CHAPTER
13 Tumors of the Gastrointestinal tract

Globally, gastrointestinal (GI) cancer presents a major oncologic problem (chapter 2), with colorectal cancer ranking the third, stomach the fourth and esophagus the eighth most common cancers (Ferlay et al, 2010). However, the profile of GI cancer shows a striking international geographic variation with predominance of colorectal cancer in Western countries (USA and Europe), whereas, China and Japan are high incidence areas of esophageal and gastric cancers respectively. This is etiologically related to dietary habits and environmental conditions. The relative frequency of GI cancers in US-SEER registry is presented in (Table 13-1).

Gastrointestinal cancer is also a major cause of cancer mortality (ranking the fourth) worldwide. In USA, colorectal cancer alone contributes about 9% of cancer mortality, ranking the second after lung cancer. Patients usually present at an advanced stage especially in developing countries. In USA, where medical care is optimal, the overall relative survival rates are 14% for esophagus, 21% for gastric and 65% for colonic cancer (Ries et al, US-SEER data, 2007). Comparable survival data are not available in most developing countries, but, much lower figures are expected.

In Egypt, GI cancer contributes 7.8% of all cancers, ranking the fifth most common cancer after breast, bladder, NHL and liver (Globocan data 2008). In males it is the fourth (8.3%) and in females it is the third (7.4%). Colorectal cancer predominates (56.4%), a profile similar to that reported from USA (Table 13.1). Data from NCI, Cairo (2003-2004 registry) is almost the same with overall GI cancer constituting 7.7% of all cancers coming in fourth rank (after breast, bladder and lymphoma). In males it is 8.4% and in females it is 7.1%. In males it is the fifth after bladder, lymphoma, leukemia and liver. In females it is third after breast and gynecological cancer.

Table 13-1 Site Distribution of Gastrointestinal Cancers

Site	No. of Patients	%
Esophagus	19,410	7.7
Stomach	39,623	15.7
Small intestine	6,879	2.7
Colorectal*	182,589	72.2
Anal canal	4,296	1.7
Total	252,797	100

*(US-SEER data, Ries et al, 2007) *Rt. colon 37.8%, Lt. colon 59.9%, Overlapping and NOS 2.3% of colorectal cancer. Rt. Colon corresponds to cecum, ascending colon, hepatic flexure, and transverse colon. Lt. colon corresponds to splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum according to the International Classification of Diseases for Oncology, 3rd edition (ICD-03).*

ESOPHAGEAL CANCER

Anatomic Landmarks

The esophagus, 25 cm long, begins at the lower border of cricoid cartilage and ends 2 cm below the diaphragmatic hiatus. At endoscopic examination, locations in the esophagus are often designated by their distance from the central incisor teeth. Accordingly, the esophagus begins at 15 cm, is crossed by the left bronchus at 25 cm and ends at 40 cm (Fig 13-1).

The esophagus is lined by stratified squamous epithelium with scattered mucous glands in the submucosa. The distal 2 cm of the esophagus may be lined by columnar epithelium (Barrett esophagus). This condition is now considered to be acquired and represents columnar metaplasia observed in 11% of patients with reflux esophagitis. The metaplastic columnar epithelium may be of gastric or intestinal type.

Epidemiology

Esophageal cancer is the eighth most common cancer worldwide (3.8% of the total, Globocan 2008), and the sixth most common cause of death from cancer (5.4% of the total, Globocan 2008). These figures encompass both adenocarcinoma and squamous cell carcinoma (SCC) types. More than 80% of the cases and of the deaths occur in developing countries. The incidence rates of esophageal cancer vary internationally more than 15-fold in men (ASR 22.3 per 100,000 in Southern Africa compared to 1.4 in Western Africa), and almost 20-fold in women (ASR 11.7 per 100,000 in Southern Africa compared to 0.6 in Micronesia/ Polynesia). Esophageal cancer is two to four times more common among men than women. However, male predominance is more pronounced with adenocarcinoma than with squamous carcinoma (males are eight times more than women, SEER data 1992-2005). The highest mortality rates are found in both sexes in Eastern and Southern Africa, and in Eastern Asia. In Egypt esophageal cancer ranks 16th and constitutes 1.8% of all cancers with ASR of 1.8/100,000 (1.7% and ASR 2.1 in males, 1.4% and ASR 1.5 in females). At NCI, Cairo, esophageal cancer constituted 1.3% of all cancers and 7.35% of all GI cancers (NCI data 2002-2003). Male to female ratio was 1.74 and median age was 60 years. In USA esophageal cancer is 7.7% of GI cancer, a figure comparable to that reported at NCI, Cairo (Table 13-1).

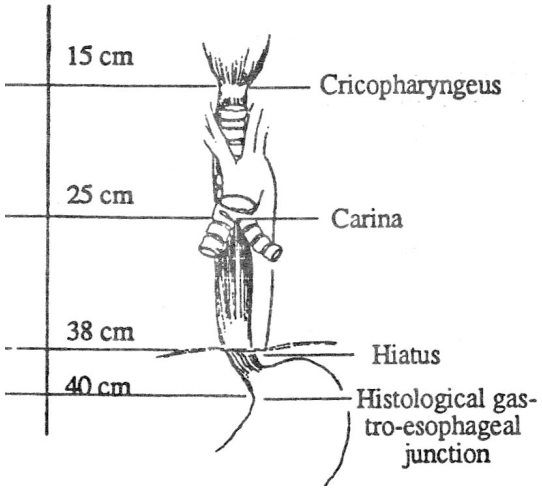

Fig 13-1 *Landmarks of esophagus by endoscopic distance.*

Etiology

Squamous cell carcinoma

1. Dietary: nitrosamines (e.g. in smoked fish and meat) , fungal toxins in pickled vegetables, burning -hot food and beverages, deficiency of Zinc, vitamin A and C.

2. Life style: smoking and alcohol, attribute to 90% of cases in the west, proportionate to duration in smoking and burden of intake in alcohol.

3. *Esophageal disorders*: caustic injury, achalasia and Plummer-Vinson syndrome.

4. *Other diseases*: celiac disease and tylosis.

Adenocarcinoma

1. Esophageal disorders: Intestinal metaplasia (Barrett esophagus, P 13-1), has been identified as the single most important precursor lesion and risk factor for adenocarcinoma of the distal esophagus, irrespective of the length of the segment with intestinal metaplasia. Intestinal metaplasia of the esophagus develops when the normal squamous esophageal epithelium is replaced by columnar epithelium during the process of healing after repetitive injury to the esophageal mucosa, typically associated with gastro-esophageal reflux disease. Intestinal metaplasia can be detected in more than 80% of patients with adenocarcinoma of the distal esophagus. Intestinal metaplasia carries a life-time risk for esophageal adenocarcinoma of about 10%.

2. Dietary: Obesity increases the risk of adenocarcinoma through increased liability to and chronicity of gastro-esophageal reflux disease.

3. Life style: smoking, attributes to about 40% of cases.

Macroscopy

The middle part of esophagus is the most common site of tumor origin (Fig 13-2). Three gross types are recognized (P 13-2) namely: polypoid (60%), ulcerating (25%) and diffuse infiltrating (15%). For adenocarcinoma, lower esophagus and gastroesophageal junction are the sites for the vast majority of cases. Exceptional cases can occur in upper and middle third from a congenital islet of heterotopic columnar mucosa (that is present in up to 10% of the population).

Histopathology

The types of carcinomas that may arise in the esophagus are presented in (Table 13-2). Classically, squamous carcinoma constitutes 75% (P 13-3) and adenocarcinoma 25% of cases. However, such ratio is geographically and ethnic dependent and shows wide variation with recent sharp increase of adenocarcinoma in the West due to increased prevalence Barrett esophagus. At the same time squamous carcinoma is decreasing or is rather stables in these countries. At present, adenocarcinoma is the predominant histology in these countries with lower esophagus and the gastro-esophageal junction being the most affected areas. In the USA adenocarcinoma is more than double squamous carcinoma in the whites whereas squamous carcinoma is nine times that of adenocarcinoma in the blacks (SEER 13 1992–2005).

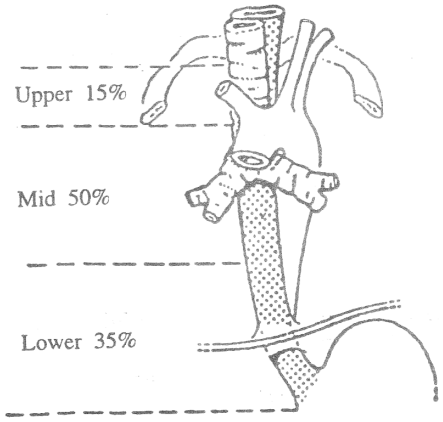

Fig 13-2 *Anatomic sites of esophageal carcinoma and their relative frequency.*

Table 13-2 Histology of Esophageal Carcinoma

Common types
Squamous carcinoma (including verrucous) and sarcomatoid)
Adenocarcinoma (on top of Barrett)
Rare types
Adenoid cystic and mucoepidermoid
Small cell undifferentiated carcinoma
Malignant lymphomas and melanomas
Metastases

(Bosman et al, 2010)

Spread

1. Local: Invasion of trachea or bronchus (fistula), aorta or mediastinum. Satellite nodules may develop away from the primary tumor.

2. *Lymph nodes*: Cancer of upper third spreads to supraclavicular, internal jugular and celiac lymph nodes. Middle third cancer spreads to peritracheal, hilar, periaortic and celiac. Lower third cancer spreads to gastric and celiac lymph nodes. In view of rich lymphatics of the esophagus, the frequency of celiac node metastases is relatively common (10% in upper third cancers, 44% in middle third and 60% in lower third).

3. Hematogenous spread to bone and liver.

Prognosis

The pathologic stage is the most important independent predictor of survival. The revised TNM system is generally recommended (Table 13-3). The overall 5-year survival of esophageal cancer is generally poor, only 5% in surgical cases and 11% in radiation series (DeVita, 1997). However, superficial tumors (stage I) have a favorable survival of about 80% of cases (Weidner, 1997). But, this stage is rarely encountered in clinical practice (5-13%). In SEER data, the 5-year relative survival is 15.6%, for localized disease it is 37.8% for regional disease it is 19.8% and for distant disease it is 3.4%. The 10-year relative survival is 11% (SEER data 2002-2008).

There is no significant difference in survival between squamous carcinoma and adenocarcinoma. But, some rare esophageal cancers may exhibit prognostic differences. Favorable tumors include the verrucous variant and unfavorable cancers include: small cell undifferentiated carcinoma and malignant melanoma.

Table 13-3 TNM Staging of Esophageal Carcinomas

Stage 0	CIS
Stage Ia	Confined to mucosa or submucosa (Tl), L. nodes -ve
Stage Ib	Confined to muscle (T2), L. nodes -ve
Stage IIa	Tumor extends to adventitia (T3), L. nodes -ve
Stage lIb	T1 or T2 with <3 + L. nodes (N1)
Stage IIIa	Invades pleura, pericardium or diaphragm T4a with -ve L. nodes T3 with <3 + L. nodes (N1) T1 or T2 with 3-6 + L. nodes (N2)
Stage IIIb	T3 with 3-6 + L. nodes (N2)
Stage IIIc	T4a with <7 + L. nodes (N1 or N2) Invades other adjacent structures (T4b), with or without node metastasis Any T with >6 + L. nodes (N3)
Stage IV	Metastatic (Ml)

(Sobin et al, 2009 / Edge et al, 2009)

GASTRIC CARCINOMA

Incidence

Gastric cancer is the fourth most common cancer in the world with a relative frequency of 7.8% of all cancers and ASR of 14/100,000. In males the ASR is 9.7/100,000 and it also comes fourth in male cancers. It is fifth in females with an ASR of 5.8/100,000. Cancer stomach is most prevalent in eastern Asia where half of cancer stomach cases occur. 70% of cancer stomach cases occur in developing countries. Cancer stomach is the second leading cause of cancer related mortality accounting for 11.3% of cancer deaths. In Egypt, cancer stomach is in the eleventh rank constituting 2.1% of all cancers with ASR of 2.3/100,000. It is commoner in males where it comes in the tenth rank with a male:female ratio of 1.55. At NCI, Cairo, cancer stomach constituted 1.8% of all cancers and 10.3% of GI cancers with a median age of 53 years (NCI data 2002-2003). This is compared to a median age of 70 years in the USA.

Cancer stomach is declining worldwide. This decline is most noted in developed countries in the West and eastern Asia (Japan and South Korea). Decline is attributed to change in nutrition habits regarding decreased use of salt preservation of meat and fish and availability of fresh fruits and vegetables throughout year in many countries. Early detection of precancerous lesions in these countries also plays a role in such decline.

Etiology

The etiologic factors involved in gastric cancer may be grouped into dietary and host factors.

Dietary factors include: the consumption of smoked or salted meat or fish (rich in nitrosamine), drinking well water high in nitrate and dietary deficiency in fruits and vegetables (vitamin A and C).

Host factors include: smoking, infection by Helicobacter pylori (P 13-5), chronic atrophic gastritis, partial gastrectomy (bile reflux), pernicious anemia, blood group A individuals, and precancerous lesions as adenomas and Ménétrier disease (atypical ductal hyperplasia, P 13-4).

Pathogenesis

Chronic gastritis (for whatever etiology) is the forerunner in the pathogenesis of gastric cancer. Chronic gastritis produces multifocal atrophy. Both gastritis and atrophy lead to gastric hypoacidity thus favoring anaerobic bacterial overgrowth which reduces nitrates into nitrites. The nitrites react with dietary amines converting them into carcinogenic nitrosamines. These nitrosamines in turn cause chronic atrophic gastritis, intestinal metaplasia and dysplasia (P 13-6). Finally, a carcinoma of the intestinal type develops. The evolving tumor is multifocal in 10% of cases due to marked field carcinogenesis.

H. pylori (P 13-5) is the most frequent cause of chronic gastritis. It decreases acid-pepsin secretion and interferes with anti-oxidant functions by decreasing intragastric ascorbic acid (AA) concentrations. The organisms predominantly occur in the mucus layer overlying normal gastric epithelium. They are absent in areas overlying intestinal metaplasia where neoplasia originates. Thus, H. pylori carcinogenic influences are exerted from a distance, via soluble bacterial products or the inflammatory response generated by the infection.

H. pylori genome. H. pylori is genetically heterogeneous, and all strains may not play the same role in the development of malignancy. Strains containing a group of genes named cag pathogenicity island (cag positive strains) induce a greater degree of inflammation than strains lacking these genes.

Additionally, some H. pylori strains can also produce a vacuolating cytotoxin named VacA (VacA positive strains). This cytotoxin is responsible for epithelial cell damage. Infection with a cag positive and/or VacA positive H. pylori strains is associated with the development of gastric carcinoma. Inoculation of a cag and VacA positive strain was able to induce intestinal metaplasia and gastric carcinoma in Mongolian gerbils, thus establishing their etiologic role in gastric carcinogenesis.

In spite of IARC definition that H. pylori infection is class I carcinogen, more than 80% among population infected with this organism remain asymptomatic. About 15-20% will suffer from one or more of chronic atrophic gastritis, intestinal metaplasia, gastric or duodenal ulcers. Less than 1% will progress to gastric carcinoma or MALT lymphoma. The explanation why a given subject will pursue one of these paths is not yet known but it is logical to think that host genetic polymorphisms, environmental factors, H. pylori strains (cag and VacA positive versus negative strains), and host immune response might affect the outcome. It is the prevalence of H. pylori infection that makes this less than one percent cancer pathway have such an impact upon the incidence of gastric cancer. More than 50% of the world's population harbor H. pylori in their upper gastrointestinal tract. Infection is more prevalent in developing countries, and incidence is decreasing in Western countries. In Western countries, about 60% of H pylori isolates are cag-positive but the majority in Eastern Asia are cag-negative.

Macroscopy

The antrum of stomach is the most frequent site of carcinoma (Fig 13-3) and the tumors are more common in lesser curvature than greater curvature. The tumors are most commonly nodular or ulcerative (Fig 13-4, P 13-7). Linitis plastica (leather bottle stomach) is characterized by diffuse and firm thickening of the wall of stomach, and it may be localized to the antral region or involve the entire stomach (P 13-8). Superficial gastric carcinoma, commonly encountered in Japan, is defined as a carcinoma confined to mucosa or submucosa regardless of the status of regional lymph nodes.

Histopathology

World-wide, adenocarcinoma constitutes about 90% of all gastric cancer. Other less common malignant tumors include: non-Hodgkin lymphoma, GIST and carcinoid tumor. According to NCI, Cairo, pathology data (2003-2004), adenocarcinoma constituted 71.2%, NHL 19.2% and GIST 7.7% of gastric cancer. There are several systems for classification of gastric adenocarcinoma, the two most commonly used are that of Lauren (1965) and the WHO (2010) both are shown in Table 13-4. Lauren (1965) classified gastric carcinomas into two major classes; intestinal and diffuse types with distinctly different clinicopathologic features (Table 13-5). The intestinal type is etiologically related to H. pylori infection and is characterized histologically by gland formation and biologically by a more favorable prognosis. Conversely, the diffuse type is more aggressive and

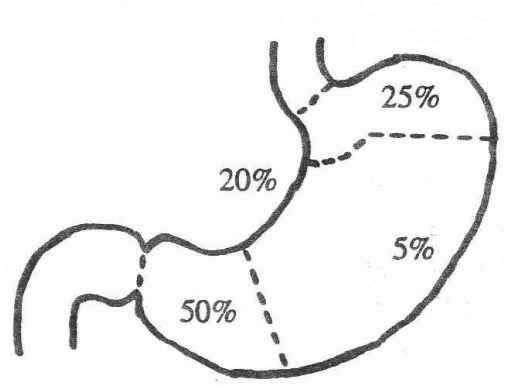

Fig 13-3 *Sites of gastric carcinoma and their relative frequency*

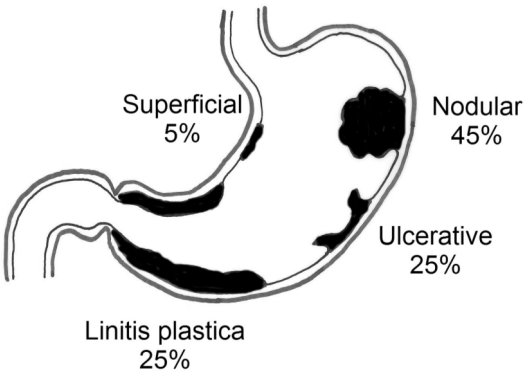

Fig 13-4 *Macroscopic types of gastric carcinoma and their relative frequency. In Japan due to endoscopic screening programs, superficial (early) carcinomas are prevalent. Three gross types are recognized: type I, protruding (nodule), type II, flat tumor and type III, excavated (ulcer).*

characterized by diffusely infiltrating scattered anaplastic cells (P 13-9, P 13-10). Tumors that contain approximately equal quantities of intestinal and diffuse components are called mixed carcinomas. Carcinomas that do not fit neatly into either category are placed in the indeterminate category (15%). At NCI (2003-2004 data) intestinal type was 67% and diffuse type was 33%.

Table 13-4 Gastric adenocarcinoma classification systems (WHO matched with corresponding Lauren classes)

WHO (Bosman, 2010)	Lauren (1965)
Papillary adenocarcinoma	Intestinal type
Tubular adenocarcinoma	
Mucinous adenocarcinoma	
Signet-ring cell carcinoma	Diffuse type
Poorly cohesive carcinoma (non-signet)	
Mixed carcinoma	Mixed Type
Adenosquamous carcinoma	Indeterminate type
Squamous cell carcinoma	
Hepatoid adenocarcinoma	
Carcinoma with lymphoid stroma	
Choriocarcinoma	
Carcinosarcoma	
Parietal cell carcinoma	
Malignant rhabdoid tumor	
Mucoepidermoid carcinoma	
Paneth cell carcinoma	
Undifferentiated carcinoma	
MANEC *	
Endodermal sinus tumor	
Embryonal carcinoma	
Pure gastric yolk sac tumor	
Oncocytic adenocarcinoma	

* Mixed adenoneuroendocrine carcinoma

Table 13-5 Lauren Classification of Gastric Adenocarcinorna

	Intestinal	Diffuse Type
Clinical		
Frequency	55%	33%
Median age	55y	48 y
Sex (M:F)	2:1	1:1
Incidence	Decreasing	Stationary
Pathologic		
Gross	Polypoid	Ulcer/L. plastica
Histology	Glands	Signet-ring cell
Growth	Expansile	Infiltrative
Int. metaplasia	Present	Absent
Prognosis	Favorable	Unfavorable

(Lauren, 1965)

Spread

Gastric carcinoma spreads by four main routes:

1. Local infiltration to duodenum (50% of cases), esophagus, colon or pancreas.

2. Lymph node metastases (50% of cases) (a) perigastric or first station (Fig 13-5) including the subpyloric, gastroepiploic, suprapyloric, nodes along the lesser curvature, as well as, Rt. and Lt. pericardial nodes, (b) extraperigastric lymph nodes include splenic artery lymph nodes, Lt. gastric nodes, celiac nodes and hepatic artery nodes, and (c) distant lymph node including Lt. supraclavicular lymph nodes (Virchow), Lt. axillary and paraumbilical nodes.

3. Transperitoneal metastases to omentum or ovaries (Krukenberg tumor).

4. Hematogenous spread to the liver.

Staging

Accurate staging is only possible after pathologic study of the resected specimen. In the TNM system (Table 13-6) nine stages are recognized, whereas, in SEER system only 3 stages are adopted namely (a) resectable with localized disease, (b) resectable with regional disease (SEER stage 2), and (c) unresectable with distant disease.

Prognosis

The overall 5 and 10-year survival of gastric carcinoma is generally poor, and is about 23.7% and 19% respectively (SEER 1988-2008). The most important prognostic factors are the stage of the disease, site of tumor, histologic type and

grade. Superficial gastric cancer carries a favorable prognosis of about 70-90%. The 5-year survival according to SEER stages (2002-2008 data) are: 62.3% for localized tumor, 27.7% for regional, 3.7% for distant, and 26.9% for all stages. Carcinomas of the distal part of stomach are more favorable than those of proximal stomach. Finally, the intestinal type histology is more favorable than the diffuse type. Table 13-7 presents SEER data of 30382 cases (1988-2001) to emphasize the impact of these prognostic factors on the five and ten-year survival as well their relative frequency.

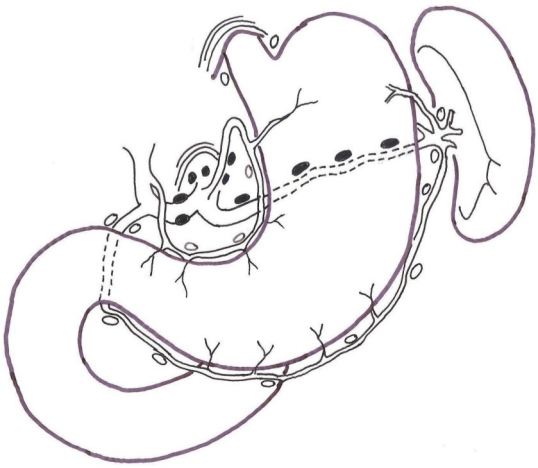

Fig 13-5 *Lymphatic drainage of stomach. Perigastric lymph nodes (white) and extraperigastric (black).*

Table 13-6 TNM Staging of Gastric Carcinoma

Stage 0	Carcinoma in situ
Stage Ia	Tumor confined to mucosa, submucosa or muscularis propria (T1), L. nodes -ve
Stage Ib	Confined to muscle (T2), L. nodes -ve T1 with <3 + L. nodes (N1)
Stage IIa	Tumor extends to subserosa (T3), L. nodes -ve T2 with <3 + L. nodes (N1) T1 with 3-6 + L. nodes (N2)
Stage IIb	Tumor invades serosa (T4a) with T3 with <3 + L. nodes (N1) T2 with 3-6 + L. nodes (N2) T1 with >6 + L. nodes (N3)
Stage IIIa	T4a with <3 + L. nodes (N1) T3 with 3-6 + L. nodes (N2) T2 with >6 + L. nodes (N3)
Stage IIIb	Tumor invades adjacent structures (T4b) T4a with 3-6 + L. nodes (N2) T3 with >6 + L. nodes (N3)
Stage IIIc	T4a with >6 + L. nodes (N3) T4b with >3 + L. nodes (N2 or N3)
Stage IV	Distant metastases

(Sobin et al, 2009)

Table 13-7 Five and Ten Year Survival for Gastric Carcinomas (30382 cases)*

Category	% of all	5 year Survival	10 year Survival
All Cases	100.0	21.0	16.9
Anatomic Localization			
Cardia	25.5	15.2	11.2
Fundus	4.1	16.5	12.0
Body	7.2	24.8	21.8
Antrum	20.7	29.2	24.8
Pylorus	3.2	30.3	21.5
Greater curvature	4.3	28.1	22.8
Lesser curvature	10%	34.9	29.9
Extent of Disease			
Localized	20.0	58.6	51.8
Regional	33.8	21.4	15.9
Distant	34.2	2.3	1.6
Tumor size			
Tumor ≤2 cm	6.8	56.8	48.0
Tumors 2.1-5 cm	23.0	29.5	23.9
Tumors 5.1-10 cm	19.2	21.9	15.8
Tumors >10 cm	8.5	9.5	7.4
Histology			
Well differentiated	4.0	41.9	36.3
Poorly differentiated	54.9	18.4	15.0

(Ries et al, 2007)* Excluding gastric carcinoid (661 cases with 71% and 66%, 5 and 10 year survival respectively)

CANCER OF SMALL INTESTINE

Tumors are rare in small intestine in comparison with that of stomach and colon. Although the small intestine represents 90% of surface area of gastrointestinal tract, tumors of small intestine contribute only 2% of gastrointestinal tumors.

A classification of the various hamartomatous and neoplastic lesions of small intestine is presented in (Table 13-8) with indication of their clinical behavior. Carcinomas are more common in the proximal part of small intestine, whereas, carcinoid tumors and lymphomas are more common in the distal part. About 50% of the carcinomas arise in the duodenum especially at the periampullary region. Precancerous conditions include Lynch syndrome, Peutz-Jeghar syndrome and Crohn disease. Carcinoid tumors and duodenal gastrinoma are discussed in chapter 19, whereas, primary lymphoma and GIST are outlined at the

Table 13-8 Tumors of Small Intestine

1. Hamartomas

Peutz-Jegher and
Gardner's syndromes

2. Benign

Tubular adenoma

3. Intermediate

Villous adenoma,
Gastrinoma and carcinoid (35%)

4. Malignant

Adenocarcinoma (30%)
Lymphoma (20%)
GIST (15%)

(Bosman et al, 2010)

end of the present chapter, hence, they will not be repeated here.

COLORECTAL CARCINOMA (CRC)

Incidence

Colorectal carcinoma is the third most common cancer in the world in both sexes constituting about 10% of all cancers. However, its incidence in developed countries is almost double that in less developed countries (13 and 7% respectively). In USA, it constitutes 10.6% of male cancers and 10.8 % of female cancers, affecting one person in twenty during lifetime, with an age-adjusted incidence rate of 54 per 100,000 in males and 40 per 100,000 among females (SEER 2005-2009). In Egypt, colorectal cancer constitutes 4.2% and comes at 7th rank (7th in men and 4th in women). In USA, colorectal cancer is the second most common cause of cancer mortality after lung cancer. The median age is 69 years in the USA and 50 years at NCI, Cairo. Younger cases usually complicate polyposis and ulcerative colitis. Male predominance is 1.35:1.

Etiology

The possible etiologic factors may be related to the diet or host.

1. *Dietary and life style factors*: Western diet with high animal fat and protein but low vegetable. Smoking and alcohol consumption are also risk factors. Inverse associations include vegetable consumption, prolonged use of non-steroidal anti-inflammatory drugs, estrogen replacement therapy, and physical activity.

2. *Host factors*: (a) Personal history of adenoma, colonic carcinoma, ulcerative colitis, female genital cancer, ureterosigmoidostomy, and pelvic irradiation, (b) Family history of familial adenomatous polyposis, Gardner's syndrome, hereditary non-polyposis colonic cancer (HNPCC or Lynch syndrome) or sporadic colorectal cancer.

A high dietary animal fat is related to colonic carcinogenesis through the action of colonic microorganisms on bile acids and fatty acids leading to high 3-ketosteroids. A high fat diet also increases serum levels of bio-available, nonprotein-bound, sex hormones. Meat-rich diet is associated with increased production during cooking of heterocyclic amines. Vegetables produce their inverse association with colorectal cancer through their anticarcinogens such as folate, antioxidants and inducers of detoxifying enzymes. Fiber fermentation produces protective volatile fatty acids. In addition, dietary fibers reduce exposure of colon to carcinogens by diluting and trapping them as well as reducing contact time with colorectal epithelium due to faster transit.

About 15 percent of all colorectal cancer patients have a family history of colorectal cancer in a first degree relative. Among all patients with colorectal cancer, the risk of a second primary colorectal cancer, either synchronous or metachronous, is about 5%. About one percent of colorectal cancer patients have a history of chronic ulcerative colitis. The risk of developing cancer in these patients is directly related to extent and the duration of active disease and is about 9% at 25 years. Involvement of greater than one half of the colon is associated with a risk to develop carcinoma of approximately 15%, whereas left sided disease may bear a malignancy risk of 5%. Ulcerative proctitis is not associated with an increased carcinoma risk.

Pathogenesis

There is strong evidence that virtually all CRCs originate from a precursor benign polyp, which makes this cancer potentially preventable by appropriate screening colonoscopy programs in patients at increased risk. The present section outlines the pathologic features of different types of intestinal polyps, as well as, their malignant potential. The section will be concluded by discussing the current two most important and more understood pathways for the genetic pathogenesis of CRC, namely the *conventional adenomatous pathway* (Fearon and Vogelstein, 1992) and the *serrated pathway* .

INTESTINAL POLYPS

Historical background

Before 1996, the majority of colorectal polyps were divided into 2 groups, the hyperplastic polyp (HPP), which, in many Western series, constituted the most common polyp, and adenomas, which were divided into several subgroups based predominantly on the degree of villous architecture. A number of less common polyps (juvenile retention polyps, various forms of hamartomatous

polyps, inflammatory polyps, and others) were considered more or less curiosities in general practice. A consensus developed that adenomas, particularly those with a villous component, were precursors to colorectal carcinoma and that HPPs were not.

However, there were clues suggesting that this dichotomy might not be so clear. These clues include the following: (1) presence of "hyperplastic polyp" at the margin of a significant percentage of adenomas, (2) HPPs were recognized as occurring in much higher frequency in populations at risk for the development of colorectal carcinoma, (3) some HPPs were recognized as becoming large, particularly in the ascending colon, and occasional large HPPs with adenocarcinoma were seen but rarely reported, (4) Urbanski et al in 1984 reported, in what may turn out to be a prescient article, a case of adenocarcinoma arising in a "mixed hyperplastic-adenomatous" polyp and suggested that this phenomenon was an under diagnosed condition. Based on such brilliant observation, Longacre and Fenoglio-Preiser (1990) analyzed a group of polyps with mixed features of HPP and adenoma and concluded that most of these cases, rather than representing a mixed tumor, were actually adenomas with a serrated configuration, leading to the term serrated adenoma.

Definitions and terms (Details in Chapter 6)

Aberrant Crypt Foci (ACF): are clusters of abnormal crypts seen on staining of colorectal mucosa (in resection specimens or during colonoscopy) with methylene blue or by chromoendoscopy examination (magnifying endoscope). Histologically they commonly show features of hyperplastic polyps (HPP) and less frequently those of microadenomas. However ACF of the microadenoma type are common with familial adenomatous polyposis (FAP).

Wnt signaling pathway: is a network of proteins that passes signals from receptors on the surface of the cell through the cytoplasm and ultimately to the cell's nucleus where the signaling cascade leads to the expression of target genes. The WNT signaling pathway is evolutionarily conserved.

BRAF gene: A proto-oncogene that encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. This protein is involved in the transduction of mitogenic signals from the cell membrane to the nucleus. It plays a role in cell division, differentiation, and secretion. Mutations in this gene have also been associated with various cancers, including non-Hodgkin lymphoma, colorectal cancer, malignant melanoma, thyroid carcinoma, non-small cell lung carcinoma, and adenocarcinoma of lung.

KRAS gene: It encodes a protein that is a member of the small GTPase superfamily. A single amino acid substitution is responsible for an activating mutation. The transforming protein that results is implicated in various malignancies, including lung adenocarcinoma, mucinous adenoma, ductal carcinoma of the pancreas and colorectal carcinoma. KRAS and BRAF mutations are mutually exclusive.

The MAPK/ERK pathway: is a chain of proteins in the cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell. The signal starts when a signaling molecule binds to the receptor on the cell surface and ends when the DNA in the nucleus expresses a protein and produces some change in the cell, such as cell division. The pathway includes many proteins, including MAPK (Mitogen-activated protein kinases, originally called ERK, Extracellular signal-regulated kinases), which communicate by adding phosphate groups to a neighboring protein, which acts as an "on" or "off" switch. Also known as the Ras-Raf-MEK-ERK pathway. When one of the proteins in the pathway is mutated, it can be stuck in the "on" or "off" position, which is a necessary step in the development of many cancers. Drugs that reverse the "on" or "off" switch are being investigated as cancer treatments.

APC gene: a key tumor suppressor gene in both sporadic and syndromic (except Lynch syndrome) CRC. APC gene product is responsible for beta-catenin degradation. Beta-catenin is a subunit of the cadherin protein complex and acts as an intracellular signal transducer in the Wnt signaling. APC mutation will lead to accumulation of beta-catenin in the cytosol with subsequent translocation into the nucleus thus inducing various effects as activation of myc and Cyclin D1 with increased cell proliferation.

CpG sites: are regions of DNA where a cytosine nucleotide occurs next to a guanine nucleotide in the linear sequence of bases along its length. Binding is through a phosphate "p". The "CpG" notation is used to distinguish this linear sequence

from the CG base-pairing of cytosine and guanine. In mammals, methylating the cytosine within a gene can turn the gene off. In mammals, 70% to 80% of CpG cytosines are methylated. Many genes show areas rich in cytosine and guanine dinucleotide within their promoter regions. These areas are termed CpG islands.

CpG island methylator phenotype (CIMP): Cancers can be classified according to their degree of methylation, and those cancers with high degrees of methylation (the CpG island methylator phenotype, or CIMP) represent a clinically and etiologically distinct group that is characterized by 'epigenetic instability'. This epigenetic instability includes loss of function of tumor-suppressor genes without mutations. Furthermore, CIMP-associated cancers seem to have a distinct epidemiology, a distinct histology, distinct precursor lesions and distinct molecular features.

Microsatellites (MS): Microsatellites are nucleotide repeat sequences that are prone to produce insertion/deletion loops during DNA replication. Mismatch repair (chapter 6) usually corrects these loops to keep these microsatellites at germline length. Deficient repair as a result in mutations in the mismatch repair gens (MMR) will lead to persistence of these loops and production of multiple alleles of varying length with repetition of DNA replication without repair. This is termed microsatellite instability (MSI or MSI-H).

WHO Classification (Table 13-9)

1. Hamartomatous Polyps

a. Inherited hamartomatous polyposis does not predispose to colonic cancer but increases cancer risk elsewhere. Examples are a) Peutz-Jeghers syndrome (P 13-11) in which cancer develops in duodenum, stomach and pancreas, and b) Cowden's syndrome which increases the risk of breast and thyroid cancers. Conversely, in non-inherited hamartomatous polyposis (Cronkite-Canada syndrome), there is no increased cancer risk in colon or elsewhere.

b. Solitary Juvenile Polyps (P 13-12): Those are acquired solitary (75%) lesions which are almost always found in children younger than the age of 10 years. They are most commonly found (75%) in the rectum, and appear as cherry-red pedunculated lesions (1-3 cm in size) which may prolapse from the anus. They result from inflammatory obstruction of glands which undergo cystic change, hence, the name retention polyp. Histologically, the glands are dilated and filled with mucin with marked inflammation in the stroma.

Table 13-9 Classification of Intestinal Polyps

A. Mucosal Polyps

1. Hamartomatous
- Peutz–Jeghers Type
- Juvenile Type
  - Sporadic
  - Juvenile polyposis JP

2. Inflammatory (pseudopolyps)

3. Inflammatory Fibrous Polyp

4. Lymphoid polyp

5. Serrated Polyps (sawtooth or stellate architecture)
- Hperplastic polyps HPP
  - Microvesicular MVHP
  - Goblet cell rich GCHP
  - Mucin-poor MPHP
- Sessile serrated adenoma/polyp SSA/P
- Sessile serrated adenoma/polyp with cytological dysplasia (old name = mixed hyperplastic and adenomatous polyp)
- Traditional serrated adenoma/polyp TSA
- Serrated polyposis

6. Adenomatous polyps (not serrated)
- Tubular
- Tubulovillous
- Villous

B. Submucosal Polyps
- Neuroendocrine neoplasms
- Stromal tumors (GIST, smooth muscle tumors, lipoma, ganglioneuroma)

(Bosman et al, 2010)

c. Juvenile polyposis (JP) is defined as: more than five juvenile polyps of the colorectum, juvenile polyps throughout the GI tract, or any number of juvenile polyps with a family history of JP. In one third of patients with JP, this is an autosomal dominant trait with high penetrance. About 10% of JP patients will develop GI cancer (mostly colonic).

2. Inflammatory Polyps: These are pseudopolyps most commonly associated with idiopathic ulcerative colitis (P 13-13), but also occur in Crohn disease, amebic colitis and chronic schistosomiasis. When located in the rectum, the lesion is termed solitary rectal ulcer syndrome. The pseudopolyps represent islands of mucosa with elongated distorted regenerative glands surrounded by prolifer-

ated smooth muscle fibers from muscularis mucosa and ulceration. The polyps characteristically have the same diameter from base to head.

3. Inflammatory Fibrous Polyp: Mostly seen in ileum (following stomach), rare in the colon. It may present with episodic pain, intussusception, and/or bleeding. Grossly it is a pedunculated polyp with surface erosion. Microscopically it shows hypocellular fibrous and myxoid stroma with CD34+ stromal cells as well as numerous small vessels with hyalinized wall. There may be increased inflammatory cells, especially eosinophils.

4. Lymphoid Polyp (P 13-14): Is composed of hyperplastic lymphoid tissue in mucosa with germinal centers. It may be a precursor of MALT lymphoma but not carcinoma.

5. Serrated Polyps: This is a heterogeneous group of lesions characterized morphologically by a serrated (sawtooth or stellate) architecture of the epithelial compartment, and includes the traditional hyperplastic polyp (HPP), sessile serrated adenoma/polyp (SSA) and traditional serrated adenoma (TSA). The differentiation between the traditional HPP, SSA and TSA is of paramount importance from management and prognostic points of view. Although serrated adenomas (both sessile and traditional) are now recognized as a discrete entity, recommendations for their management followed the general guidelines for the traditional adenomatous polyps.

a. Hyperplastic Polyps (HPP): These are the most common type of serrated polyps (>75%). They are found mainly in distal colon and rectum (86%). They are identified in about 10% during colonoscopic examination of asymptomatic patients, and appear as multiple, sessile lesions, 1-5 mm in size and rarely >1 cm. In distal colon they may be multiple (10-20). Their recognition and diagnosis is enhanced by the newer high-definition endoscopes and chromoendoscopy. They are characterized by elongated and straight crypts resulting in variable degrees of serration in the luminal aspect of polyps. Proliferative zone (undifferentiated less mucigenic cells) is located in the lower third of crypts (P 13-15). HPPs are of three types; microvesicular (MVHP), goblet-cell rich (GCHP) and mucin-poor (MPHP). MVHP is most common with wide distribution in colon and prominent serration. They show BRAF mutation and may harbor CIMP. GCHP is second common, limited to left colon with subtle serration. They tend to carry KRAS mutation. MPHP is rare and due to mucin depletion they show reactive atypia.

b. Sessile serrated adenoma/polyp (SSA/P): They constitute 15-25% of all serrated polyps and are found in 9% of those undergoing screening endoscopy. They are the precursor to sporadic carcinomas with microsatellite instability (MSI) and probably also the precursor for CpG island-methylated microsatellite-stable carcinomas. SSAs are recognized and differentiated from HPP by their "architectural dysplasia" rather than "cytologic dysplasia" (P 13-16). These architectural features seem to emanate from the abnormal proliferation and/or decreased apoptosis that is the basis for the abnormal growth in these polyps. These architectural features include: 1) branching of crypts, 2) dilatation of the base of the crypts, 3) a peculiar growth pattern in which the crypts seem to grow parallel to the muscularis mucosae, often creating an inverted T- or L-shaped crypt, 4) displacement of the proliferative zone from base of crypt to one side of the crypt and is often asymmetrical. This growth pattern is accompanied by the presence of mature cells with a goblet cell or gastric foveolar cell phenotype at the base of the crypt, replacing the proliferative zone of normal mucosa and HPPs. Serration often is seen at the base of the crypts. Pseudostratification and eosinophilic change of the surface epithelium is less commonly seen. Subtle nuclear alterations, including small prominent nucleoli, open chromatin, and irregular nuclear contours, also might be present, along with mitoses in the upper third of the crypts or on the surface itself.

c. Sessile serrated adenoma with cytological dysplasia (formerly mixed hyperplastic adenomatous polyp): with the acquisition of more genetic alterations that qualify SSA to progress to carcinoma, cytological dysplasia is acquired thus imparting an adenomatous phenotype on these polyps. Such phenotypic changes are usually coupled with methylation of MLH1 gene and the development of MSI. The new terminology of this lesion is meant to emphasize that adenomatous change seen in these lesions is not biologically the same as conventional adenomas. APC gene mutation is never seen in SSA with cytological dysplasia. The behavior of these lesions with methylation of MLH1 leading to MSI may be more aggressive than that of conventional adenomas.

d. Traditional serrated adenoma (TSA): They constitute <1% of all polyps. This term refers to a protuberant growth with overall complex (villiform or filiform) configuration. This pattern is attributed to loss of crypt anchoring to muscularis

mucosa with formation of ectopic crypts. The cells lining villi are columnar with eosinophilic cytoplasm and oval nuclei. These lining dysplastic cells are different from these seen in conventional adenomas and SSA with cytological dysplasia in two important respects: lack of pseudostratification and absence of mitosis (as confirmed by Ki-67). Additionally ectopic crypts show maturation near surface and proliferation. TSA never show methylation of MHL1 and 25% of TSAs show KRAS mutation. TSA is related to low MSI carcinomas.

e) Serrated polyposis: Formerly known as hyperplastic polyposis. Polyps are SSAs and MVHPs, so they may show BRAF or KRAS mutations. For diagnosis at least five serrated polyps proximal to sigmoid with at least two > 10 mm, or any number of serrated polyps proximal to sigmoid in an individual with first degree relative with serrated polyposis, or > 20 serrated polyps of any size distributed throughout colon. Two types exist, type 1 with more larger and proximal SSA/P and substantial risk for cancer, and type 2 with numerous small (5 mm or less) conventional HPP throughout colon with moderate or no risk for subsequent cancer. Type 1 is suggested to have KRAS mutations while type 2 have BRAF mutations. The development of cancer is preceded by the development of dysplasia. Few cases of serrated polyposis are familial.

6. Adenomatous (neoplastic) polyps

Adenomatous polyp or adenoma represents a monoclonal proliferation of crypt stem cell progeny, as a result of mutation of adenomatous polyposis coli (APC) gene on the long arm of chromosome 5. Grossly, adenomas may be pedunculated, sessile or flat (Fig 13-6). Architecturally, adenomas may be tubular (P 13-16), tubulovillous or villous (P 13-17, Fig 13-7). Tubular adenomas have complex branching glands, villous adenomas have glands arranged in long fingerlike projections, and tubulovillous type shows both patterns (25-75% villous component).

Microscopically, adenomatous polyps are differentiated from serrated polyps by the presence of cytological dysplasia (also known as adenomatous dysplasia) as compared to architectural dysplasia in the latter (P 13-15 and P 13-17). In adenomas, mitotic activity is evident both in crypts, as well as, surface epithelium, and the nuclei appear hyperchromatic and cigar-shaped. There is marked depletion of goblet cells and carcinoembryonic antigen (CEA) may be expressed. Dysplasia can be low-grade or high-grade, depending on the degree of architectural complexity, extent of nuclear stratification and severity of abnormal nuclear morphology. High-grade dysplasia is found in 6.6% of all adenomas removed at initial colonoscopy. The frequency of malignant change is related to the type, size and number of the polyps, as well as, the presence of dysplasia (Table 13-10). Carcinomas developing in a polyp are classified into two types (Fig 13-8, P 13-18 and P 13-19), namely: (*a) Type I:* The carcinoma is limited to the mucosa (either CIS or microinvasion of lamina propria). Since the mucosa of colon lacks lymphatics, there is no risk of metastases and hence polypectomy may be an adequate treatment. (*b) Type II:* The carcinoma has invaded the muscularis mucosa and reached the submucosa which is rich in lymphatics, hence, colectomy and lymphadenectomy should be performed.

Adenomatous polyps fall into one of the following seven groups:

1. Sporadic Polyps: In the West, it affects about 35% of the individuals by the age of 70 years. It affects right and left colon almost equally. The frequency of malignant change is about 5% in tubular adenomas. Acquired sporadic polyps may develop at the site of ureterosigmoidostomy and is induced by nitrosamine action. Villous adenoma is

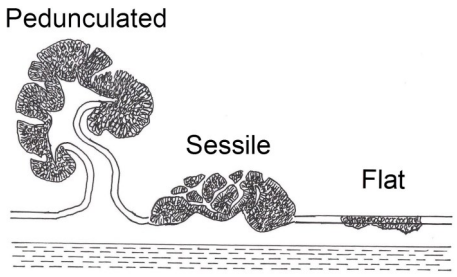

Fig 13-6 *Macroscopy of colonic adenomas*

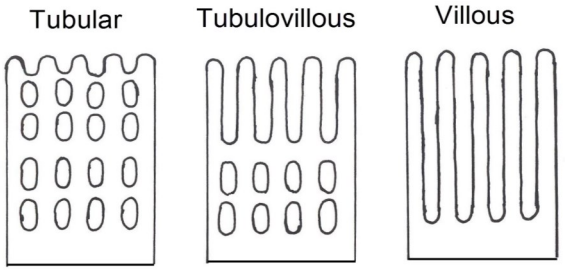

Fig 13-7 *Histopathological patterns of colonic adenomas*

Table 13-10 Adenomatous Colonic Polyps

Type	Size	% Malignant
Tubular	<1 cm	5
Tubulovillous	1-2 cm	23
Villous	>2cm	41

(Bosman et al, 2010)

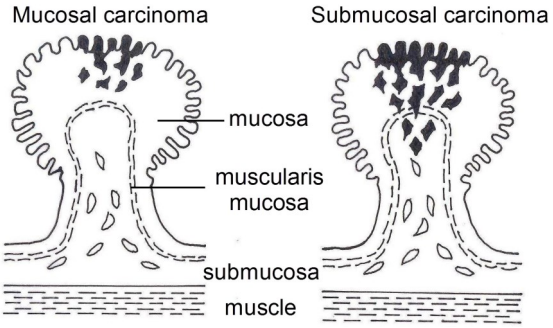

Fig 13-8 *Types of carcinomas in a polyp. Type I is confined to mucosa where type II invades submucosa*

usually sessile, most common in rectum and sigmoid, usually associated with electrolyte imbalance with malignancy incidence of 41%.

2. Familial Adenomatous Polyposis (FAP): About 1% of colorectal cancer patients have FAP. This is a rare condition that occurs in 1:20,000 births and inherited as an autosomal dominant trait (germline mutation of APC gene on long arm of chromosome, 5q21-22). By definition, the colon contains more than 100 polyps (P 13-20). The average age at onset of polyposis is 25 years, onset of symptom is 33 years and diagnosis of colon cancer is 42 years. If left untreated, almost 100% of patients will develop colonic cancer by the age of 40 years. Familial adenomatous polyposis also has an impact on carcinogenesis at other sites including the duodenum, stomach and thyroid.

3. Attenuated FAP: In this variant the number of colorectal adenomas is approximately 30 but the number of polyps is extremely variable. Extraintestinal growths are far less common than classical AFP.

4. Gardner Syndrome: This is a variant of FAP that includes abdominal desmoid tumors (10%), osteomas of the jaws and epidermal cysts of skin, in addition to the expected gastrointestinal polyps.

5. Turcot Syndrome: Also known as glioma-polyposis, is another variant of AFP and is characterized by the typical intestinal polyposis and malignant brain tumors (typically medulloblastoma).

6. Lynch Syndrome (previously termed Hereditary Non-Polyposis Colorectal Cancer, HNPCC): It is inherited as an autosomal dominant trait caused by a defect in DNA mismatch repair (MMR) gene. The syndrome is characterized by the development of colorectal carcinoma (10-53%), endometrial carcinoma (15-44%) and certain other cancers (< 15%). Currently to label an individual of having Lynch Syndrome he should carry a germline mutation in one of the DNA MMR genes, inactivation of MSH2 or methylation of MLH1. Half of the families formerly labeled as HNPCC do not show microsatellite instability (MSI) in tumors nor a germline defect in a MMR gene. They are referred to as having a non-Lynch syndrome colorectal cancer predisposition or simply having "familial colorectal cancer type X". Florid polyposis is not a feature but multiple adenomas may be observed. They tend to occur at an early age, have villous component and are more dysplastic than adenomas detected in general population. Colonic cancers developing on top of Lynch syndrome are characterized by developing at a young age, are often mucinous, common in females and are located on the right side of the colon (60%). It is noteworthy to emphasize that the pathology of Lynch tumors is very similar to that of sporadic colorectal carcinoma with high frequency of MSI (MSI-H).

7. MUTYH-associated polyposis (MAP): This is a recently recognized (2002) autosomal recessive disorder affecting the MUTYH gene which is involved in base-excision repair thus causing failure to repair oxidative DNA damage. Such deficient function of the MUTYH gene will preferably target the APC gene causing somatic mutations in this gene. MAP is characterized by a variable number of colorectal polyps with different histological phenotypes (low grade adenomatous, serrated and hyperplastic polyps are common) and tendency to progress to malignancy. Small intestinal (duodenal) and gastric polyposis are part of MAP. This syndrome is suspected when multiple (usually > 10), late onset, synchronous colorectal adenomas are detected in absence of germline mutation in the APC gene. Both attenuated AFP and Lynch syndrome are important differential diagnoses. MAP constitutes less than 1% of colorectal cancer and 3 -42% of colorectal adenomatous polyposis nega-

tive for APC mutation.

The Risk of Malignancy

In syndromic cancer, penetrance is defined as the rate of expression of phenotype in patients with a given genotype. The frequency of penetrance varies among colonic polyps and is dependant also on the duration of follow up. Malignancy in the polyp may be evident at initial presentation or develop subsequently. In familial adenomatous polyposis penetrance is 100% by the age of 70 years.

The malignant potential of epithelial colonic adenomatous polyps is determined by several factors: histologic type, size, number and extent of dysplasia (low grade versus high grade).

For practical purposes, adenomatous polyps may be classified according to their potential risk of malignancy into three main groups, namely: no-risk, low risk and high-risk. a) No risk adenomas include solitary juvenile inflammatory polyps, usual single hyperplastic polyps and hamartomatous polyps of Peutz-Jeghers syndrome. b) Low risk adenomas (risk <5%) include solitary tubular adenoma < 1 cm. c) High-risk polyps (risk > 5%) include juvenile polyposis (10%), dysplastic serrated polyp (15%), tubulovillous adenomas (23%), villous adenomas (41%) and familial adenomatous polyposis (100%).

Despite the established cancer risk of serrated polyps, yet quantification of this risk is not established yet as the serrated pathway is relatively recent. Different studies showed that a patient with identified sessile serrated polyp is about four times more likely to harbor other serrated polyps compared to unselected patients. Moreover, the risk of associated malignancy is higher in those patients (the risk of synchronous neoplasia is about 3 times in those patients compared to those without adenomas). Sessile serrated polyps tend to be larger (> 1 cm) and more common than traditional serrated polyps and are located more in the proximal colon compared to traditional serrated polyps which are located in the distal colon.

Molecular Oncogenesis of CRC

Over the past 20 years, our understanding of CRC pathogenesis has evolved from the concept of a single disease progressing through a sequence of morphologic and genetic alterations to the concept of molecular heterogeneity and tumor uniqueness (a unique tumor arising in a unique individual). The nature of the precursor polyp is an essential classifier of CRC because each tumor is thought to develop from a unique benign polyp with its own set of morphologic and molecular characteristics. The heterogeneity of CRC translates to a certain extent into the multiplicity of precursor polyp subtypes that we have only recently started to understand. Conventional adenomas are the precursor lesions to CRCs developing via the traditional adenoma–carcinoma pathway characterized by chromosomal instability (except in patients with Lynch syndrome). Serrated polyps are the precursors of CRCs developing through the serrated neoplasia

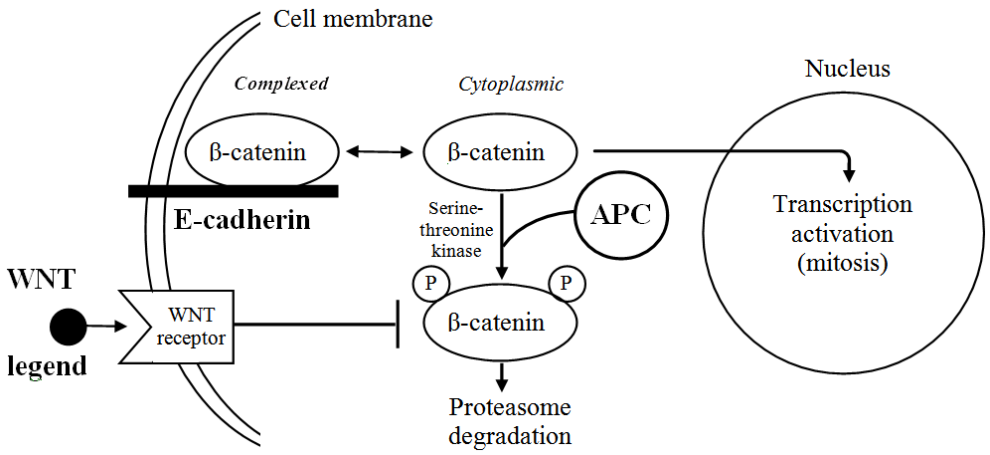

Fig 13-9 *The role of β-catenin in colonic oncogenesis. B-Catenin is an activator of mitosis. It is stored with E-cadherin, its degradation is promoted by APC and inhibited by WNT expression, and hence E-cadherin or APC mutation and WNT expression will lead to cytoplasmic accumulation of β-catenin and activation of mitosis*

pathway characterized by BRAF mutation, CpG island methylator phenotype (CIMP), with or without microsatellite instability (MSI).

In both pathways, promoted proliferation with production of ACF is an early event. Dysregulation of Wnt signaling leading to beta-catenin stabilization and nuclear translocation with subsequent activation of mitosis is an initiator (Fig 13-9). It can be caused by different (epi)mutations. In the conventional adenomatous pathway, the most frequent cause is APC mutation. Other early events have also been documented, including mutations affecting components of the MAPK/ERK cascades (i.e., KRAS or BRAF mutations, which are mutually exclusive) and chromosomal changes, like CIN (lower-level compared to that seen in advanced adenocarcinomas) or CIMP. There are undoubtedly others that have yet to be discovered and they account for roughly half of all adenocarcinomas, i.e., those with no evidence of the early alterations listed above. Mutations involving "survival signaling" cascades (e.g., MAPK/ERK) alter the normal homeostatic equilibrium between proliferation, checkpoint repair of DNA damage, and apoptosis, allowing preinvasive lesions to survive for years. Additional mutations are necessary to allow the tumor to move on into the advanced stage, where malignancy is imminent. The nature of these "brake-releasing" events differs, depending on which pathway the tumor is moving along. These brake-releasing events will result in entrance of about 5-10% of these preinvasive lesions into the advanced stage of frank malignancy. The process is accelerated in the colon cancer predisposition syndromes, leading to high-speed transformation. Examples include FAP for the adenomatous pathway and serrated polyposis for the serrated pathway (Cattaneo et al, 2011).

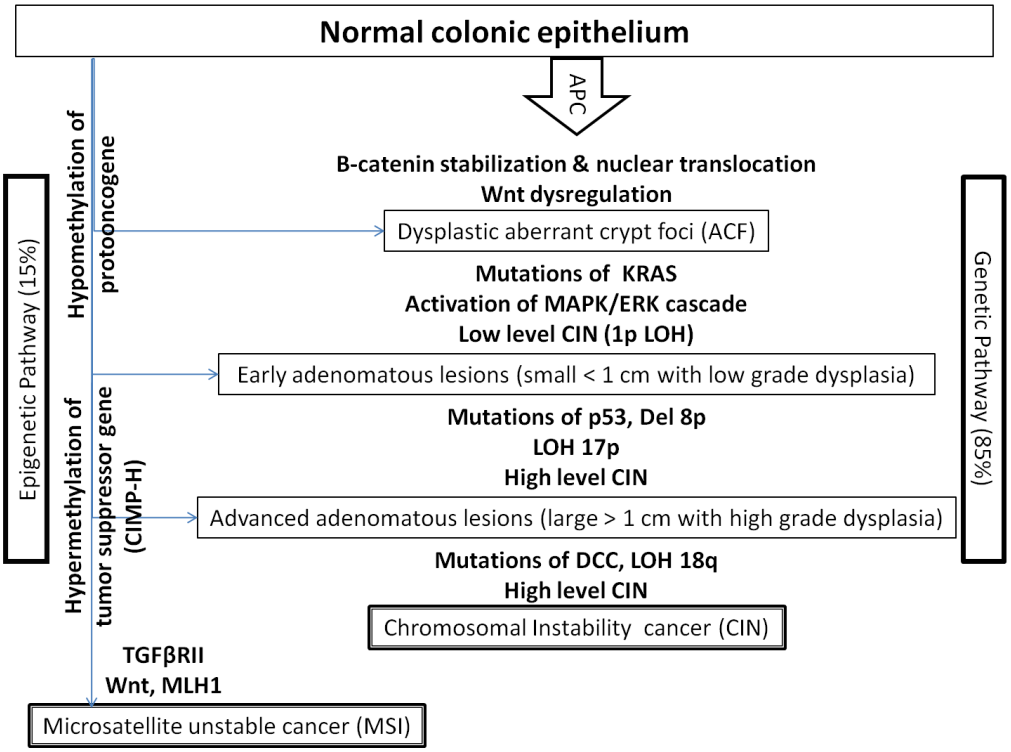

Fig 13-10 *Molecular oncogenesis of colorectal carcinoma. The adenomatous Pathway (so called, Adenoma-Carcinoma sequence). This model is involved in Lt. colon carcinoma and is related to adenomatous polyps. Early gene mutations include: adenomatous polyposis coli (APC) gene and KRAS, whereas, late events affect deleted cancer colon (DCC) gene and TP53 (Adapted from: Bommer and Fearon, 2008, Bosman et al, 2010, Legget and Whitehall, 2010, Cattaneo et al, 2011, and Rosty et al, 2012).*

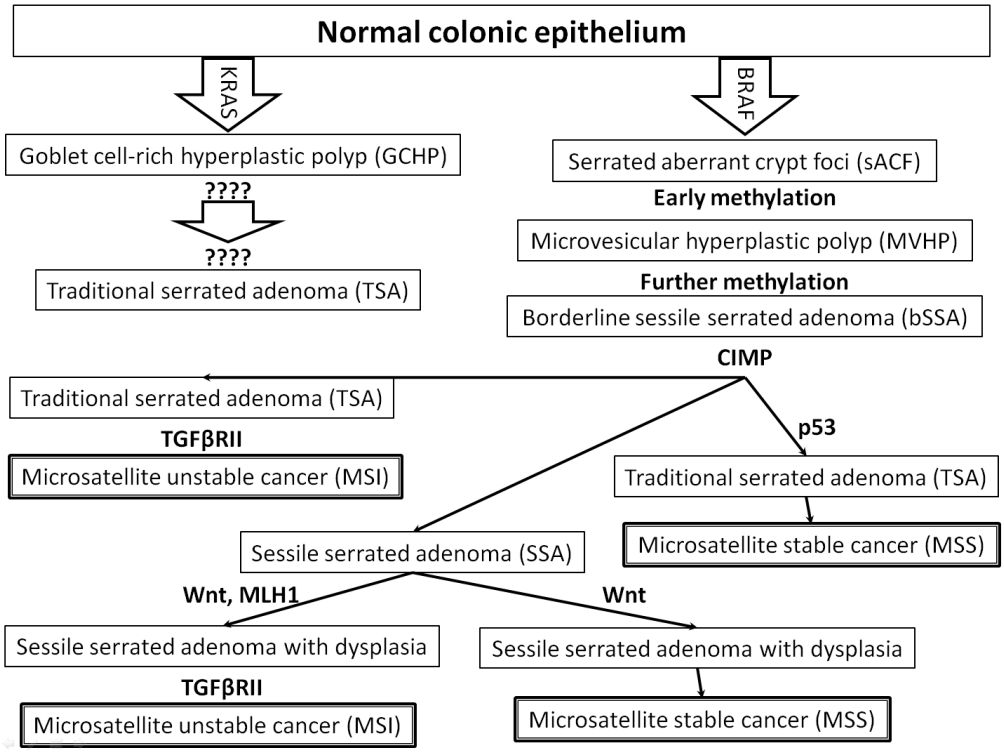

Fig 13-11 *Molecular Oncogenesis of CRC. The serrated pathway. This pathway is responsible for about 20% of sporadic CRC and almost all CRCs occurring in Lynch syndrome (HNPCC). This model is involved in carcinoma of Rt. colon and is related to serrated adenomas. It is characterized by genomic instability due to mutation of DNA mismatch repair (MMR) genes which also leads to alteration of other nucleotide sequences (microsatellite instability). (Adapted from: Bommer and Fearon, 2008, Bosman et al, 2010, Legget and Whitehall, 2010, Cattaneo et al, 2011, and Rosty et al, 2012).*

1. Adenomatous Pathway (Adenoma-Carcinoma sequence, Fig 13-10)

Fearon and Vogelstein in 1990 presented CRC to be a multistep carcinogenesis with morphological-genomic association (adenoma-carcinoma sequence). This pathway is characterized by gross chromosomal abnormalities, hence the name chromosomal instability (CIN) pathway. This pathway is responsible for about 75% of sporadic CRC and most of syndromic CRC (except Lynch syndrome). This pathway can produce tumors anywhere but they are more often in the left colon and rectum and are polypoid. Both early and progressive cellular and architectural dysplasias are a hallmark for this pathway. More than 90% of these tumors show APC mutation, KRAS mutation in about 50%, p53 in about 70% and 18q allelic loss in about 80%. Some tumors have BRAF mutation instead of KRAS (Bommer and Fearon, 2008, Legget and Whitehall, 2010, Cattaneo et al, 2011, Rosty et al, 2012).

2. Serrated Pathway (Fig 13-11)

This pathway is responsible for about 20% of sporadic CRC and almost all CRCs occurring in HNPCC patients. Architectural abnormalities are an early feature of this pathway, whereas cellular dysplasia appears late. Cancers are often in the right colon, sessile or non-polypoid, more mucinous and affect females more. 75% (15% of all CRC) of these tumors develop along the MSI pathway due to loss of MMR function. In sporadic MSI-H cancers, loss of MMR function and consequently MSI-H are mainly due to hypermethylation of MLH1 gene promoter with subsequent epigenetic loss of MLH1 protein expression. Therefore, sporadic MSI-H cancers frequently show CIMP. In Lynch syndrome, loss of MMR function is through germline mutation of one of four of these genes (MSH2, MLH1, MSH6 or PMS2) or mutation in the TACSTD1 regulatory gene. Five microsatellite markers are used to diagnose MSI-H, at least two should

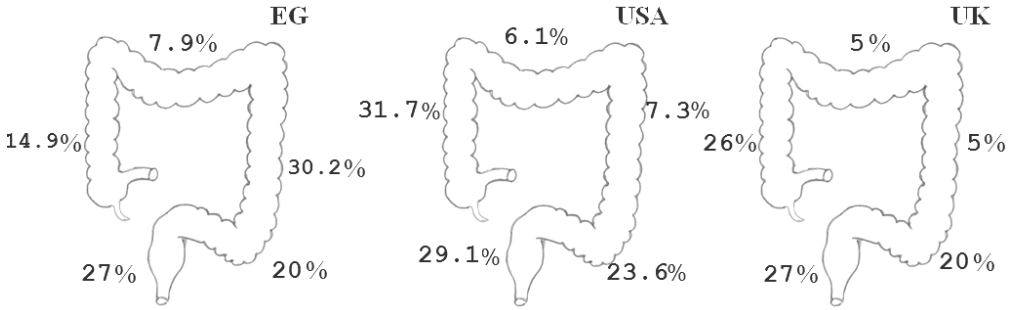

Fig 13-12 *Comparison of site distribution of colonic carcinoma in Egyptian and Western series. In Egyptian patients the left colon is more commonly affected (Data from: Egypt, El Bolkainy et al, 2006, USA, Ries et al, 2007, UK, Cancer Research UK, Office for National Statistics. Cancer Statistics: Registrations Series MB1, 2007-2009 data).*

show altered size. Tumors with one abnormal marker or >40% of markers in larger sets are termed MSI-L, clinical significance of this set is controversial. MSI-H are less responsive to 5-FU but more responsive to irinotecan (Bommer and Fearon, 2008, Legget and Whitehall, 2010, Cattaneo et al, 2011, Rosty et al, 2012).

More than half of CIMP carcinomas are microsatellite stable. CIMP tumors with frequent MSI-H and BRAF mutations are referred to as CIMP1. CIMP tumors that are microsatellite-stable with high frequency of KRAS mutations are referred to as CIMP2. Microsatellite-stable tumors that are CIMP-negative frequently show TP53 mutations. It is noteworthy, 10-15% of CRC do not show the classic pathways of genome instability; namely MSI or CIN pathways (Microsatellite - stable and chromosome-stable CRC)(Bosman et al, 2010).

Macroscopy

The site distribution of colorectal cancer is presented in (Fig 13-12). The sigmoid colon is the most common primary site in both males and females. It is noteworthy, that there is a recent increase in the incidence of carcinoma of Rt. colon especially in elderly females. The ratio of colon to rectal cancer in developed countries is 3:1, but, in Africa it is 1:1. However the pattern in Egypt is more in concordance with that of developed countries with more common affection of Lt. colon.

Grossly, colorectal carcinoma may appear nodular, ulcerative (P 13-21), stricture (annular, P 13-22) or multiple.

Table 13-11 Histologic Classification of Colorectal Cancer

Epithelial
Conventional Gland-forming adenocarcinoma
Mucinous carcinoma
Signet ring cell carcinoma
Rare adenocarcinoma (medullary, micropapillary, cribriform comedo and serrated)
Adenosquamous carcinoma
Squamous cell carcinoma
Spindle cell carcinoma
Undifferentiated carcinoma
Neuroendocrine Tumors
Neuroendocrine tumor (NET)
NET G1 (carcinoid)
NET G2
Neuroendocrine carcinoma (NEC)
Large cell NEC
Small cell NEC
Mixed (adenoneuroendocrine carcinoma)
Mesenchymal
GIST
Leiomyosarcoma
Kaposi sarcoma
Lymphomas
Secondary Tumors

(Bosman et al, 2010)

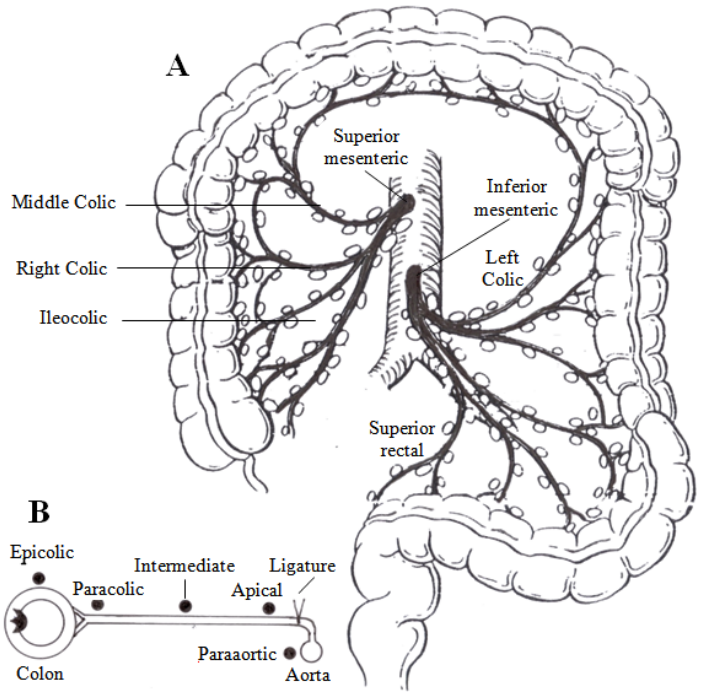

Fig 13-13 *Lymphatic drainage of colon. A. The lymph node groups are related to vascular supply. B. Five lymph node stations are recognized: epicolic, paracolic, intermediate, apical and paraaortic*

Histopathology

The colon and rectum are affected by a wide spectrum of malignant tumors (Table 13-11). Compared to typical adenocarcinoma (gland-forming, P 13-23), mucinous adenocarcinoma (P 13-24), signet ring cell carcinomas, small cell carcinomas, and undifferentiated carcinomas are associated with a worse prognosis. Mucinous adenocarcinoma is characterized by abundant extracellular mucin in at least 50% of tumor area, and they constitute about 15% of colorectal carcinomas. Small cell carcinomas usually show evidence of neuroendocrine differentiation and behave aggressively. Lesions with the histological characteristics of adenocarcinoma which do not invade through the muscularis mucosa into the submucosa and are removed completely have no risk of metastasis and can be treated conservatively. Hence, "intramucosal carcinoma" is better to be used to avoid inappropriate overtreatment.

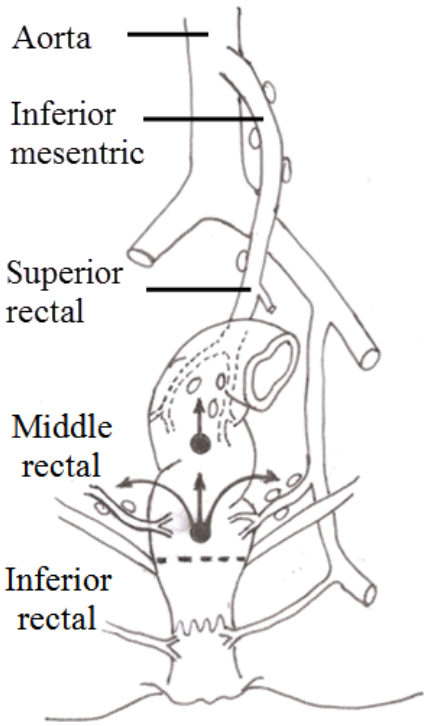

Fig 13-14 *Lymph drainage of rectum. The lower rectum drains mainly to pelvic lymph nodes, but upper rectum drains to nodes along inferior mesenteric and superior rectal nodes.*

Immunohistochemistry and Molecular Characteristics

Most CRC are negative for CK7 and positive for CK20 and also express CDX2. Some CRC are negative for CK20 and these tend to be MSI-H.

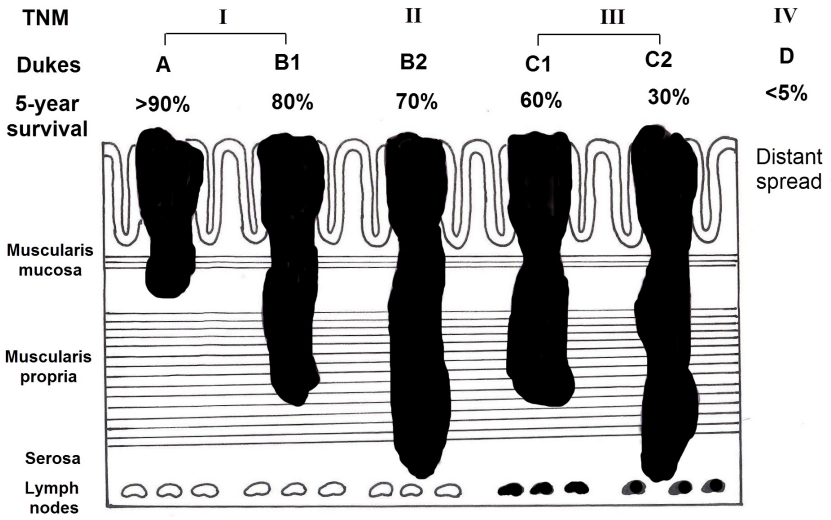

Fig 13-14 *Staging of colorectal carcinoma, TNM stages, their corresponding modified Dukes and survival data (Ries et al 2007/Astler-Coller, 1954)*

MSI-H tumors are usually low grade. Many mucinous adenocarcinomas, almost all medullary carcinomas, some of signet ring cell, undifferentiated and serrated carcinomas are MSI-H and are subsequently low grade and usually show a more favorable prognosis. Tumors which are MSS or MSI-low are usually high grade and behave in a more aggressive manner. This includes many mucinous carcinomas, most of signet ring cell carcinoma, most of cribriform comedo-type adenocarcinoma and many of undifferentiated carcinomas.

Spread

Colorectal carcinoma spreads by four main routes.

1. Local spread, mainly in circumferential direction and perineural.

2. Lymphatic spread to pericolic lymph nodes, then main vessel lymph nodes and finally retrograde spread may occur (Fig 13-13 and Fig 13-14).

3. Hematogenous spread to liver.

4. Implantation may occur transluminal to fistula or hemorrhoid, transperitoneal to omentum or ovaries or during surgery to surgical wounds.

Staging

The original Dukes classification was modified by his coworkers to further split and refine stages B and C, as well as, to recognize distant spread (stage D) in order to improve its predictive value. In the Astler-Coller (1954) modified version (Fig. 13.15) the stages are described as follows: stage A is a tumor limited to mucosa, stage B1 is invasion of submucosa or muscularis propria, stage B2 is penetration of muscularis propria to subserosa, stage Cl is Bl with lymph node metastases, stage C2 is B2 with lymph node metastases and stage D is distant metastases.

In the UICC staging system, the TNM elements are arranged into 4 stage groupings that resemble the modified Dukes system (Fig 13-15). The TNM stage I includes Dukes A and B1, stage II includes Dukes B2, stage III includes Dukes Cl and C2, and stage IV includes Dukes D.

Prognosis

The following are unfavorable prognostic factors in colorectal carcinoma:

1. Advanced stage, either locally advanced (stage C2) or distant spread (stage D) are associated with 5-year survival of 30% and < 5% respectively. Lymph node positivity is also an independent prognostic factor. The 5-year survival of CRC according to SEER stage are: 89.9% in localized stage, 69.6% in regional, 11.9% in distant and 64.3% for all stages (SEER data 2002-2008). The 10-year survival for all stages is 57.7% (Ries et al, 2007).

2. Unfavorable histology: The 5-year survival is less than 30% in small cell carcinoma (18.6% and 16.6

for colon and rectum), signet ring cell carcinoma (28.2 % and 23.9 for colon and rectum), colonic adenosquamous carcinoma (26.7%) and rectal undifferentiated carcinoma (10.7%). This is compared to 58 and 60% for the conventional gland forming rectal and colonic adenocarcinoma, respectively. The classical knowledge that all mucinous carcinomas have poorer prognosis than the conventional adenocarcinoma was proved to be not true by better segregation of cases of signet ring carcinoma from that of mucinous carcinoma. For mucinous adenocarcinoma the 5-year survival is 61.5% for colon and 52.8% for rectum (Ries et al, 2007). This can be attributed to the fact that many of mucinous carcinomas are MSI-H, hence behaving as low grade tumors (Bosman et al, 2010).

3. Short longitudinal clearance and proximity to circumferential margin, extramural venous invasion, angiolymphatic invasion and involvement of perineural spaces and nerves, are all adverse prognostic factors in CRC.

4. Prognostic genes and biomarkers: None of the tens of these is adopted as a routine in clinical practice. The marker with the highest level of evidence is MSI-H which is associated with improved stage-specific survival. Good prognosis is also reported with increased infiltration of tumor by cytotoxic T-cells. This is observed to associate MSI-H tumors. Markers of poor prognosis include mutations of BRAF, allelic imbalance at 18q, or high expression of the stem-cell marker CD133.

5. Predictive genes and biomarkers: These are genes or biomarkers that indicate the likelihood of response or resistance to specific therapies. The selection of used marker is dictated by the tumor pathway targeted and the drug under testing. With increased number of efficacious therapeutic agents for CRC which are often expensive and may be associated with high toxicities, mandates the need for these predictive markers. Successful examples include the detection of KRAS mutation before the administration of the anti-EGFR antibodies as cetuximab and pantitumumab. These antibodies cause upstream inhibition of EGFR. Mutations of KRAS/BRAF will cause downstream autoactivation of the KRAS/BRAF pathway thus rendering tumors with these mutations unresponsive to anti-EGFR antibodies. On the other hand, amplification of EGFR in absence of KRAS mutation is a favorable predictive marker for responsiveness. Another example is the utilization of MSI-H as a predictor of unresponsiveness to 5-flurouracil and

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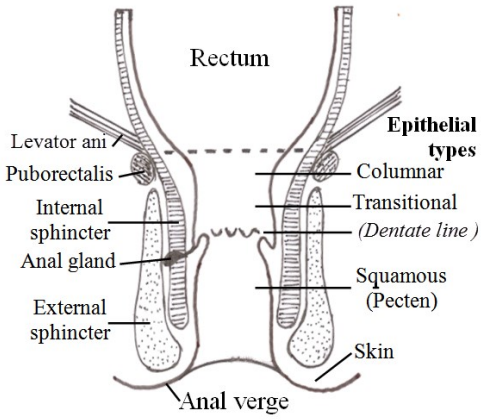

Fig 13-16 *Anatomy of anal canal. It extends from pelvic floor (puborectalis) to the anal verge. The dentate (pectinate line) separates an upper columnar and transitional mucosa from a lower squamous epithelium*

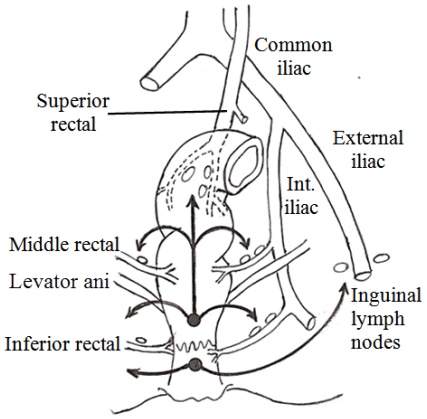

Fig 13-17 *Lymph drainage of the anal canal. The lower anal canal (below dentate line) drains to inguinal lymph nodes, but, upper anal canal drains to pelvic nodes.*

aliplatin. These drugs induce apoptosis of tumor cells in presence of intact mismatch repair. Presence of MSI-H leading to lost mismatch repair will cause failure of recognition of alterations produced to DNA by these drugs and subsequently their failure to induce apoptosis.

6. DNA aneuploidy and high S-phase fraction.

7. Serum biomarkers: high levels of CEA and CA 19-9 correlate with tumor burden and unfavorable prognosis.

Prevention

1. Primary prevention: This involves a low fat diet (only 20% of total calories) and high fiber (wheat bran), as well as, antioxidants (vitamin C, vitamin E), calcium and non-steroidal anti-inflammatory drugs NSAID.

2. Secondary prevention: The screening recommendations for early detection in average risk individuals include: digital rectal examination and stool blood test every year from age 50, as well as, flexible sigmoidoscopy every 3-5 years after age 50. The interval to the next endoscopy is determined by the pathologic findings. High-risk patients should be screened at an earlier age and followed much more closely with total colonic evaluation every 3 years. The US Screening Preventive Service Task Force (USPSTF) recommends screening for colorectal cancer (CRC) using fecal occult blood testing, sigmoidoscopy, or colonoscopy, in adults, beginning at age 50 years and continuing until age 75 years.

A peroxidase test (Hemoccult) remains the most widely used screening test for fecal occult blood. However, the test has a false positive rate of 2.5% and a false negative rate of 25%. Digital rectal examination detects only 15% of colorectal cancers, whereas, flexible sigmoidoscopy can detect 64% of all colorectal cancers. Diagnostic endoscopy fails to visualize the proximal colon in 10% of cases and has a 0.2% complication rate. Biomarkers that may help in the diagnosis include: CEA, CA 19-9 and RAS oncogene analysis in intestinal secretions.

ANAL CANCER

Anatomy

For most surgeons, the anal canal is the area between the anorectal ring and anal verge. But, according to the World Health Organization WHO (Bosman et, 2010), the anal canal extends from the anorectal ring proximally to the dentate line distally (Fig 16-16). The anal canal is lined mainly by transitional epithelium, but also shows areas of squamous and columnar cells. But, below the pectinate line the anal margin is lined by squamous epithelium only. Lymph drainage is also different. Thus, above the dentate line drains to pelvic nodes, but, below the dentate line drains to inguinal lymph nodes (Fig 16-17).

Incidence and Etiology

In USA, cancer of the anal region accounts for 1% to 2% of all large bowel cancers, with a male predominance of 6:1 (DeVita, 1997). Anal cancer is related to HPV infection (especially HPV type 16), smoking, condylomata acuminata and anal fistulas. There is a clear-cut association with male homosexuality and AIDS.

Pathology

The major histologic types of malignant tumors of the anal region are presented in (Table 13.12). Squamous cell carcinomas with its variants predominate (P 13-25 and P 13-26). Squamous carcinoma may be keratinizing or nonkeratinizing. The latter is classified into basosquamous or basaloid (so called cloacogenic) carcinoma (P 13-27). Adenocarcinoma of the anal region may arise from columnar cells in anal canal or the apocrine paraanal glands (p13-28). Rarely, Paget and Bowen diseases may be encountered. In anal Paget disease (P 13-29), there is associated invasive adenocarcinoma in 59% of cases (Jensen, 1988) and the intraepithelial malignant cells are PAS (periodic acid Schiff) positive. Conversely, Bowen disease is not associated with an underlying adenocarcinoma,

Table 13-12 Histologic Types of Anal Cancer

Histologic Type	Relative frequency %	5-year relative survival %
Squamous carcinoma	60.4	67
Basaloid or cloacogenic	17.9	70
Adenocarcinoma	17.6	53
Melanoma	1.7	27
Others	2.3	37

(SEER data 1981-2001, 4296 cases, Ries et al, 2007)

Table 13-13 Cancer of Anal Region

	Anal canal	Anal margin
Incidence	85%	15%
Histology	Squamous (G2-3)	Squamous (Gl)
	Cloacogenic	Paget
	Adenocarcinoma	Bowen
	Melanoma	Basal cell Ca.
Lymph spread	pelvic and inferior mesentenc	inguinal
Prognosis (5 y)	50-80%	80-100%

Table 13-14 TNM Staging of Anal Canal Cancers

Stage 0	Carcinoma in situ
Stage I	Tumor confined to anal region and less than 2 cm in size (T1), L. nodes -ve
Stage II	Tumor confined to anal region and size more than 2 cm (T2 and T3), L. nodes -ve
Stage IIIA	Tumor of any size confined to anal region (T1, T2, T3) with metastasis to perirectal L. nodes. Tumor of any size invading adjacent structures (T4), L. nodes -ve
Stage IIIb	Tumor of any size invading adjacent structures (T4) with metastasis to perirectal L. nodes.
	Tumor of any size with unilateral metastasis to internal iliac and/or inguinal L. nodes (N2)
	Tumor of any size with bilateral metastasis to internal iliac and/or inguinal L. nodes (N3)
	Tumor of any size with metastasis to perirectal and inguinal L. nodes (N3)
Stage IV	Distant metastases

(Sobin et al, 2009 / Edge et al, 2009)

and the malignant cells are PAS negative. Melanoma of the anal canal and anus (P 13-30 and P 13-31) constitutes 1.7% of their tumors with 5-years relative survival of about 27%.

Table 13-13 compares the pathobiology of malignant tumors of anal canal with those of anal margin. Generally, malignant tumors of the anal margin are more favorable than those of anal canal.

Staging

A unified AJCC/UICC staging system developed in 1987 is the system in current use.

The TNM categories are grouped into the stages shown in Table 13-14.

Unfortunately, much of the information needed for staging (e.g. tumor size, depth of invasion and lymph node status) is difficult to obtain clinically. However, recently, transrectal ultrasonogra-

phy (TRUS) has been increasingly utilized as a useful adjunct to the TNM system.

Prognosis

The prognosis is much dependent on stage than on histology. Combined modality treatment with irradiation and chemotherapy has resulted in improved 5-year survival rate (around 80% for localized disease compared to 57% for regional) and in sphincter preservation for most patients with epidermoid carcinoma of the anal region (DeVita, 1997). Well differentiated tumors have better survival figures (about 76% for G1 compared to 55% for G3 poorly differentiated tumors). Table 13.12 shows relative survival in relation to histology. The importance of recognizing anal melanoma lies in its poor prognosis with a 5-year survival rate of 27%.

NEUROENDOCRINE NEOPLASMS

In the gastrointestinal tract neuroendocrine neoplasms occur predominantly in the small intestine (44.7%) followed in descending order by the rectum (19.6%), appendix (16.7%), colon (10.6%), and stomach (7.2%). Neuroendocrine neoplasms are discussed in detail in chapter 19. The new WHO classification of these tumors is shown in Table 19-17. The current section will emphasize points particular to gastrointestinal neuroendocrine tumors.

1. Esophageal neuroendocrine neoplasms are exceedingly rare constituting less than 0.5% of this class of tumors with almost the same proportion compared to esophageal tumors. The majority are poorly differentiated neuroendocrine carcinomas (NECs) or mixed adenoneuroendocrine carcinomas (MANEC). Patients were dominantly males (M : F = 6 : 1) and were old (6th and 7th decade).

2. Most of *gastric* neuroendocrine neoplasms are neuroendocrine tumors (NETs). They are well differentiated nonfunctioning enterochromaffin-like (ECL) cell carcinoids (ECL cell NETs). They dominantly affect the corpus-fundus regions of the stomach. Three types of these tumors are known: (1) type I, associated with autoimmune chronic atrophic gastritis (A-CAG). This type represents 74% of all gastric NETs; (2) type II, associated with multiple endocrine neoplasia type 1 (MEN1) and Zollinger-Ellison syndrome (ZES). This type represent 6% of gastric NETs; and (3) type III, sporadic (not associated with A-CAG or MEN1-ZES). This type constitutes 13% of gastric NETs. Mean age for type I is 63 years, for type II 50 years and for type III is 55 years. Type I is more dominant in females (M : F = 1 : 2.5) in contrast to type III where males are 2.8 times more affected than females.

NECs and MANECs are rare and may arise at any part of the stomach. As a result of advancement of endoscopic techniques and increased awareness of these lesions, gastric NETs incidence showed marked increase from 2-3% of all GI NETs to 11-41%. The incidence is high in Japan due to prevalence of CAG and intensive gastric screening.

3. In the *small intestine*, NETs show different characteristics based on anatomy. NET of the duodenum and proximal jejunum are mainly functioning NETs; mostly somatostatin-producing and rarely serotonin producing enterochromaffin (EC) NETs. NECs and MANECs are rare so as the functional (syndromic) gastrinoma. Neuroendocrine neoplasms of the duodenum are 5.7-7.9% of those of the GI tract. Jejunal tumors on the other hand represent 1% of all gut neuroendocrine neoplasms.

In the distal jejunum and ileum only well differentiated NETs (carcinoid) have been reported. Ileal NETs (P 13-32) represent about half of all small intestinal NETs. This incidence is increasing from 52% in the seventies to 63.6% in 1988-2002. Males and females are equally affected by ileal and distal jejunal NETs with a peak incidence in the 6th and 7th decades (age range 3rd – 10th decade).

4. Neuroendocrine neoplasms of the *appendix* (P 13-33) are discussed later in this chapter.

5. NETs of the *colon* (P 13-34 and P 13-35) makes about 0.4% of colorectal tumors. NETs of midgut (caecum to transverse colon) are 8% of GI NETs, while those of the hindgut (descending colon and rectosigmoid) represent 27%. Rectum is the second site after ileum to be affected by NETs. Rectal NETs are particularly prevalent in Asian/Pacific islanders, Native Americans and African Americans.

Despite the fact that NECs are rare in the large bowel, yet the large bowel is the more common location of these tumors in the GI tract. Rectal NETs occur at younger age (mean 56 years) than colonic NETs (mean 66 years). Rectal NETs affects males and females almost equally but colonic NETS are more common in females (M:F= 0.66:1). MANEC (P 13-36) is exceeding rare. Many high grade NECs have a minor exocrine component but it is enough (minimum of 30%) to

be labeled as MANEC.

Prognosis of GI neuroendocrine neoplasms is summarized in (Table 19-18).

PRIMARY GASTROINTESTINAL LYMPHOMAS

Incidence

Gastrointestinal tract is the most common site of extranodal involvement by lymphoma constituting 4-20% of all NHL in Asia, North America and Europe. The lymphomas are almost exclusively of non-Hodgkin type. In the Middle East the incidence is higher representing 25% of all NHL. The lymphomas are almost exclusively of non-Hodgkin type. Stomach is the most frequently affected site (50-70% of cases), followed by the small intestine (10-30% of cases) and the large intestine (5-10%). Esophagus is rarely the site of primary involvement by NHL representing less than 1% of all lymphomas. Esophageal lymphomas are mostly an extension from the mediastinum or stomach. Lymphomas constitute 5-10% of gastric malignancies. The incidence is increasing worldwide. Lymphomas constitute about 30-50% of small intestinal tumors as both epithelial and mesenchymal tumors of small intestine are uncommon. Colorectal lymphomas constitute only 0.2-0.4% of all colorectal malignancies.

Esophageal lymphomas mostly affect males and age is >50 years. For stomach, both sexes are equally affected and most patients are also >50 years. For small intestine, geographical variations in age at incidence are more pronounced as the dominant lymphoma subtypes are different in Middle East and Africa compared to Asia, Europe and North America. In the Middle East and Africa, small intestinal lymphomas are tumors of children and young adults. In North America and Europe, the peak incidence of small intestinal lymphoma is in the seventh decade of life with slight predominance in males. For colorectal lymphomas, males are twice affected than females and mean age in Europe and North America is 50-70 years with lower incidence in immunocompromised individuals. The age is much lower in the Middle East.

Etiology

1. Immunodeficiency whether acquired (AIDS or iatrogenic) or congenital is associated with increased risk of B-cell lymphoma in extranodal sites, especially the gastrointestinal tract.

2. Esophageal lymphomas are related to *HIV infection* and chronic immunosuppression. MALT lymphoma is related to H. pylori infection.

3. Gastric lymphomas are related to *H. pylori* infection (P 13-37). Treatment of this infection may eradicate the disease in its early phases.

4. Infection with *Campylobacter* has shown to be associated with IPSID. Response to treatment with antibiotics is typical of the early phases of the disease. Chronic inflammatory Bowel disease (Crohns and ulcerative colitis) are risk factors for intestinal B-cell lymphomas. Endemic Burkitt lymphoma is related to EBV infection and in some cases to HIV infection.

5. *Enteropathy-associated* T-cell lymphoma (EATL) is related to celiac disease.

6. The major risk factor for colonic lymphomas is immunosuppression. Long term treatment with corticosteroids and inhibitors of tumor necrosis factor alfa and AIDS are examples of inducers of such state of immunodeficiency. However, cases of B-cell lymphomas associating AIDS have declined due to the wide use of highly active antiretroviral therapy (HAART). It is believed that, it is the treatment of inflammatory bowel disease and it is not the disease itself, that underline the increased risk for B-cell lymphoma in these patients. EBV infection is a common mediator for immunosuppression to produce lymphoma.

Lymphoma subtypes

In the esophagus, the majority of lymphomas are diffuse large B-cell lymphomas (DLBCL) or extranodal marginal zone lymphoma of the MALT type. 30-60% of gastric lymphomas are MALT lymphomas the remainder are DLBCL. The incidence of MALT lymphoma shows remarkable variations in relation to prevalence of H. pylori infection.

In North America, Europe and Asia, DLBCL constitute about 40-60% of all small intestinal lymphomas. Non-IPSID MALT lymphoma comes next in frequency. Mantle cell lymphoma, follicular lymphoma, sporadic non-endemic Burkitt lymphoma and lymphoma with intermediate features between Burkitt and DLBCL are other types of B-cell lymphomas that affect the small intestine. Unlike other parts of The GI tract, small intestine may be affected by T-cell lymphoma. This type of lymphoma is uncommon in most parts of the

world. Two forms of T-cell lymphoma affect the small intestine, namely; enteropathy-associated T-cell lymphoma (EATL) representing 80-90% of cases of intestinal T-cell lymphoma, and monomorphic CD56+ intestinal T-cell lymphoma (10-20% of cases). Both types arise from intraepithelial T-lymphocytes. EATL is seen with increasing frequency in areas where high prevalence of celiac disease is seen (North Europe) and is extremely rare in oriental population where celiac disease is also rare. The relative risk of EATL in patients with clinical celiac disease is 1020 that of unaffected subjects. Monomorphic CD6+ intestinal T-cell lymphoma affect populations where celiac disease is rare.

In the Middle East and Africa DLBCL and Burkitt lymphoma are the two most common types of small intestinal lymphomas. In the Middle East, MALT lymphoma IPSID type is also seen.

In the large intestine, DLBCL constitutes 55% of cases followed by MALT lymphoma, follicular lymphoma, mantle cell lymphoma and Burkitt lymphoma. In mantle cell lymphoma, secondary involvement of the colon by systemic lymphoma is seen in 88% of cased and is diagnosed by colonoscopy.

Lymphomas of the gastrointestinal tract are similar to their nodal counterparts and for details please refer to chapter 25. The following paragraphs emphasize points of interest in some of these lymphomas.

1. Gastric MALT lymphoma: Primary lymphoma of the stomach is a classic example of mucosa-associated lymphoid tissue (MALT) lymphoma. The normal stomach contains no lymphoid tissue. After infection with H. pylori, lymphoid tissue accumulates, from which a low grade B-cell lymphoma may arise. The disease affects elderly patients and may multi-centric (P 13-37-38).

Histologically it shows the classic picture of MALT lymphoma, namely: small or monocytoid lymphocytes, marginal distribution, lymphoepithelial lesions, presence of reactive follicles, presence of multi-nucleated giant cells simulating Reed-Sternberg cells, and presence of plasma cell infiltrate in adjacent mucosa. The disease remains confined to stomach rarely spreads to liver or bone marrow due to the phenomenon of circulation and homing of neoplastic lymphocytes. However, regional lymph node spread may occur.

2. Immunoproliferative small intestinal disease (IPSID, P 13-39, P 13-40 and P 13-41): This condition is a subtype of MALT lymphoma that occurs almost exclusively in the Middle East. It is a disease of young adults (20-40 years), and usually presents with severe malabsorption. In the early stages, this malabsorption may be responsive to broad spectrum antibiotics. The jejunum is usually involved by a B-cell MALT lymphoma, and the disease runs a prolonged course. The serum usually contains an abnormal immunoglobulin, an alpha heavy chain which is an IgA molecule devoid of light chains. Immunopathologic studies of IPSID also confirm the synthesis of this alpha heavy chain, by the neoplastic lymphocytes, as well as, the associated plasma cells. IgA is always of subclass IgA 1.

3. Mantle cell lymphoma (MCL): This is an uncommon disease also known as lymphomatous polyposis. It affects patients older than 50 years. The ileocecal region is involved by multiple polyps and nodules (0.5-2cm). Histologically, it is a small-cleaved cell lymphoma, but contrary to MALT lymphoma, it lacks lymphoepithelial lesions. Positivity to CD5 by immunohistochemistry is characteristic.

4. Enteropathy-associated T-cell lymphoma (EATL): This is a T-cell lymphoma that may complicate chronic celiac disease. It commonly affects the jejunum, and the lesions usually present as circumferential ulcers rather than tumor masses. Three histologic variants are described, namely: immunoblastic, pleomorphic and small lymphocytic variants. In most cases, tumor cells are CD3 positive. Ulcerative jejunitis occurring in patients with celiac disease is in most cases a manifestation of EATL.

5. Large cell B-cell lymphoma (LBCL), immunoblastic: This is an aggressive lymphoma, of the B- immunophenotype, commonly observed in the immunocompromised patients such as post-transplant or AIDS.

6. Burkitt lymphoma (P 13-42 and P 13-43): Endemic Burkitt's lymphomas frequently present with head and neck disease. In contrast, Burkitt-like or sporadic Burkitt's lymphoma in the Western world and areas of the Middle East often present with abdominal localization. It affects mainly children and the lymphoma is most common in the ileocecal region. The histology is small non-cleaved type with very high growth fraction, high rate of apoptosis, and characteristic starry sky pattern of histiocytes. The lymphoma is B-cell type. Epstein - Barr virus genomes are found in tumor cells in about one third of sporadic cases. Expression of c-myc oncogene is also commonly ob-

served.

Prognosis

The Ann Arbor staging system is not easily applied to GI lymphomas. The Paris staging system of 2003 is a modification of the TNM staging system taking into account the depth of tumor infiltration, the extent of nodal involvement and the extent of local tissue infiltration by lymphoma. MALT lymphoma has an indolent course with complete remission being achieved in 60-100%. The 5-year survival for gastric DLBCL varies from 60-90%, irrespective of treatment modality (surgery, radiotherapy and chemotherapy alone or in combinations). Deep invasion in gastric lymphoma is a risk factor for even-free survival but not for overall survival.

Burkitt lymphoma is a highly aggressive but curable disease. Intensive combination chemotherapy regimens resulted in cure rates of up to 90% in patients with low stage disease and 60-80% in patients with advanced stage disease. Results are better in children than in adults.

Mantle cell lymphoma is an aggressive neoplasm. Blastoid cytology, elevated mitosis, high Ki67 index, p53 mutation and peripheral blood involvement are adverse factors for prognosis of this lymphoma.

EATL is an aggressive disease with poor prognosis. Death usually occurs as a result of the complications induced by the uncontrolled malabsorption. Long term survivals are uncommon.

GASTROINTESTINAL STROMAL TUMORS

Definition

Gastrointestinal stromal tumor (GIST) is the most common primary mesenchymal tumor in the gastrointestinal tract and spans a clinical spectrum from benign to malignant. It is generally immunopositive for CD117 (KIT). Morphologically, these tumors simulate Cajal-cell differentiation. Most GISTs contain KIT- or PDGFRA-activating mutations. Before the concept of GIST is adopted, the majority of smooth muscle and nerve sheath tumors diagnosed in GI tract (especially stomach) are actually GISTs. The so called gastric and small intestinal leiomyoblastomas and gastrointestinal autonomic nerve tumors (GANTs) are all actually GISTs.

Epidemiology

Population-based studies in Scandinavia have suggested an annual incidence of GIST of 11-15 per 100000; approximately 55% of these tumors arise in the stomach. However, incidental microscopic GISTs are more common: a frequency of 10% was reported in gastro-esophageal carcinoma specimens. Approximately 25% of gastric GISTs (excluding minimal incidental tumors) are clinically malignant. SEER data indicate that GISTs (interpolated from data on leiomyosarcomas) account for 2.2% of all malignant gastric tumors. According to NCI Pathology registry (2003-2004), gastric GISTs are 7.7% of malignant gastric tumors, and about 2% of each of colonic anorectal tumors. GISTs are tumors of older adults (median age, 60-65 years) equally affecting males and females. They rarely occur in children and when this happens it is almost always in the stomach.

Etiology

Most GISTs are sporadic, but 10% are associated with a variety of syndromes. Examples include neurofibromatosis type 1 (NF1) which is associated with intestinal GISTs that are often multiple and usually indolent. A minute subset of GISTs occur in familial GIST syndrome caused by KIT- or rarely PDGFRA-activating germ line mutations. These patients can develop multiple or diffuse GISTs that often evolve into a malignancy.

Sites of involvement

Approximately 54% of all GISTs occur in the stomach, 32% in the small intestine, including duodenum, 5% in the colon and rectum, around 1 % in the esophagus, and 9% are primarily disseminated with unspecified site or origin. Isolated cases have been reported in the appendix. Extra-gastrointestinal GIST is a rare condition mostly presenting as solitary masses in the omentum or the mesentery. Most such extra-gastrointestinal GISTs are metastatic or may be detached from a gastrointestinal primary source. GISTs often present by vague abdominal complaints or ulcer symptoms, acute or chronic bleeding, abdominal mass, obstruction, or tumour perforation. Many smaller GISTs are detected incidentally during endoscopy, surgery, or CT scan.

Macroscopy and Spread

GISTs vary from minimal mural nodules to large complex masses of >20-30 cm with variable

intra- and extraluminal components. Gastric GISTs often show substantial intraluminal components (P 13-44), whereas serosal masses are more commonly seen with intestinal GISTs (P 13-45). Extra-gastrointestinal GISTs are connected only by a narrow pedicle or are disconnected from any gastrointestinal site of origin. On sectioning, GISTs vary in color from pale to pink tan and often show microcystic change. Hemorrhage and cystic Change are typical of larger tumors.

Malignant GISTs frequently extend into surrounding structures, such as spleen and pancreas. Spread in the omentum, mesentery and retroperitoneal space can involve the abdominal cavity from the diaphragm to the pelvis. Malignant GISTs spread into peritoneal cavity and retroperitoneal space, and often metastasize to the liver. Pulmonary metastases are distinctly rare, in contrast with leiomyosarcomas. Bone, skin and soft tissue metastases are infrequent. GISTs may metastasize after a long latency, in some cases, patients survive long periods even with liver metastases. Gastric GISTs can recur locally due anatomic limitations of resection. On the other hand, intestinal GISTs removed by segmental resections do not recur locally.

Histopathology

Generally, GISTs are spindle cell tumors with divergent histology and sometimes show epithelioid histology (P 13-46). Anatomic localization appears to affect histology, about 20-25% of gastric GISTs are epithelioid. Intestinal GISTs on the other hand are more neural in appearance. Intestinal GISTs are usually composed of spindled or ovoid cells, and many show distinct extracellular collagen fibers (skeinoid fibres), they often contain anuclear zones similar to Verocay bodies or neuropil, reflecting entangled complex cell processes, and vascular hyalinization and thrombosis similar to that of schwannoma are commonly seen. While nuclear palisading is fairly common in intestinal GISTs, cytoplasmic vacuolization is less prominent than in gastric GISTs. Nuclear pleomorphism occurs more often in epithelioid tumors. Divergent skeletal muscle differentiation may be seen after imatinib therapy.

Immunophenotype

Most GISTs show strong positivity for CD117 (KIT) (P 13-47), which can be cytoplasmic, membrane-associated, or sometimes seen as perinuclear dots. However, 5% of GISTs, especially those gastric GISTs with mutant PDGFRA, may have very limited or no CD117 positivity. Anoctamin-1 (Ano -1), a chloride-channel protein detected by DOG 1 - antibody, is an equally sensitive and specific marker that often reacts with CD117- negative GISTs. Most spindle cell GISTs (especially the gastric ones) are positive for CD34, whereas epithelioid GISTs are less consistently positive. Some GISTs express h-caldesmon, a minority expresses SMA, and rare examples show positivity for desmin, keratins (usually keratin 18 only), or S100 protein. It is noteworthy both KIT and DOG-1 are expressed by interstitial cells of Cajal supporting the postulated histogenesis of GISTS from a stem cell-like subcohort of cells of Cajal.

Genetics

KIT oncogenic mutations, leading to constitutive activation of KIT-dependent signaling pathways, are detected in approximately 80% of sporadic GISTs. Mutations most frequently occur in exon 11 (67%). KIT exon 9 mutations are also common (10% of cases) and are almost invariably found in intestinal tumors. The location and type of mutation are important in prognostication and prediction of response to targeted therapy. Thus, gastric GISTs with exon 11 deletions have a worse prognosis than those with missense mutations. Most exon 11 and some other KIT mutants are extremely sensitive to imatinib mesylate, a KIT/PDGFRA tyrosine kinase inhibitor widely used in treatment of metastatic and unresectable GISTs, and for adjuvant therapy. On the other hand, KIT exon 9 mutant GISTs respond less well to imatinib, prompting dose escalation or use of alternative inhibitors, such as sunitinib or nilotinib. A subset of gastric GISTs, especially tumors with epithelioid morphology, has mutations in PDGFRA, which is closely homologous to KIT and these mutant tumors are notably resistant to imatinib. Most KIT mutations are heterozygous, but homozygous mutations can occur and these tumors are often more aggressive than corresponding heterozygous mutants.

Recurrent cytogenetic changes in sporadic GISTs include deletions/monosomy of chromosomes 14 (70%) and 22 (50%). High expression of ROR2 (receptor tyrosine kinase-like orphan receptor 2) has been identified in a subset of GISTs; this is associated with increased invasiveness in vitro and a poor clinical outcome. The secondary mutations conferring imatinib-resistance mutations are concentrated in two regions of the KIT

Table 13-15 WHO 2010 Prognostic Groups for GIST based on Long-term Follow up, correlated with NIH Risk groups and Tumor Stage

Tumor Parameters			Tumor Class		Gastric GISTs*		Intestinal GISTs	
Size	**Mitosis /50 HPF**	**WHO Prognostic Group**	**NIH Risk Group**	**Biological Category**	**Stage**	**Progressive disease %**	**Stage**	**Progressive disease %**
2	≤ 5	1	Very low	benign	Stage IA	0	Stage IA	0
>2 ≤ 5	≤ 5	2	Low	benign	Stage IA	1.9	Stage IA	4.3
>5 ≤ 10	≤ 5	3a	Intermediate	benign	Stage IB	3.6	Stage II	24
>10	≤ 5	3b	High	Malignant	Stage II	12	Stage IIIA	52
≤ 2	>5	4	NA	UMP	Stage II	0	Stage IIIA	50
>2 ≤ 5	>5	5	High	Malignant	Stage II	16	Stage IIIB	73
>5 ≤ 10	>5	6a	High	Malignant	Stage IIIA	55	Stage IIIB	85
>10	>5	6b	High	Malignant	Stage IIIB	86	Stage IIIB	90

(Bosman et al, 2010 / Fletcher et al, 2002) * Based on observation of 1784 patients (AFIP study)

kinase domain. One is the ATP-binding pocket, encoded by exons 13 and 14, mutations of which directly interfere with drug binding . The second is the activation loop, where mutations can stabilize KIT in the active conformation and thereby hinder drug interaction. GISTs associated with NF1 do not contain KIT or PDGFRA mutations.

Differential Diagnosis

From other spindle cell tumors of GI tract (all are CD117–ve): Smooth muscle tumors (SMA +ve), peripheral nerve sheath tumors (S-100 protein +ve), fibromatosis (beta-catenin +ve), inflammatory myofibroblastic tumor (ALK +ve), follicular dendritic tumor (CD21 +ve). Epithelioid GISTs may need to be differentiated from carcinomas (CK +ve).

Prognostic factors

Prognosis depends on tumor size, mitosis and anatomic site (Table 13-15).

In the TNM classification, grading is based on mitotic rate (5/50 HPFs is a low mitotic count, while >5/50 HPFs is a high count). There is no formal grading system for GISTs; grading for soft tissue sarcoma is not applicable because relatively low levels of mitotic activity may confer high malignant potential. The stage combines tumour size and mitotic activity. Estimates of metastatic rate for prognostic groups defined by tumour size and mitotic rate are shown in (Table 13-15) which compares WHO 2010 prognostic groups with NIH 2002 consensus as well as tumor stage. It should be noted that staging criteria are different for gastric and small-intestinal GISTs to reflect the more aggressive course of small-intestinal GISTs with similar parameters (Table 13-15).

Syndromic GISTs which are deficient in succinate dehydrogenase (SDH) which occurs only in gastric GISTS (8% of these tumors), at younger age with more female predilection, are more unpredictable group of tumors . Even tumours with low mitotic counts in this group can develop liver metastases, while tumours with high mitotic counts may never metastasize. In this group, latency between primary tumour and metastasis can be long, > 40 years, and patients with metastases can survive for long periods even without specific treatment. While many metastatic GISTs were formerly fatal within 1-2 years, these patients often now survive 5 years or more with tyrosine-kinase inhibitor treatment.

TUMOR-LIKE CONDITIONS

A variety of tumor-like conditions could occur in the GI tract and may produce clinical or endoscopic picture that mimics cancer. Examples include large inflammatory gastric ulcers (P 13-48), intestinal bilharziasis producing inflammatory stricture (P 13-49) or pericolic inflammatory mass (P 13-50 and P 13-51), inflammatory strictures (P 13-52) with or without pericolic masses (e.g. complicating diverticulosis), omental bilharzial granulomas which may be so extensive to simulate omental metastases (P 13-53), and abdominal endometriosis (P 13-54, P 13-55 and P 13-56).

Disseminated leiomyomatosis (P 13-57) is a very rare condition and a benign disease characterized by the development of multiple smooth muscle-like nodules in the peritoneal cavity. It is associated with increased serum levels of gonadal steroids. It is suspected that this disease originates from a metaplasia of submesothelial multipotent mesenchymal cells. Female gonadal steroids play an important role in the pathogenesis of this condition, hence surgical castration or gonadotropin releasing hormone agonist seems the appropriate treatment of such conditions. These nodules express smooth muscle actin, ER and PR receptors.

APPENDICULAR TUMORS

Appendicular tumors constitute less than 1% of colorectal tumors (SEER Data 1988-2001). Table 13-16 shows the WHO classification of appendicular tumors of 2010. Appendicular tumors are morphologically related to their colonic counterparts. Special consideration is given to appendicular neuroendocrine tumors and some types of appendicular mucinous tumors associated with pseudomyxoma peritonei, which will be discussed in details in the following section.

Neuroendocrine Neoplasms

Neuroendocrine tumors (NETs) account for 50-77% of appendiceal tumors and for 19% of all GI NETs. NETs are seen in 0.3-0.9% of appendicectomy specimens. Appendiceal neuroendocrine carcinomas (NECs) are exceedingly rare. The mean age for appendiceal NETs is 32-43 with tubular carcinoid occurring at younger age (mean 29 years) and goblet cell carcinoids occurring at an older age (mean 53 years). Females are more affected than males. Most appendiceal NETs are asymptomatic and incidental affecting distal end (P

Table 13-16 WHO Classification of Appendicular Tumors

Epithelial
Premalignant
Adenomas (tubular, villous and tubulovillous)
Intraepithelial neoplasia (dysplasia)
Low grade
High grade
Serrated polyps (hyperplastic, sessile and traditional)
Malignant
Adenocarcinoma
Low grade appendiceal mucinous neoplasm
Mucinous
Signet ring
Undifferentiated carcinoma
Neuroendocrine Neoplasms
Well-differentiated neuroendocrine tumor (Carcinoid = NET G1)
NET G2
Neuroendocrine carcinoma NEC
Large cells NEC
Small cell NEC
Mixed adenoneuroendocrine carcinoma
Goblet cell carcinoid
Mesenchymal
Leiomyoma
Lipoma
Neuroma
Kaposi sarcoma
Leiomyosarcoma
Lymphomas
Secondary tumors

(Bosman et al, 2010)

13-33). Carcinoid syndrome is extremely rare and if present it usually indicates disseminating disease, usually to liver. About 80% of appendiceal NETs are <1 cm, 14% 1-2 cm and 6% >2 cm. Mixed adenoneuroendocrine carcinomas (as goblet cell carcinoid) affect any part of appendix and often form larger masses with average of 2 cm. Histologically, appendiceal NETs shoe insular, nested, tubular, acinar and clear cell morphologies (P 13-35).

Prognosis: Appendiceal NETs <1 cm hardly ever metastasize. Non-functioning, non-angio-invasive tumors confined to appendix and <2 cm are cured by complete local resection with a 1% or less risk of nodal metastasis. Tumors >2 cm, invading deeply into the mesoappendix/subserosal fat or showing angioinvasion, carry a 21-44% risk of lymph node metastasis. Overall 5-year survival for appendiceal NETs is 88-94% for localized disease, 78-83% for regional disease and 25-31% for metastatic disease (Yao et al, 2008). Tubular NETs are benign tumors. Patients with appendiceal NETs are at higher risk for other GI malignancies, hence follow up of these patients by colonoscopic screening is advised.

Pseudomyxoma Peritonei

Pseudomyxoma peritonei applies to the growth of neoplastic mucin-secreting cells within the peritoneal cavity so producing a slow but relentless accumulation of mucin resulting in gelatinous ascites. Appendix is the source of these mucin-producing cells in the majority of cases. However, mucinous carcinoma of other sites can produce this condition. These other sites include: colorectum, gall bladder, stomach, pancreas, fallopian tubes, urachus, lungs and breast. Ovaries are rarely the source of such condition when they harbor an intestinal type of low grade mucinous carcinoma.

Pseudomyxoma peritonei (carcinoma peritonei) is classified into low-grade and high grade according to the lesion causing them. *Low grade pseudomyxoma (carcinoma) peritonei* (P 13-58) is often produced by a low grade appendiceal mucinous neoplasm (LAMN). Appendix shows a villous, serrated or undulating architecture simulating an adenoma which show broad front compression of the underlying submucosa and musculosa which are atrophic and fibrosed with no desmoplasia. Lining cells are in a single layer with regular nuclei showing low grade dysplasia or bland looking. Large intracytoplasmic mucin vacuoles are seen in columnar cells. Mitosis is rare. Peritoneal fluid may be acellular or show occasional small strips or small islands of columnar or cuboidal cells. These cells are bland or show low grade dysplasia. The term peritoneal adenomucinosis is to be avoided even if ascitic fluid is acellular. The concept of ruptured adenoma as a cause of these lesions is also to be abandoned as it did not reflect the clinical course. LMAN are not to be termed borderline as borderline ovarian tumors of same histology will show more favorable prognosis.

Mucinous adenocarcinoma of the appendix produces high grade pseudomyxoma (carcinoma) peritonei (P 13-59). This tumor shows invasive pattern

of growth into appendicular wall with desmoplasia. Lining cells show at least focal high grade dysplasia. Associated residual LAMN may be seen denoting a continuous spectrum. Peritoneal fluid in these cases show strips, small islands or cribriform structures of cytologically malignant mucin producing cells (some may be signet ring cells). Mitosis is seen and abnormal figures may be seen.

Prognosis and Predictive Factors

For appendiceal adenocarcinoma, high grade, advanced stage and non-mucinous histology are associated with poor prognosis. Low grade pseudomyxoma peritonei shows better prognosis than high grade pseudomyxoma and a cellularity of the gelatinous ascites may improve prognosis. The overall 5-year and 10-year survival for appendicular tumors is 60% and 50% respectively (SEER data 1988-2001). For stages 0 and I, the 10-year survival is 83% compared to 16% in stage IV.

Table 13-17 Classification of Peritoneal Tumors

I. Non-neoplastic (Tumor-like lesions)
Peritoneal inclusion cysts
Unilocular or multilocular
Endometriotic cysts
Endosalpingiotic cysts
Chylous cysts
Mesothelial hyperplasia
Peritoneal fibrosis
II. Multiple Peritoneal Implants
Disseminated peritoneal leiomyomatosis
Splenosis, gliomatosis and melanosis
III. Benign Tumors
Adenomatoid tumor
Papillary mesothelioma
Solitary fibrous tumor
IV. Primary Malignant Tumors
Malignant mesothelioma
Primary carcinomas, Mullerian type
Desmoplastic small round cell tumor
V. Secondary Malignant Tumors
From intra-abdominal primary (pseudomyxoma or GI metastasis)
From Extra-abdominal primary (breast carcinoma)

PERITONEAL TUMORS

Serous membranes are derived from mesoderm and are composed of mesenchymal cells and surface flattened cells (mesothelium). These cells retain the potentiality to differentiate to a variety of cells (transitional, squamous, glandular epithelium, as well as, sarcomatous differentiation from submesothelial mesenchyme).

Peritoneal mass lesions are classified on clinicopathologic basis into five main groups (Table 13-17). *Non-neoplastic tumor-like lesions* include cysts of various origin and mesothelial hyperplasia. Multiple peritoneal i*mplants* may arise from normal tissue (e.g. splenosis after rupture of spleen), related to pregnancy or benign tumors (leiomyomatosis P 13-57), or rupture of benign cystic teratoma (gliomatosis and melanosis). *Benign peritoneal tumors* may be of epithelial or mesenchymal differentiation.

Malignant peritoneal tumors may be primary or secondary. The main primary tumors are malignant mesothelioma, Müllerian type carcinomas which may simulate those of ovary (serous and mucinous types) and desmoplastic small round cell tumor. Inflammatory myofibroblastic tumor is potentially malignant tumor (25% recurrence and 5% metastasis) arising from peritoneal mesenchyme.

In secondary malignant tumors, the primary may be intra-abdominal neoplasm. Examples are pseudomyxoma peritonei (P 13-58 and P 13-59) and gastrointestinal carcinoma with omental metastasis (P 13-60). Breast cancer is the most common extra-abdominal primary source of peritoneal metastases.

MALIGNANT ASCITES

Not all cancer patients with ascites exfoliate malignant cells in the ascitic fluid and 90% are negative. Thus, ascites may be classified on etiologic basis into: non-malignant, paramalignant and malignant.

1. Non-malignant ascites represents transudates resulting from liver cirrhosis, heart failure, nephrosis, infections and ovarian fibroma (Meig syndrome).

2. Paramalignant ascites is indirectly related to the tumor and malignant cells are absent in the effusions. It results from lymphatic obstruction (chylous ascites), vascular obstruction or may be due to chemotherapy related reactive mesothelial

hyperplasia or peritoneal mucinosis.

3. Malignant ascites: It accounts for 10% of cases of ascites associating malignancy. There is involvement of peritoneal surface by malignant cells (peritoneal carcinomatosis) with exfoliation of tumor cells which could be detected in cytology smears. In 80% of malignant ascites, a primary tumor could be discovered (gastrointestinal, ovarian, breast, lung, lymphoma, mesothelioma, soft tissue sarcoma or pediatric tumors). However in 20% of cases the primary tumor is unknown. In such cases, serum biomarkers and immunophenotyping on core tissue biopsies or cell blocks from fluid sediment may be of help (DeVita et al, 2011).

Ascites is often a manifestation of advanced cancer and its presence denotes a worsening prognosis. Survival is dependent on site of origin, with a mean survival of 17 months in lymphomas, 8 months in ovarian cancer, 4 months in GI cancers and only 3 months in patients with unknown primary (Dobson, 2010).

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