell carcinoma

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J.R. Howe L.H. Sobin
F.P. Rossini N.J. Carr
N.A. Shepherd I. Talbot
Carcinomas may be polypoid, infiltrating or stenosing. Jejunal and ileal carcinomas are usually relatively large, annular, constricting tumours with circumferential involvement of the wall of the intestine (189). Most have fully penetrated the muscularis propria and there is often involvement of the serosal surface (16). Adenocarcinoma of the ileum may mimic Crohn’s disease clinically, radiologically, endoscopically, and at macroscopic pathological assessment (745). Although circumferential involvement can occur, duodenal carcinomas are usually more circumscribed, with a macroscopically demonstrable adenomatous component in 80% of cases (966, 496). Thus, they are often protuberant or polypoid, and the central carcinomatous component may show ulceration (1267). Carcinomas arising at the ampulla of Vater tend to cause obstructive jaundice before they have reached a large size; they are usually circumscribed nodules measuring not more than 2-3 cm in diameter. They may be within the wall of the duodenum or project into the lumen as a nodule.

Unusual macroscopic features, e.g., the lack of ulceration, the predominance of an extramural component and the presence of multicentricity, should alert the pathologist to the possibility that the tumour is a metastasis.

Microscopy
Histologically, small bowel carcinomas resemble their more common counterparts in the colon, but with a higher proportion of poorly differentiated tumours (496, 1006). Some are adenosquamous carcinomas (624, 1345, 1525). Carcinomas with prominent neoplastic endocrine cells (821) and with tripartite differentiation, i.e. with glandular, squamous, and neuroendocrine components (111, 207), have also been reported. Small cell carcinomas (poorly differentiated endocrine carcinomas) are rare (2196) (see next chapter).

In metastatic carcinoma of the small intestine, evidence of a pre-existing adenomatous component can be mimicked by the ability of the intestinal mucosa to cause differentiation of the metastatic tumour (1732); this phenomenon can give the erroneous impression of a primary carcinoma of the small intestine.

Tumour spread and staging
Spread of small bowel carcinomas is similar to that of the large bowel. Direct spread may cause adherence to adjacent structures in the peritoneal cavity, usually a loop of small intestine, although the stomach, colon or greater omentum may also be involved. Lymphatic spread to regional lymph nodes is common. Haematogenous and transcoelomic spread also occur. Diffuse involvement of the ovaries, Krukenberg tumour, has been reported (1089). Staging of carcinomas of the small intestine is by the TNM classification (1, 66). For tumours of the ampulla of Vater, because of the complicated anatomy at this site, a separate TNM classification is used. Alternative staging systems have been proposed (1888).

Grading
Grading of small intestinal carcinomas is identical to that used in the large bowel, namely, well, moderately and poorly differentiated, or high- and low-grade.

Precursor and associated lesions

Adenomas
There is good evidence for an adenoma-carcinoma sequence in the small intestine as in the colon (1506, 1709). Residual adenomatous tissue at the margins is seen in 80% of duodenal adenocarcinomas (966). Perzin and Bridge (1505) described 51 patients with adenomas of the small intestine – 65% had coexisting carcinoma. In patients with familial adenomatous polyposis (FAP), 38/45 (84%) of duodenal carcinomas harboured adenomatous tissue (1709); whereas 30% of 185 sporadic adenomas showed carcinoma (1706). The age at diagnosis of adenomas without carcinoma is lower than for adenomas with carcinoma or for carcinomas, and there is a nearly identical spatial distribution of these three types of tumour in the small intestine (1706).

Since the advent of endoscopic techniques, the earliest stages of malignant changes can be followed in adenomas of the duodenum and peri-ampullary region (147), where often the size of the lesion may warrant extensive sampling. In a study of post-colectomy patients with FAP, random biopsy specimens of ileal mucosa showed foci of abnormal, dysplastic crypts resembling dysplastic aberrant crypt foci of the colon in some patients, supporting the concept that, at least in patients with FAP, oligocryptal adenomas are a step in the development of epithelial neoplasms of the small intestine (132).

Although adenomas can occur throughout the small intestine (399), the commonest site is the ampullary and peri-ampullary region (1366). Adenomas can be multiple, even in patients without a history of FAP (958, 1317, 685).
Histologically, adenomas in the small intestine are similar to those in the colon, but with a propensity to be more villous or tubulovillous in architecture (2127A, 1342). The adenomatous cells resemble those of colonic adenomas, with varying degrees of dysplasia, but the columnar cells are unequivocally enterocytic in nature; goblet cells are frequent and some lesions have Paneth and endocrine cells (500, 1237).

Other associated conditions
Juvenile polyposis and Peutz-Jeghers syndrome have a recognized association with small intestinal carcinoma (1830, 1604, 1506).

Genetic susceptibility
These include: familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC), Crohn’s disease, coeliac disease, ileostomies, ileal conduits and pouches (especially after colectomy for FAP), Peutz-Jeghers syndrome and juvenile polyposis. The highest risk is in FAP. Duodenal adenomas develop in a high proportion of FAP patients (228), and the relative risk of duodenal carcinoma is over 300 times that of the normal population (1397); these carcinomas represent a major cause of death in FAP patients after total colectomy.

In FAP, carcinomas are usually associated with a macroscopically definable adenomatous component and are usually accompanied by many other adenomas in the second and third parts of the duodenum (1808, 204). Adenomas do occur elsewhere in the small bowel in FAP, including the ileum and the pelvic ileal reservoir (1376), but carcinomas are distinctly unusual.

It has been proposed that patients with carcinoma of the small intestine have an increased incidence of multicentric carcinomas of the gastrointestinal tract, with an increased incidence of gastric and colonic carcinomas in first-degree relatives (1830). Primary small bowel carcinoma can be the presenting neoplasm in hereditary non-polyposis colorectal cancer (HNPCC), occurring at an earlier age than sporadic cases and carrying a better prognosis (1604, 125).

Genetics
Patients with HNPCC and germline mutations of hMSH2 or hMLH1 have an approximately 4% lifetime risk of small bowel cancer, which exceeds the risk of the normal population 100 fold (2005). In Peutz-Jeghers syndrome, the most common site of polyps is in the small intestine, and 2-3% of patients are at risk for developing intestinal carcinoma (431, 721). In juvenile polyposis, small intestinal polyps occur with less frequency, but duodenal carcinoma has been reported (749). Genes mutated in the germline of patients with inherited syndromes that
Definition
Peutz-Jeghers syndrome (PJS) is an inherited cancer syndrome with autosomal dominant trait, characterized by mucocutaneous melanin pigmentation and hamartomatous intestinal polyposis, preferentially affecting the small intestine. Associated extra-intestinal neoplasms are less common and include tumours of the ovary, uterine cervix, testis, pancreas and breast.

MIM No. 175200

Synonyms and historical annotation
The syndrome was first described by Peutz [1512] and Jeghers [850]. Several designations have been used synonymously, including Peutz-Jeghers polyposis, periorificial lentiginosis, and polyps-and-spots syndrome.

Incidence
As the condition is rare, well documented data on the incidence are not available. Based on numbers of families registered in the Finnish Polyposis Registry, the incidence of PJS is roughly one tenth of that of familial adenomatous polyposis.

Diagnostic criteria
The following criteria are recommended: (1) three or more histologically confirmed Peutz-Jeghers polyps, or (2) any number of Peutz-Jeghers polyps with a family history of PJS, or (3) characteristic, prominent, mucocutaneous pigmentation with a family history of PJS, or (4) any number of Peutz-Jeghers polyps and characteristic, prominent, mucocutaneous pigmentation. Some melanin pigmentation is often present in unaffected individuals, hence the emphasis on the prominence of the pigmentation.

Intestinal neoplasms
Penetration appears to be high, and both sexes are equally affected [691]. Polyps are most common in the small intestine,
but may occur anywhere in the gastrointestinal tract.

**Signs and symptoms**
These include abdominal pain, intestinal bleeding, anaemia, and intussusception. Typical age at clinical manifestation is from two to twenty years. Characteristic pigmentation allows diagnosis of asymptomatic patients in familial cases.

**Imaging**
The presence of polyps may be demonstrated by upper gastrointestinal and small bowel contrast radiography, and by air contrast barium enema. Periodic small bowel X-ray examination at two to five-year intervals is advisable in the follow-up of the affected patients. Endoscopy is superior to radiological imaging in that it enables polypectomy for diagnostic and therapeutic purposes. Upper gastrointestinal tract endoscopy and colonoscopy every two years with snare excision of all polyps detected is presently recommended. Small bowel polyps may be reached by an enteroscope but rarely for the full bowel length; thus, imaging remains an integral component of clinical management.

**Macroscopy**
Peutz-Jeghers polyps occur within the stomach, small and large intestines, and rarely within oesophagus, nasopharynx and urinary tract. The small intestine is the site of predilection. The polyps are lobulated with a darkened head and closely resemble adenomas. The stalk is short and broad or absent. Size is typically 5 to 50 mm.

**Histopathology**
A typical Peutz-Jeghers polyp has a diagnostically useful central core of smooth muscle that shows tree-like branching. This is covered by the mucosa native to the region, heaped into folds producing a villous pattern. Diagnostic difficulty occurs when there is secondary ischaemic necrosis. This complication arises when a polyp has caused intussusception, a common form of presentation. Some polyps may lack diagnostic features. Epithelial misplacement involving all layers of the bowel wall (pseudoinvasion) has been described in up to 10% of small intestinal Peutz-Jeghers polyps (1728). Mechanical forces associated with intussusception or raised intraluminal pressure due to episodic intestinal obstruction are the likely explanation for this observation. Epithelial misplacement may be florid and extend into the serosa, thereby mimicking a well differentiated adenocarcinoma. Useful diagnostic features are the lack of cytological atypia, presence of all the normal cell types, mucinous cysts and haemosiderin deposition (1728).

**Dysplasia and cancer in Peutz-Jeghers polyps**
While the Peutz-Jeghers syndrome is associated with a 10 to 18-fold excess of gastrointestinal and non-gastrointestinal cancers (579, 154), the question of whether or not the Peutz-Jeghers polyp is itself precancerous has proved difficult to resolve. Epithelial misplacement has apparently been overdiagnosed as cancer in the past (1728), but it is likely that the increased risk of malignancy in the stomach, small bowel and colon (154, 1807) is due to malignant progression from hamartoma to adenocarcinoma. The evidence is threefold: (1) intraepithelial neoplasia (dysplasia), though uncommon, has been described in Peutz-Jeghers polyps (1506, 2017); (2) carcinomas may occur in contiguity with Peutz-Jeghers polyps (317, 1506); (3) the responsible gene LKB1 (STK11) is located on chromosome 19p, and loss of heterozygosity at this locus has been demonstrated in the majority of Peutz-Jeghers polyps and associated intestinal cancers (633, 691, 2052).

**Extraintestinal manifestations**
Predisposition to cancer of multiple organ systems is an important feature of the syndrome (579, 154). The most well documented extra-intestinal neoplasms include sex cord tumours with annular tubules (SCTAT) of the ovary (2188), adenoma malignum of the uterine cervix (2188), Sertoli cell tumours of the testis...
Tumours of the small intestine (231, 2118), carcinoma of the pancreas (579), and carcinoma of the breast (1587, 1952).

The cutaneous melanin pigmentation occurs typically around the mouth as freckle-like spots. Other sites commonly affected are digits, palms and feet, buccal mucosa, and anal region. While dramatic pigmentation is a helpful sign, it may fade with time, and some affected individuals never display pigmentation.

**Genetics**

**Chromosomal location and mode of inheritance**

PJS is an autosomal dominant trait with nearly complete penetrance. The PJS gene, \( LKB1 \) (STK11), maps to 19p13.3, and there is some evidence suggestive of locus heterogeneity (1210).

**Gene structure**

\( LKB1 \) consists of 9 coding exons. The open reading frame consists of 1302 base pairs, corresponding to 433 amino acids. Codons 50 to 337 encode the catalytic kinase domain of the gene.

**Gene product**

The human \( LKB1 \) gene is ubiquitously expressed in adults (853, 690). It encodes a protein of 433 amino acids which possesses a serine/threonine kinase domain framed by a short N-terminus sequence (48 residues) and a more extended C-terminus region of 122 amino acids (853, 690). \( LKB1 \) shares a significant sequence similarity with the Saccharomyces cerevisiae SNF1 kinase which phosphorylates transcriptional repressor and regulates glucose-repressible genes. Homologs of \( LKB1 \) have been identified in several species including mouse, *Xenopus*, and *Caenorhabditis elegans* (1852, 1768, 2072). Sequence alignments revealed that these proteins are most conserved within the kinase domain, with 96% of identity between human and mouse and 42% identity between human and the nematode. Human \( LKB1 \) contains a nuclear localization signal (NLS) flanking the N-terminus part of the catalytic domain (1343, 1768) and a putative prenylation motif within the C-terminus (325). The \( LKB1 \) gene product is located both in the nucleus and in the cytoplasm (1343). \( LKB1 \) displays an autocatalytic activity in vitro, and is the substrate of the cAMP-dependent protein kinase (PKA) (325). Although the function of \( LKB1 \) remains to be determined, it is worth noting that PAR-4, the *C. elegans* orthologue of \( LKB1 \), is required for establishing polarity during the first cell cycles of the embryo (2072). PAR-4 expression is also essential for embryonic viability and for intestinal organogenesis. Since the cardinal clinical feature of PJS is the presence of intestinal hamartomatous polyps, it appears plausible that the function of \( LKB1 \) has been conserved across evolution as it exerts a key regulatory role during intestinal development.

**Gene mutations and their relationship to clinical manifestations**

Germline mutations are usually truncating, but missense type mutations have also been described (853, 690). Wild type \( LKB1 \) is capable of autophosphorylation (1210, 2176), and the effect of missense mutations occurring in the kinase domain can be evaluated observing this property in autophosphorylation assays. Somatic mutations of \( LKB1 \) in tumours have been reported but are rare.

**Prognosis**

While intussusception has been a major source of mortality in PJS kindreds (2093) surgery constitutes an effective treatment. Thus, prognosis of the affected individuals is mainly related to the risk of malignancy in PJS (579, 154). Due to the rarity of the syndrome, there is little information on prognosis, but one report suggests that PJS-associated cancers are particularly aggressive (1807).
Endocrine tumours of the small intestine

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Definition
Endocrine tumours of the small intestine exhibit site-related differences, depending on their location in the duodenum and proximal jejunum or in the distal jejunum and ileum. They include carcinoid tumours (well differentiated neoplasms of the diffuse endocrine system), small cell carcinomas (poorly differentiated endocrine neoplasms) identical to carcinoid tumours (well differentiated neoplasms) and PP-cell hyperplasia in the mucosa, suggesting a relationship between D-cell growth and a long standing chronic inflammatory process [233].

ICD-O Codes
- Carcinoid tumour 8240/3
- Gastrin cell tumour 8153/1
- Somatostatin cell tumour 8156/1
- EC-cell, serotonin-producing neoplasm 8241/3
- L-cell, glucagon-like peptide and PP/PYY producing tumour
- Gangliocytic paraganglioma 8683/0
- Small cell carcinoma 8041/3

Endocrine tumours of the duodenum and proximal jejunum

Epidemiology
Incidence and time trends
Endocrine tumours of the duodenum were rare in some older series, accounting for 1.8-2.9% of gastrointestinal endocrine tumours [587, 2016]. However, in recent histopathology series, duodenal tumours amount to 22% of all gastrointestinal endocrine neoplasms (1780). Jejunal tumours account for about 1% [587, 1780] of all gut endocrine tumours. Gastrin-cell (G) tumours represent the largest group (62%) in reported series of endocrine tumours arising in the upper small intestine, followed by somatostatin-cell tumours (21%), gangliocytic paragangliomas (9%), undefined tumours (5.6%) and PP-cell tumours (1.8%) (1780).

Age and sex distribution
In a series of 99 cases of endocrine tumours of the duodenum, males were more frequently affected (M/F ratio: 1.5:1), with a mean age at manifestation of 59 years (range, 33 to 90 years) [208]. G-cell tumours associated with overt ZES (gastrinomas) differ from their apparently nonfunctioning counterpart in arising earlier in life (mean age at diagnosis is 39 years, as opposed to 66 years) (1780). Somatostatin-cell tumours affect females slightly more frequently than males (1.2:1) and become clinically manifest at a mean age of 45 years (range 29 to 83 years) [1780]. Gangliocytic paragangliomas are slightly more common in males than in females and affect patients ranging in age from 23 to 83 years, with an average of 54 years (210). The few cases of small cell carcinoma recorded in the literature were in males ranging in age from 51 to 76 years.

Aetiology
Apart from genetic susceptibility (see below), there is little knowledge about possible aetiological factors involved in the pathogenesis of duodenal and proximal jejunal endocrine tumours. An isolated report demonstrates that a sporadic gastrin-cell tumour of the duodenum originated from hyperplastic and differentiated G-cells located in the mucosal crypts [1114]. A case of a small multifocal somatostatin-cell tumour of the proximal duodenum has been reported in a patient with celiac sprue, showing somatostatin-cell hyperplasia in the mucosa, suggesting a relationship between D-cell growth and a long standing chronic inflammatory process [233].

Localization
In a series of duodenal endocrine tumours [208], 43 lesions were located in the first part, 41 in the second part, 2 in the third part, and 2 in the fourth part. Nonfunctioning G-cell tumours are located in the duodenal bulb, while the site of about 1/3 gastrinomas associated with overt ZES is in the first, second or third part of the duodenum or in the upper jejunum (1780). The preferential location of somatostatin-cell tumours, gangliocytic paragangliomas and small cell carcinomas is at, or very close to, the ampulla of Vater [206, 210, 233, 1149, 1780, 1870, 2196].

Clinical features
Endocrine tumours of the duodenum produce symptoms either by virtue of local infiltration causing obstructive jaundice, pancreatitis, haemorrhage, and intestinal obstruction (nonfunctioning tumours) or, less frequently, by secreted peptide hormones (functioning tumours). The prevalent position of somatostatin-cell tumours, gangliocytic paragangliomas, and small cell carcinomas in the ampullary region explains their frequent association with obstructive biliary disease. About 20% of the tumours, especially those located in the duodenal bulb, are asymptomatic and often incidentally discovered, e.g. by imaging analysis, endoscopy or pathological examination of gastrectomy and duodenopancreatectomy specimens removed for gastric and pancreatic cancers. Zollinger-Ellison Syndrome (ZES) with hypergastrinaemia, gastrin hypersecretion, and refractory peptic ulcer disease, is the only syndrome of endocrine hyperfunction consistently observed in association with endocrine tumours of the duodenum and upper jejunum [208, 429, 726, 1780, 2076]. The association with ZES is found in about 15% of duodenal
gastrin-cell tumours (1780). Tumours associated with overt ZES differ from their apparently nonfunctioning counterpart in arising earlier in life and having a higher incidence of metastatic and nonbulbar cases [1780].

Argentaffin, serotonin-producing, carcinoids are unusual in the upper small intestine. It follows that duodenal carcinoids only exceptionally give rise to a clinical carcinoid syndrome, associated with liver metastases of the tumour (233, 1816). In none of the cases of somatostatin-cell tumours, so far reported, did the patients develop the full ‘somatostatinoma’ syndrome (diabetes mellitus, diarrhoea, steatorrhoea, hypo- or achlorhydria, anaemia and gallstones) that has been described in association with some pancreatic somatostatin-cell tumours (1780).

Macroscopy

Endocrine tumours of the duodenum and upper jejunum usually form small (< 2 cm in diameter), grey, polypoid lesions within the submucosa with an intact or focally ulcerated overlying mucosa. However, some examples appear as infiltrative intramural nodules of rather large size (up to 5 cm in diameter). The tumours are multiple in about 13% of cases [208]. In a large series of 96 cases, the mean size was 1.8 cm (range, 0.2 to 5.0 cm) [208]. The mean size was 0.8 cm for gastrin-cell tumours [233], 2.3 cm for somatostatin-cell tumours [1816] and 1.7 cm for gangliocytic paragangliomas [233]. Small cell carcinomas typically measure 2-3 cm, and present as focally ulcerated, or pro-tuberant lesions [1870, 2196].

Microscopy

Gastrin cell tumours. These tumours are formed by uniform cells with scanty cytoplasm, arranged in broad gyriform trabeculae and vascular pseudo-rosettes and show predominant immunoreactivity for gastrin. Other peptides detected in tumour cell sub-populations are cholecystokinin, pancreatic polypeptide (PP), neurotensin, somatostatin, insulin, and the α-chain of human chorionic gonadotrophin (233). Interestingly, somatostatin, which is known to inhibit gastrin release from gastrinomas, is detected more frequently in nonfunctioning G-cell tumours than in tumours associated with ZES [233]. Ultrastructurally, typical G-cells with vesicular granules are found [233].

Somatostatin cell tumours. These neoplasms usually exhibit a mixed architectural pattern with a predominant tubulo-glandular component admixed with a variable proportion of insular and trabecular areas. Concentrically laminated psammoma bodies are detected mostly within glandular spaces. The glandular pattern and psammoma bodies may be so prominent that these tumours have been misdiagnosed as well differentiated ampullary adenocarcinomas. Unlike adenocarcinomas, however, the somatostatin cell tumours are composed of uniform cells with rather bland nuclei and few mitotic figures. Grimelius silver stain and chromogranin A are not very useful to diagnosis this tumour, because they are negative in about 50% of cases. The presence of somatostatin in tumour cells can be demonstrated by immunohistochemistry. In addition to the somatostatin cells, some tumours have minor populations positive for calcitonin, pancreatic polypeptide and ACTH [233, 381]. In addition, the apical cytoplasm of glandular structures binds WGA and PNA lectins and expresses epithelial membrane antigen [233, 1780]. Ultrastructural examination shows large, moderately electron dense secretory granules, similar to those found in normal D-cells of the intestinal mucosa [233].

EC-cell, serotonin-producing carcinoid. The classic argentaffin ‘midgut’ EC-cell carcinoid, with its characteristic pattern of solid nests of regular cells with brightly eosinophilic serotonin-containing granules and other morphological characteristics of ileal argentaffin EC-cell carcinoid, is very rare both in the duodenum and upper jejunum.

Gangliocytic paraganglioma. This tumour appears as an infiltrative lesion composed of an admixture of three cell types: spindle cells, epithelial cells, and ganglion cells. The spindle cells, which usually represent the major component, are neural in nature. They form small fascicles or envelop nerve cells and axons and show intense immunoreactivity for S-100 protein. The epithelial cells are larger cells with eosinophilic or amphophilic cytoplasm and uniform ovoid nuclei that are arranged in ribbons, solid nests, or pseudo-glandular structures. These are non-argentaffin and frequently non-argyrophil endocrine cells, often containing somatostatin [233, 1816]. In addition, PP cells and rare glucagon or insulin cells have been detected in gangliocytic paragangliomas, suggesting that they may be a hamartoma of pancreatic anlage [655, 1502]. The ganglion cells may be scattered singly or aggregated into clusters. The three components of the gangliocytic paraganglioma also intermingle with the normal smooth muscle and small pancreatic ducts at the ampulla to produce a very complex lesion. Ultrastructurally, the epithelial cells have...
abundant cytoplasm packed with dense-core secretory granules, while the ganglion cells are larger and contain a small number of neuroendocrine granules of small size and more numerous secondary lysosomes. The spindle cells are packed with intermediate filaments and resemble either sustentacular cells or Schwann cells (1502).

Genetic susceptibility

**MEN-1.** This inherited tumour syndrome is significantly associated with gastrin-cell tumours, but not with other types of endocrine tumours of the duodenum and upper jejunum. The prevalence of MEN-1 in all gastrin cell tumours of the duodenum-upper jejunum has been reported to be 5.3% (1780). Among duodenal-upper jejunal cases with an overt ZES, the association with MEN-1 syndrome is found in 7 to 21% of cases (1780, 2076). Loss of heterozygosity (LOH) at MEN-1 gene locus has been found in 4/19 (21%) duodenal MEN-1 gastrin cell tumours (1105), while a slightly higher 11q13 LOH rate for MEN-1 gastrinomas (41%; 14 of 34 tumours) was reported in an extended study of MEN-1 and sporadic gastrinomas (395). A low incidence of LOH on 11q13 in MEN-1-associated gastrinomas suggests that these tumours could arise due to inactivation of the wild-type allele via point mutations or small deletions rather than via a loss of a large segment of chromosome 11 (1105).

**Neurofibromatosis type I.** Patients with von Recklinghausen disease are at significant risk for development of periampullary neoplasms (210, 233, 933, 1780). The majority of these lesions are somatostatin cell tumours, gastrointestinal stromal tumours or gastrointestinal autonomic nerve tumours, but other neoplasms of neural crest and non-neural crest origin are known to occur. Somatostatin cell tumours were the most common perampullary neoplasms identified in one review (933), whereas carcinoids account for only 2-3% of perampullary tumours in the general population (1149). Some patients with neurofibromatosis and ampullary somatostatin cell tumour also have a phaeochromocytoma involving one or both adrenal glands, a clinical situation that can have considerable implications for complicated patient management (210). Association of gangliocytic paraganglioma with neurofibromatosis type I (906) and somatostatin-cell tumour has been reported (1822).

Genetics

Point mutations of KRAS at codon 12, which are detected in small bowel adenocarcinomas, are absent in endocrine tumours of the small intestine, including the duodenal ones (2185). Incidental gastrin cell tumours do not overexpress either basic fibroblast growth factor (bFGF), acidic fibroblast growth factor (aFGF), transforming growth factor-α (TGFα), or their respective receptors FGFR4 and EGFR (995). On the contrary, these tumours overexpress the βA-subunit of activin, which may be involved in the regulation of proliferation of tumour cells (994).

Prognosis and predictive factors

Aggressive endocrine tumours include gastrin cell, somatostatin cell, and EC-cell tumours that invade beyond the submucosa or show lymph node or distant (liver) metastases. Aggressive tumours have been reported to be 10% of all gastrin cell duodenal-upper jejunal tumours (233), 58% of sporadic ZES cases (429) and 45% of ZES-MEN-1 cases (429). In the case of somatostatin cell tumours, about two-thirds were aggressive in one study (381).

Gastrin cell tumours associated with an overt ZES are prognostically less favourable than their nonfunctioning counterparts, having a higher incidence of metastases (3 of 14 cases as against 0 of 28), and being deeply infiltrative (7 of 14 as against 3 of 19) (1780). These findings suggest a different natural history of gastrin cell tumours in the two conditions. Nonfunctioning tumours represent a generally benign condition, while ZES tumours have a low-grade malignancy, especially when arising in sites where gastrin cells are not normally present, such as in the jejunum or pancreas (233). Metastases in regional lymph nodes have been reported in 4 of 8 cases of duodenal gastrinomas with ZES-MEN-1 syndrome (1521), in 2 of 3
cases of jejunal gastrinomas (233) and in 25% of 103 cases of duodenal tumours with ZES, 24% of which also had MEN-1 syndrome (724). Local lymph node metastases seem to have little influence on survival of patients with ZES (398, 2076). In a study focusing on metastatic rate and survival in patients with ZES, no difference was found in the frequency of metastases to lymph nodes (429), when comparing primary pancreatic (48%) and duodenal (49%) tumours. In contrast, the same study found a significantly higher frequency of metastases to the liver in patients with pancreatic gastrinomas than in patients with duodenal gastrinomas (52% vs. 5%). The 10-year survival rate of patients with duodenal gastrinomas (59%) is significantly better than for patients with pancreatic gastrinomas (9%) (2076). The more favourable prognosis of duodenal tumours is mainly linked to their smaller size and less frequent association with liver metastases.

Somatostatin cell tumours are often malignant, despite their rather bland histological appearance (1780, 210, 381). Malignant somatostatin cell tumours are \(< 2 \text{ cm in diameter (381)}, \text{ invade the duodenal muscularis propria, the sphincter of Oddi, and/or the head of the pancreas, and can metastasise to paraduodenal lymph nodes and liver.}

Gangliocytic paragangliomas are usually benign, in contrast to gastrin and somatostatin cell tumours that arise in the same area. However, occasional large tumours (size > 2 cm) may spread to local lymph nodes, mainly attributable to the endocrine component of the lesion (197, 783).

Small cell carcinomas show histological signs of high-grade malignancy (high mitotic rate, tumour necrosis, deep mural invasion, angioinvasion, and neuroinvasion). Metastases are present in all cases (2196) and patients die usually within 7-17 months of diagnosis.

Endocrine tumours of the distal jejunum and ileum

Endocrine tumours of this segment of the small intestine are mainly EC-cell, serotonin-producing carcinoids, and, less frequently, L-cell, glucagon-like peptide and PP/PYY-producing tumours.

Epidemiology

Incidence and time trends

Endocrine tumours of the lower jejunum and ileum have an incidence of 0.28-0.89 per 100,000 population per year (60, 587). Jejuno-ileal lesions account for 23-28% of all gastrointestinal endocrine tumours, making this site the second most frequent location for endocrine tumours, following the appendix (587, 2016). A recent SEER analysis of 5468 cases found an increase in the proportion of ileal and jejunal carcinoids and decrease in the proportion of appendiceal carcinoids (60).

Age and sex distribution

Endocrine tumours of lower jejunum and ileum are distributed more or less equally between males and females. Patients range in age from the third to the tenth decade, with a peak in the 6th and 7th decades (211, 587, 1253, 1780).

Aetiology

At present, there is little knowledge about the aetiology of jejuno-ileoal EC-cell carcinoids. Although endocrine tumours of lower jejunum and ileum are not generally associated with preneoplastic lesions, there have been reports of focal microproliferations of EC-cells in cases of multiple ileal tumours (1736) and of intraepithelial endocrine cell hyperplasia in the mucosa adjacent to jejuno-ileoal carcinoids (1291).

Approximately 15% of carcinoid tumours of the small intestine are associated with non-carcinoid neoplasms, most frequently adenocarcinomas of the gastrointestinal tract (1251, 1253), supporting the hypothesis that secretion of growth factors is involved in their aetiopathogenesis (1251).

Localization

In the AFIP series of 167 jejuno-ileoal endocrine tumours (211), 70% were located in the ileum, 11% in the jejunum, 3% in Meckel diverticulum. These data suggest that small bowel endocrine tumours occur 6.5 times more frequently in the ileum than in the jejunum. The majority of the tumours are located in the distal ileum near the ileocaecal valve.

Clinical features

Patients with jejuno-ileoal endocrine tumours present most commonly with intermittent crampy abdominal pain, suggestive of intermittent intestinal obstruction (1253). Patients frequently have vague abdominal symptoms for several years before diagnosis, reflecting the slow growth rate of these neoplasms (1253). Preoperative diagnosis is difficult.
since standard imaging techniques rarely identify the primary tumour. Scintigraphic imaging with radiolabeled somatostatin (octreotide) is widely used to localise previously undetected primary or metastatic lesions [991]. The ‘carcinoid syndrome’ is found in 5–7% of patients with EC-cell carcinoid tumours [587, 1253] that typically arise in the ileum, all of which metastasise, mostly to the liver. Symptoms include cutaneous flushing, diarrhoea, and fibrous thickening of the endocardium and valves of the right heart.

**Macrosopy**

Jejuno-ileal endocrine tumours are multiple (ranging from 2 to 100 tumours) in about 25–30% of cases [211, 1253, 1845]. The size of the tumours is < 1 cm in 13% and ≥ 2 cm in 47% of cases [211]. They usually appear as deep mucosal-submucosal nodules with apparently intact or slightly eroded overlying mucosa. Deep infiltration of the muscular wall and peritoneum is frequent. Extensive involvement of the mesentery stimulates considerable fibroelastic or desmoplastic reaction, with consequent angulation, kinking of the bowel and obstruction of the lumen. Infarction of the involved loop of the small intestine may occur as a consequence of fibrous adhesions, volvulus, or occlusion of the mesenteric blood vessels.

**Microscopy**

EC-cell, serotonin-producing carcinoids are formed by characteristic rounded nests of closely packed tumour cells, often with peripheral palisading (Type A) [1775]. Often, within the solid nests, rosette type, glandular-like structures are detected. This variant of the fundamental structure designated as mixed insular + glandular (A + C) structure seems prognostically more favourable than the pure type A structure [1780]. In areas of deep invasion with abundant desmoplastic reaction, the cell nests may be oriented into cords and files. Mesenteric arteries and veins located near the tumour, or away from it, may be thickened and their lumen narrowed or even occluded by a peculiar elastic sclerosis, which may lead to ischaemic lesions in the intestine (72). Most tumour cells are intensely argyrophilic and reactive with chromogranin A and B antibodies. In about 30% of cases, a variable number of cells is also reactive for prostatic acid phosphatase [211]. The identification of tumour cells as EC-cells can be accomplished using histochemical methods for serotonin, including argentaffin, diazonium, and immuno-histochemical tests. Because serotonin occurs in some non EC-cell and related tumours [655], electron microscopic examination of serotonin-immunoreactive tumours (particularly those failing to react with histochemical tests) can confirm their EC-cell nature by detecting characteristic pleomorphic, intensely osmiophilic granules [1778]. Substance P and other tachykinins, such as neurokinin A, are reliable markers of a fraction of jejuno-ileal EC-cell tumours [144, 1173]; foregut (gastric, pancreatic and duodenal) EC-cell tumours remain mostly unreactive [1780]. Minor populations of enkephalin, somatostatin, gastrin, ACTH, motilin, neurotensin, glucagon/glicentin, and PP/PYY immunoreactive cells, unassociated with pertinent hyperfunctional signs, have been reported in some ileal and jejunal tumours mostly composed of EC-cells [1173, 2168]. Dopamine and norepinephrine have also

**Fig. 4.16** Multiple carcinoids of the ileum with mesenteric lymph node metastases.

**Fig. 4.17** EC-cell carcinoid. A Typical mixed insular-acinar structure. B Positive Grimelius silver reaction. C Immunoexpression of TGFβ.
been detected in addition to serotonin in a type A (insular) argentaffin carcinoid of the ileum [588]. In many cases of jejuno-ileal EC-cell tumours, however, no other hormones apart from serotonin and substance P or related tachykinins are detected [1173].

The main criteria for considering a jejuno-ileal carcinoid to have an aggressive potential are deep invasion of the wall (muscularis propria or beyond) and/or presence of metastases. According to these criteria, in the large AFIP series [211], 141 of 159 cases (89%) of jejuno-ileal carcinoids were considered aggressive.

**Genetic susceptibility**

Unlike gastric ECL-cell tumours and duodenal gastrin cell tumours, jejuno-ileal carcinoids are only occasionally associated with MEN-1 [1444]. Rare examples of familial occurrence of ileal EC-cell carcinoids have been reported [1252A].

**Genetics**

A recent study [829] reported frequent (78%) LOH on chromosome 11q13 in sporadic carcinoids of both foregut (lung and thymic) and midgut/hindgut (intestinal, including EC-cell tumours, and rectosigmoidal) origin. Other studies, however, have shown retention of heterozygosity on 11q13 in sporadic carcinoids of midgut and hindgut (intestinal, including EC-cell tumours, and rectosigmoidal) origin. Nevertheless, these findings suggest the involvement of an autocrine loop [22]. A similar growth promoting role in midgut carcinoid tumour cells is assigned to IGF-1 [22], PDGF, TGFα, bFGF, and aFGF seem to be mainly involved in tumour stromal reaction, including stromal desmoplasia [22, 993, 995], by acting on receptors expressed on fibroblasts or stimulating the promotion of new vasculature and tumour progression [22, 993, 995].

Neural adhesion molecule (NCAM), a member of the immunoglobulin superfamily of cell adhesion molecules, is highly expressed in midgut carcinoid tumours [22]. Because NCAM has not been shown in normal gut endocrine cells, the novel expression of this adhesion molecule in carcinoids may be of importance for growth and metastases.

**Prognosis and predictive factors**

A recent report revealed a 21% mortality rate for jejuno-ileal carcinoids, compared with 4% for duodenal, 6% for gastric, and 3% for rectal carcinoids [211]. In two studies, the overall 5-year survival rate of patients with jejuno-ileal endocrine tumours was about 60% and the 10-year survival rate was 43% [211, 1845]. In patients with no liver metastases, the 5- and 10-year survival rates were 72% and 60%, respectively, as opposed to 35% and 15% for patients with liver metastases [1845], demonstrating the relatively slow rate of growth of some EC-cell tumours. Metastases are generally confined to regional lymph nodes and liver. Extra-abdominal metastases were found in only 0.5% of the cases reported by Moertel et al. [1253]. In one study, univariate analysis showed that survival was negatively correlated with distant metastases at the time of surgery, mitotic rate, tumour multiplicity, the presence of carcinoid syndrome, depth of intestinal wall invasion, and female gender; by multivariate analysis, survival was negatively associated with distant metastases, carcinoid syndrome, and female gender [211].

In summary, jejuno-ileal carcinoid tumours that are clinically nonfunctioning, 1 cm or less in diameter, confined to submucosa and non-angioinvasive, are generally cured by complete local excision. Invasion beyond submucosa or metastatic spread indicates that the lesion is aggressive. If the lesion, although confined to the mucosa/submucosa, shows angioinvasion, or is over 1 cm in size, it is of uncertain malignant potential.
B-cell lymphoma of the small intestine

Definition
Primary small intestinal lymphoma is defined as an extranodal lymphoma arising in the small bowel with the bulk of disease localized to this site. Contiguous lymph node involvement and distal spread may be seen, but the primary clinical presentation is the small intestine, with therapy directed to this site.

ICD-O codes
- MALT lymphoma: 9699/3
- IPSID: 9764/3
- Mantle cell lymphoma: 9673/3
- Burkitt lymphoma: 9687/3
- Diffuse large B-cell lymphoma: 9680/3

Epidemiology
In contrast to lymphomas involving the stomach, primary small intestinal lymphomas are uncommon in Western countries [792]. However, since epithelial and mesenchymal tumors are uncommon in the small bowel, lymphomas constitute a significant proportion (30-50%) of all malignant tumors at this site. Lymphomas of mucosa-associated lymphoid tissue (MALT) type are the most frequent lymphomas of both the small intestine and the colorectum, although controversy surrounds the histogenesis of de novo diffuse large B-cell lymphoma arising along the gastrointestinal tract. A unique form of intestinal MALT lymphoma occurs predominantly in the Middle East and Mediterranean areas, and is referred to as immunoproliferative small intestinal disease (IPSID) [1649]. This entity represents a spectrum of small intestinal lymphoproliferations, including alpha heavy chain disease (αHCD) and may represent different manifestations or phases of the same disease. αHCD and IPSID occur predominantly in the Mediterranean area, but may be seen outside this region. They typically affect young adults, whereas small intestinal lymphomas in the Western world increase in frequency with age with a peak incidence in the 7th decade. Most studies have shown a slight male predominance [424].

Aetiology
In contrast to the well-established relationship between Helicobacter pylori and gastric MALT lymphoma, no infectious organism has been clearly implicated in the pathogenesis of small intestinal MALT lymphoma. IPSID appears to be related to bacterial infection, as antibiotic responsiveness is typical of the early phases of the disease. However, no specific organism has been identified. Lymphomas involving the small intestine or colorectum may occur in distinct clinical settings. Chronic inflammatory bowel disease, including Crohn disease and ulcerative colitis, are recognized risk factors for non-Hodgkin lymphoma at this site. Importantly, the risk is much less than that associated with gluten-sensitive enteropathy and primary T-cell lymphomas of the small bowel (see T-cell lymphoma section). Crohn disease is more often implicated in the development of lymphoma in the small intestine, while ulcerative colitis is associated with lymphomas of the colorectum [1733]. An increased incidence of lymphoma has been associated with both acquired and congenital immunodeficiency states, including congenital immune deficiency, iatrogenic immunodeficiency associated with solid organ transplantation, and acquired immunodeficiency syndrome (AIDS) [357]. In general, lymphomas associated with immunodeficiency show a predilection for extranodal sites, particularly the gastrointestinal tract, irrespective of the cause of the immunodeficiency [1057, 787].

Clinical features
Symptoms produced by small intestinal lymphomas depend upon the specific histological type. Indolent lymphomas of B-cell lineage typically present with abdominal pain, weight loss and bowel obstruction [424]. Occasional cases present with nausea and vomiting, while rare cases are discovered incidentally. More aggressive tumours, such as those of T-cell lineage (described separately) or Burkitt lymphoma, may present as a large intra-abdominal mass or acutely with intestinal perforation. IPSID often manifests as abdominal pain, chronic severe intermittent diarrhoea and weight loss [1649]. The diarrhoea is mainly the result of steatorrhoea, and a protein-losing enteropathy can be seen. Peripheral oedema, tetany and clubbing are observed in as many as 50% of patients. Rectal bleeding is uncommon in small bowel lymphoma, but a common presenting sign in primary colonic lymphoma. Burkitt lymphoma is most frequently seen in the terminal ileum or ileocaecal region, and may cause intussusception.

Imaging and endoscopy
Radiological studies are useful adjuncts to the diagnosis of small intestinal lymphomas, including barium studies and computerized tomography scans. T-cell lymphomas are typically localized in the jejunum, presenting as thickened plaques, ulcers, or strictures. Most B-cell lymphomas manifest as exophytic or annular tumour masses in the ileum [792]. B-cell lymphomas of both low- and intermediate-grade may produce nodules or polyps that can be seen both endoscopically and by imaging. Most small intestinal lymphomas are localized to one anatomic site, but multifocal tumours are detected in approximately 8% of cases. Multiple lymphomatous polyposis consists of numerous polypoid lesions throughout the gastrointestinal tract [791]. Most often, the jejunum and terminal ileum are involved, but lesions can appear in the stomach, duodenum, colon, and rectum. This entity produces a characteristic radiological picture that is virtually diagnostic. As discussed below, the majority of such cases is caused by mantle cell lymphoma, but other subtypes of lymphoma may produce a similar radiological pattern [1034]. IPSID. The macroscopic appearance of IPSID depends on the stage of disease. Early on, the bowel may appear endoscopically normal, with infiltration appar-
The disease may then progress to thickening of the upper jejunum together with enlargement of the mesenteric lymph nodes and the development of lymphomatous masses. Typically, the spleen is not involved and may even be small and fibrotic, as described in coeliac disease. Distal spread beyond the abdomen is uncommon (1649, 798).

**Histopathology**

**MALT lymphoma**

The majority of intestinal lymphomas involving the small bowel are B-cell lymphomas of MALT type, including both low-grade and aggressive types (792, 793, 796). These so-called ‘Western’ types are distinct from IPSID and αHCD. The histological features of Western type small intestinal lymphoma are similar to gastric MALT lymphoma, except that lymphoepithelial lesions are less prominent (792).

In contrast to gastric MALT lymphomas, diffuse large B-cell lymphomas arising in the small bowel are much more common than low-grade B-cell lymphomas of MALT-type (796). Some of these lymphomas may have a low-grade MALT component, providing evidence that their histogenesis is related to the mucosal immune system. Precise criteria for defining a MALT lymphoma of large cell type are lacking, as are the criteria for distinguishing transformation within a low-grade MALT lymphoma (383). When both histologies are evident, the lesion is best described as composite. When small foci of large transformed cells or early sheeting-out of large cells are detected within a background of low-grade intestinal MALT lymphoma, their presence should be noted. Currently, the prognostic impact of these findings and their effect on treatment are underdetermined. Diffuse large B-cell lymphomas arising in the small bowel that lack a background of low-grade MALT lymphoma are currently best classified as extranodal diffuse large B-cell lymphoma, not otherwise specified (670).

**IPSID / αHCD**

**Immunoproliferative small intestinal disease** and **α heavy chain disease** are part of a spectrum of lymphoproliferative diseases prevailing in the Middle East and Mediterranean countries (792). They are subtypes of small intestinal MALT lymphoma characterized by the synthesis of α heavy chain. The histology is characteristic of MALT lymphoma with marked plasma cell differentiation.

Three stages of IPSID are recognized. In stage A, the lymphoplasmyacytic infiltrate is confined to the mucosa and mesenteric lymph nodes, and cytological atypia is not present. Although the infiltrate may obliterate the villous architecture, endoscopic examination appears normal. Resection specimens reveal reactive lymphoid follicles, lymphoepithelial lesions and small clusters of parafollicular clear cells. This phase of the disease is typically responsive to antibiotic therapy. In stage B, nodular mucosal infiltrates develop and there is extension below the muscularis mucosae. A minimal degree of cytological atypia is apparent. This stage appears to represent a transitional phase, can be seen macroscopically as thickening of mucosal folds, and is typically not reversible with antibiotics. The characteristic features of MALT lymphoma are now evident, and follicular colonization may be so marked as to mimic follicular lymphoma. Stage C is characterized by the presence of large masses and transformation to frank large cell lymphoma. Numerous centroblasts and immunoblasts are present. Plasma cytotic activity is increased. Mesenteric lymph node involvement occurs early in the course of disease, with both plasma cell infiltration of nodal sinuses and marginal-zone areas distended by small atypical lymphoma cells with moderate amounts of pale, clear cytoplasm. Immunohistochemical studies demonstrate the production of α heavy chain without light chain synthesis (798). The IgA is almost always of the IgA1 type, with intact carboxy-terminal regions and

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**Fig. 4.19** Malignant lymphomatous polyposis. A Typical polypoid mucosa. B Polypoid mantle cell lymphoma.

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deletion of most of the V and all of the CH1 domains. The molecular characterization of individual cases is variable. The small lymphoma cells express CD19 and CD20, but fail to express CD5, CD10 and CD23.

**Mantle cell lymphoma**

Mantle cell lymphoma (MCL) typically involves both spleen and intestines and may present as an isolated mass or as multiple polypos throughout the gastrointestinal tract where it is referred to as *multiple lymphomatous polyposis* (424, 791, 1292). Importantly, other histological subtypes of non-Hodgkin lymphoma can also produce this clinicopathological entity.

The polyps range in size from 0.5 cm to 2 cm with much larger polyps found in the ileocaecal region. The histology of MCL involving the small bowel is identical to MCL at nodal sites (110). The architecture is most frequently diffuse, but a nodular pattern and a less common true mantle-zone pattern are also observed. Reactive germinal centers may be found and are usually compressed by the surrounding lymphoma cells, thereby appearing as replacing the normal mantle zones. Intestinal glands may be destroyed by the lymphoma, but typical lymphoepithelial lesions are not seen. The low power appearance is monotonous with frequent epithelioid histiocytes, mitotic figures and fine sclerosis surrounding small blood vessels. The lymphoma cells are small to medium sized with irregular nuclear outlines, indistinct nucleoli and scant amounts of cytoplasm. Large transformed cells are typically not present. The lymphoma cells are mature B-cells and express both CD19 and CD20. Characteristically the cells co-express CD5 and CD43. Surface immunoglobulin is found including both IgM and IgD. Light chain restriction is present in most cases, with some studies demonstrating a predominance of lambda. CD10 and CD11c are virtually always negative. Bcl-1 (cyclin D1) is found in virtually all cases and can be demonstrated within the nuclei of the neoplastic lymphocytes in paraffin sections.

MCL is an aggressive lymphoma, which typically presents in advanced stage with involvement of mesenteric lymph nodes and spread beyond the abdomen, including peripheral lymph nodes, spleen, bone marrow and peripheral blood involvement (84).

**Burkitt lymphoma**

Burkitt lymphoma occurs in two major forms, defined as endemic and sporadic. Endemic Burkitt is found primarily in Africa and typically presents in the jaw, orbit or paraspinous region, and is strongly associated with Epstein-Barr virus (EBV).

In other endemic regions however, it is relatively common for Burkitt lymphoma to present in the small intestine, usually involving the ileum, with preferential localization to the ileocaecal region (792). In parts of the Middle East, primary gastrointestinal Burkitt lymphoma is a common disease of children. Sporadic or non-endemic Burkitt lymphoma is a rare disease, not associated with EBV infection, that frequently presents as primary intestinal lymphoma. Burkitt lymphoma is also seen in the setting of HIV infection when it often involves the gastrointestinal tract (236).

The histology in all cases is identical and is characterized by a diffuse infiltrate of medium-sized cells with round to oval nuclear outlines, 2-5 small but distinct nucleoli and a small amount of intensely basophilic cytoplasm. Numerous mitotic figures and apoptotic cells are present. The prominent starry-sky appearance is caused by benign phagocytic histiocytes engulfing the nuclear debris resulting from apoptosis. Thin sections often show an unusual finding for lymphomas, whereby the cytoplasmic borders of individual cells ‘square-off’ against each other. Burkitt lymphoma may rarely demonstrate a true follicular architecture, consistent with the proposed germinal center histogenesis of this neoplasm. It is a mature B-cell lymphoma and the neoplastic cells express pan-B-cell antigens.
CD19, CD20, CD22, and CD79a. In approximately 60-80% of cases, the neoplastic cells co-express CD10, but fail to express CD5 or CD23. Surface immunoglobulin expression is moderately intense and is nearly always IgM with either kappa or lambda light chain restriction. The growth fraction, as assessed by Ki-67 or the paraffin equivalent MIB-1, is typically in excess of 90% of tumour cells. Burkitt lymphoma cells uniformly fail to express bcl-2.

Burkitt-like lymphoma
This group of atypical Burkitt lymphomas appears to represent a morphological overlap between Burkitt lymphoma and diffuse large B-cell lymphoma. The overall cell size is similar to Burkitt, but with greater pleomorphism [827]. These cases lack the typical monomorphic appearance of Burkitt lymphoma and demonstrate slight variation in both cell size and shape. The cells may have multiple nuclei as in Burkitt lymphoma or a single distinct nucleolus. A starry-sky pattern may be evident and the mitotic rate is usually significantly increased. These lymphomas have a predilection for the gastrointestinal tract of adults, and also occur in the setting of HIV infection.

Other B-cell lymphomas
Any subtype of B-cell lymphoma can present as a primary small intestinal lymphoma, including those thought to arise from peripheral lymph node equivalents. De novo diffuse large B-cell lymphomas are the commonest lymphomas in the small bowel, and may develop from low-grade MALT lymphomas. Indolent lymphomas such as small lymphocytic lymphoma, lymphoplasmacytic lymphoma and follicular lymphoma (centroblastic/centrocytic) can present as primary small intestinal disease. The latter subtype can occasionally produce the clinico-pathological entity of multiple lymphomatous polyposis, but can usually be distinguished from MCL by immunophenotypic and molecular genetic analysis [1034]. Lymphoblastic lymphoma may underlie small intestinal lymphoma and frequently produces a mass in the ileocaecal region. Characteristic nuclear features and the expression of terminal nucleotidyl transferase may aid in establishing the diagnosis.

Genetics
MALT lymphoma
Cytogenetic and molecular features of intestinal MALT lymphomas are incompletely understood; the presence of either t(1;14)(p22;q32) or t(11;18)(q21;q21) and the corresponding molecular abnormalities, rearrangement of bcl-10 or AP12-MALT, have not been described at this site; thus their relationship to gastric MALT lymphomas is unclear [2116, 412]. Trisomy 3 is common in gastric MALT lymphomas, but the frequency of this cytogenetic abnormality in primary intestinal lymphomas is unknown [413].

IPSID
Although cytogenetic abnormalities have been detected in IPSID, no consistent changes have been described. Southern blot analysis reveals clonal immunoglobulin heavy-chain (IgH) gene rearrangements, but consensus IgH polymerase chain reaction (PCR) strategies may yield false negative results.

Mantle cell lymphoma
MCL is cytogenetically characterized by a t(11;14)(q13;q32) translocation which deregulates expression of the bcl-1 oncogene on chromosome 11. Rearrangement can be detected using Southern blot analysis, PCR or fluorescent in situ hybridization (FISH).

Burkitt lymphoma
Burkitt lymphoma demonstrates a consistent cytogenetic abnormality in all cases, with rearrangement of the c-myc oncogene on chromosome 8. The characteristic translocation, t(8;14)(q24;q32), is seen in most cases; the remainder shows variant translocations including the immunoglobulin light chain loci, t(2;8)(p12;q24) or t(8;22)(q24;q11), involving kappa and lambda light chain genes, respectively. In the classical t(8;14), the c-myc oncogene is translocated from chromosome 8 to the heavy chain locus on chromosome 14. In the variant translocations, a part of the light chain constant region is translocated to chromosome 8, distal to the c-myc gene. Thus, in the variant translocations, c-myc remains on chromosome 8 and is deregulated by virtue of its juxtaposition to the immunoglobulin light chain genes. The molecular characteristics of the c-myc translocation also differ between endemic and sporadic cases. In endemic Burkitt lymphoma, the chromosome 8 breakpoints are usually far 5' of the c-myc gene, while their chromosome 14 breakpoints most often occur in the location of the IgH gene joining segments. The variable chromosome 8 breakpoints and their location far from the c-myc coding sequences make it impossible in most cases to demonstrate c-myc rearrangements by Southern blot analysis. In contrast, sporadic cases frequently have c-myc breakpoints within non-coding introns and exons of the gene itself, typically in the first exon or intron, or in the 5' flanking regions of the gene. In most of these cases, c-myc rearrangements can be demonstrated using Southern analysis [670].

Burkitt-like lymphoma/
Atypical Burkitt lymphoma
This category is cytogenetically heterogeneous and may contain three or more biological groups [1387]. Importantly, the frequency of variant c-myc translocations precludes the accurate recognition of cases using molecular techniques alone.

Prognostic factors
The main determinants of clinical outcome in small intestinal lymphomas are histological grade, stage, and resectability [424]. Advanced age at diagnosis, an acute presentation with perforation, and the presence of multifocal tumours have an adverse impact on survival. The behaviour of diffuse large B-cell lymphoma is not affected by the presence of a low-grade MALT component [424]. The expression of bcl-2 protein and the presence of TP53 mutations may adversely affect outcome in this group, but a systematic study of small intestinal lymphomas is lacking [567, 770]. MCL is an aggressive neoplasm. A blastoid cytology, increased mitotic index and peripheral blood involvement are recognized as adverse factors [84]. Mutations in the p53 gene and homozygous deletions of p16 have recently been shown to be associated with poor prognosis [1099, 700]. Burkitt-like lymphomas with ‘dual translocation’ of both bcl-2 and c-myc oncogenes have a markedly shortened overall survival [1137].
Intestinal T-cell lymphoma

Definition
A peripheral T-cell lymphoma arising in the intestine, usually as a complication of coeliac disease (gluten sensitive enteropathy), histologically characterised by differentiation towards the intestinal intraepithelial T-cell phenotype.

ICD-O codes
T-cell lymphoma 9702/3
Enteropathy associated 9717/3

Epidemiology and aetiology
Intestinal T-cell lymphoma (ITL) is rare, accounting for only about 5% of all gastrointestinal lymphomas, and is normally associated with coeliac disease (305). There is marked geographic variation in the incidence of ITL, with a high incidence in Northern Europe, reflecting the notion that ITL arises against the same genetic background as that predisposing to coeliac disease (753). There is no clear sex predominance and in Europe, the median age at diagnosis is around 60 years (305, 424, 374). In contrast, a small series of Mexican patients had a median age of 24 years and there was circumstantial evidence for a possible aetiological role of the Epstein Barr virus, which is absent in European cases (1552, 795). Congenital or acquired immunodeficiency disorders are not known to be associated with ITL.

Localization
The proximal jejunum is the most frequent site of disease, although it may occur elsewhere in the small intestine and, rarely, in the stomach and colon (305).

Clinical features
The most frequent symptoms are abdominal pain and weight loss (303). About 40% of patients present as acute abdominal emergencies due to intestinal perforation and/or obstruction (305, 424). Patients may have a short history of malabsorption, sometimes diagnosed as adult coeliac disease which is usually gluten-insensitive or, less frequently, a long history of coeliac disease lasting for years or even decades (796). Signs and symptoms of the disease may mimic inflammatory bowel disease (IBD), particularly Crohn disease. Radiographic studies may be helpful, but they are often interpreted as consistent with a segmental or diffuse inflammatory process. Except for leukocytosis, laboratory data are usually unremarkable, including normal levels of lactate dehydrogenase (303).

Tumour spread and staging
About 70% of the patients present with localized intestinal disease with or without contiguous lymph node involvement (305). Disseminated disease involves liver, spleen, lung, testes, and skin, but rarely the bone marrow (303, 794).

Histopathology
The histological appearances of ITL are variable both between cases and between different tumour sites in the same patient. The most frequently encountered type is composed of highly pleomorphic, medium to large cells, followed by a morphology most consistent with anaplastic large cell lymphoma. The border between these two histologies is not sharp and transition from one to the other may occur, even within the same tumour (307). About 20% of ITL are characterized by the monotonous appearance of densely packed small to medium-sized cells almost without any recognizable stroma components. Most of the rather monomorphic cells contain only slightly

Fig. 4.22 Intestinal T-cell lymphoma. Histological features of the most common variants. A Pleomorphic medium and large cells. B Anaplastic large cells. C Monomorphic small to medium cells.
irregular nuclei with small nucleoli and moderately wide, pale or sometimes clear cytoplasm \( (307) \). Rare variants of ITL are composed predominantly of pleomorphic small cells or immunoblasts. Irrespective of morphology, the lymphoma cells often invade and destroy the overlying epithelium. Most frequently, the enterocytes of the upper and intermediate villous regions, or in cases of severe villous atrophy, the epithelium of the upper parts of the elongated crypts are the preferential targets of lymphoma cell attack. These features are best appreciated at the borders of ulcerated tumours. However, they may also be present as band-like or patchy microscopic lesions entirely confined to the mucosa \( (303) \). Fibrosis and admixed inflammatory cells are constant features of the pleomorphic medium and large cell and the anaplastic large cell ITL types; in the former, an abundance of eosinophils may mask the neoplastic infiltrate \( (1731) \). In contrast, the monomorphic small to medium-sized variant characteristically lacks fibrotic changes and inflammatory background \( (307) \).

**Histopathology of the enteropathic mucosa**

In the vast majority of cases, the macroscopic normal intestinal mucosa shows features of coeliac disease, i.e. increase in normal appearing intraepithelial lymphocytes (IEL), villous atrophy, and crypt hyperplasia \( (794) \), which has prompted O’Farrell and co-workers to coin the term ‘enteropathy associated T-cell lymphoma’ \( (1383) \). An increase in normal appearing IEL (duodenum / jejunum, ≥ 40/100 enterocytes; ileum, ≥ 20/100 enterocytes) represents the single most important feature suggestive of coeliac disease \( (1172) \). The severity of these enteropathic changes is highly variable and similar to coeliac disease; they are most pronounced proximally and improve distally so that the lower jejunum and ileum may appear normal. Furthermore, enteropathy may be minimal or absent if the patient is on a gluten free diet, or if enteropathic sites are missed because of their patchy distribution. Occasionally, the non-neoplastic mucosa in ITL shows a strikingly intense or florid intraepithelial lymphocytosis \( (2142) \).

**Immunological phenotyping**

Similarities of the immunophenotypes in normal or activated (reactive) intraepithelial lymphocytes (IEL) and the tumour cells in ITL provide an important part of evidence that ITL cells are the neoplastic counterpart of IEL. The expression of the HML-1 defined α-β \( (CD103) \) on non-neoplastic IEL and in > 50% of ITL, but not in resting peripheral blood T-cells, strongly supports this view \( (1802) \). The vast majority of normal IEL are resting cytotoxic CD3+CD8+CD4-CD2+CD7+CD5+ T-cells using the αβ T-cell receptor, but minor subsets such as CD4-CD8- or CD56+ are present as well as predominantly CD4-CD8- γδ T-cells \{1113, 304\}. In ITL, most cases are CD3+CD4-CD8-CD7+CD5- and co-express the cytotoxic granule-associated protein TIA-1, often together with the activation-dependent cytotoxic molecule granzyme B \( (305, 382) \). Some correlations between ITL morphology and phenotype exist; pleomorphic medium and large cell lymphomas and lymphomas of anaplastic large cell histology are often CD4-CD8-, the latter express CD30+ but are always ALK1 negative; the monomorphic small to medium-sized variant is frequently associated with a CD56+CD8+ phenotype \( (307) \).

Cytologically normal IEL abundantly present in the intact enteropathic mucosa in ITL, in ulcerative jejunitis, and in refractory coeliac disease share an identical aberrant phenotype with ITL and are monoclonal, as demonstrated by PCR \( (103) \). They therefore are considered a neoplastic population which, in the absence of concurrent overt ITL, may represent the first step in ITL lymphomagenesis (‘intraepithelial lymphoma’) and may have already persisted for years \( (238) \).

**ITL diagnosis of endoscopic biopsies**

Most cases of ITL are diagnosed on surgical resection specimens. In a minority however, endoscopic biopsies, usually taken from the stomach, duodenum, or colon, are available. These patients frequently have a longer than 6 months history of abdominal pain and weight loss. Some of them are clinically suspected to have inflammatory bowel disease, and occasionally patients had already been biopsied with the diagnosis of IBD or an unclear inflammatory process, thus emphasizing the challenging task of ITL diagnosis in endoscopic biopsies. The immunohistochemical demonstration of an aberrant phenotype is essential in diagnosing ITL, especially in cases which lack overt cytological atypia and/or invasiveness. Furthermore, the neoplastic infiltrate may be subtle or superficial and therefore easily overlooked in routinely stained sections.

**Genetics**

Very few data on chromosomal abnormalities in ITL exist. Deletion of the Y chromosome and chromosome 9 abnormalities were found among a phenotypically aberrant intraepithelial T-cell population \( (2142) \); a t(4;16)(q26;p13) translocation was present in a mesenteric...
lymph node associated with extensive ITL [239]. In two cases of anaplastic large cell ITL very complex abnormalities were detected in ascitic fluid and lymph node, respectively [1436]. Southern blotting and PCR studies demonstrated monoclonal rearrangements of the T-cell receptor (β-chain) in ITL, consistent with the derivation from αβ T-cells [799]. ITL using the γδ T-cell receptor are rare [86], but nevertheless seem to outnumber the few well documented cases of true intestinal natural killer (NK) cell lymphomas [1176]. The latter finding is not surprising as NK cells are not present among IEL.

**Prognosis and predictive factors**
The clinical course is very unfavorable due to complications from peritonitis and malnutrition and later from progressive disease typically characterized by intestinal recurrences. The malabsorption due to underlying coeliac disease is detrimental to these patients, particularly when recovering from surgery or receiving multiagent chemotherapy [444]. Consequently, only one half of the patients is amenable to chemotherapy and only a proportion of these is able to finish the complete course. The overall median survival in the largest published series is only 3 months, and 5-year survival in this and other series ranges from 8-25% [305, 424, 444]. The small group of long-term survivors usually received chemotherapy and, interestingly, none had a previous diagnosis of coeliac disease [305, 444].

![Fig. 4.24 CD3 immunoexpression in a T-cell lymphoma of the small intestine.](image)
Mesenchymal tumours of the small intestine

Definition
A variety of benign and malignant mesenchymal tumours can arise in the small intestine, but the neoplasms that occur in any appreciable numbers are gastrointestinal stromal tumours (GISTs).

Epidemiology
Sarcomas account for approximately 14% of malignant small intestinal tumours (1928). Males are affected somewhat more than females (M:F 1.2:1). The peak incidence is in the 6th to 8th decade. Age of onset for sarcomas was lower than for carcinomas, with black females showing the lowest median age, 50 years. In the U.S. SEER database, the incidence rate for sarcoma was 0.2 per 100,000 per year compared to 0.3 for lymphomas, 0.4 for adenocarcinomas and 0.4 for carcinoids, and appears to be stable.

Localization
Sarcomas show a much more even distribution throughout the small bowel compared to adenocarcinomas and carcinoids (1928). GISTs have been specifically identified in duodenum, jejunum, and ileum (183, 594, 1980).

Clinical features
Vague abdominal discomfort is the usual complaint. Mesenchymal neoplasms of small bowel are more difficult to diagnose by endoscopy or imaging studies than those in the stomach.

Macroscopy
Small bowel sarcomas generally appear macroscopically as those in the stomach. Some small intestinal tumours may cause aneurysmal bowel dilatation, while others have a diverticulum-like appearance.

Histopathology
Gastrointestinal stromal tumours
Small bowel GISTs resemble those of the stomach histologically, although epithelial lesions are uncommon. Globoid extracellular collagen accumulations (so-called skeinoid fibres) are frequently observed, especially in benign small intestinal GISTs (1235). Factors that correlate with malignancy are tumour size > 5 cm, mitotic count > 5 per 50 HPF, dense cellularity, and mucosal invasion (rarely observed). Even with low or absent mitotic activity, tumours larger than 5 cm are considered to have malignant potential. Small intestinal GISTs are positive for KIT (CD117) and usually for CD34, and a subset (30-50%) are positive for α-smooth muscle actin; most tumours are negative for desmin and almost all are negative for S100-protein.

Leiomyomas and leiomyosarcomas are rare in the small intestine, and can be identified immunohistochemically by their smooth muscle actin and desmin expression and lack of KIT.

Angiosarcomas are recognized by an anastomosing proliferation of atypical endothelial cells. Immunohistochemical demonstration of CD31, less consistently von Willebrand factor, is diagnostically useful (1904).

Kaposi sarcomas may involve small intestine, either the mucosa alone or more extensively. Histologically typical are elongated spindle cells with vascular slits. Cytoplasmic PAS-positive hyaline globules are present in some tumour cells. Immunohistochemically, the lesional cells are positive for CD31 and CD34. Human herpesvirus 8 can be demonstrated by PCR.

Lipomas exhibit the same morphological features as their colonic counterparts.

Genetics
Small intestinal GISTs show similar c-kit mutations in exon 11 as observed in gastric GISTs, and most mutations occur in the malignant cases. Comparative genomic hybridization shows common losses in chromosomes 14 and 22 similar to those seen in gastric GISTs.

Prognosis
The prognosis of small bowel sarcomas is largely dependent on the mitotic count, size, depth of invasion, and presence or absence of metastasis. In the SEER database, 5-year survival for localized tumours was 45% for sarcomas, compared to 92% for carcinoids and 63% for carcinomas (1928). In a study of over one thousand stromal/smooth muscle sarcomas, the 5-year survival rate was 55% for sarcomas of small bowel, 60% for colorectum, 70% for stomach and 75% for oesophagus (462).
Secondary tumours of the small and large intestines

Definition
Tumours of the intestines that originate from an extra-intestinal neoplasm or which are discontinuous with a primary tumour elsewhere in the gastrointestinal tract.

Epidemiology
Metastatic spread to the small intestine is more frequent than to any other site in the gastrointestinal tract (see Table 3.02). Secondary carcinomas of the small bowel are as common as primary carcinomas at this site [1234].

Origin
For small intestine, melanoma, lung, breast, colon and kidney are the most frequent primary sites (see Table 3.02) [130, 1022, 1378, 1209, 1457, 458]. Metastatic spread from primary lung cancer to the small intestine is more frequent than to stomach and colon (Table 4.01). Virtually all primary cancers can occasionally lead to metastases in the small intestine and, because of the low frequency of primary small bowel cancer, a high proportion of small intestinal malignancies are metastatic. The pathogenesis of intestinal metastasis usually involves haematogenous spread of tumour cells. Invasion from neighbouring primary tumours also occurs, e.g. pancreatic carcinoma to duodenum and prostate carcinoma to rectum.

Primary melanomas of the intestine are very rare. Although most melanomas found in the small bowel have no history

Table 4.01
Frequency of metastasis from breast (695 cases) and lung (747 cases) to gastrointestinal tract [130].

<table>
<thead>
<tr>
<th>Primary site</th>
<th>Stomach</th>
<th>Small intestine</th>
<th>Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>3.6%</td>
<td>1.7%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Lung</td>
<td>1.3%</td>
<td>4.4%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

Fig. 4.27  A Tumour is beneath swollen mucosa. B Tumour in muscularis propria. Submucosa is oedematous.

Fig. 4.28  A, B Metastatic malignant melanoma, small intestine.
of a primary tumour, the general consensus is that they are virtually all secondary, usually from misdiagnosed or regressed primary melanomas [458].

Clinical features
Small intestinal metastases can cause bleeding and obstruction as well as non-specific symptoms such as abdominal discomfort, gas distension, and diarrhoea [1378, 580].

Imaging
The identification of a small bowel tumour always raises the question of whether the tumour is primary or secondary. Contrast radiography shows narrowing and abnormalities of the small intestinal wall. Advanced cases result in stenosis with distension due to obstruction.

Macroscopy
Typical features of intestinal metastases include intestinal wall thickening, submucosal spread, and ulcers. Melanomas may not be pigmented and may appear as nodules or polyps.

Histopathology
Metastases are typically submucosal or subserosal making the distinction between primary and secondary tumours relatively easy. Cytokeratin immunohistochemistry may help to differentiate between primary colon cancer (positive for cytokeratin 20), metastases from ovary and breast (usually positive for cytokeratin 7) and those from liver, kidney and prostate (usually negative for both cytokeratins 7 and 20) [2047, 129]. On the other hand, the distinction between multiple primary small bowel carcinoids and their metastases may not be possible. This also applies to leiomyosarcomas/stromal tumours of the small intestine.

Prognosis
Intestinal metastases usually represent a late stage of disease in which other haematogenous metastases are also frequently found. Therefore, the prognosis is poor. Exceptions are melanoma and renal cancer in which metastases confined to the bowel may be associated with prolonged survival after resection.