

Section 10

LECTURE

Gastrointestinal Neoplasms

Gastrointestinal Neoplasms

Gastrointestinal neoplasms account for nearly a quarter of cancer deaths in the United States. This is led by colon cancer, the second leading cause of cancer deaths overall, followed by the pancreas, liver and biliary tract, stomach, esophagus, and the small intestine. Histopathologically, gastrointestinal neoplasms can be classified in more than one hundred distinct entities. This lecture will only describe the most common benign and malignant tumors of the digestive tract. Common tumors of the pancreas, liver, and the biliary tract will be described in other lectures.

I. EPITHELIAL TUMORS

This group consists of tumors that are generally neoplastic in origin (such as carcinomas, and adenomas) and those that are not (such as hyperplasias and hamartomas). Both groups typically (but not always) present as protrusions of mucosal tissue into the lumen (*polyps*). Polyps may be attached to the wall by a narrow stalk (*pedunculated polyps*) or have a broad base (*sessile polyps*).

A. EPITHELIAL POLYPS

- Inflammatory Polyps** are localized areas of mucosal swelling due to a combination of active inflammation and regenerative response. Histopathology includes an inflamed lamina propria with granulation tissue, ulcerated and/or regenerating epithelium, and cystically dilated glands. The most common situation in which inflammatory polyps are seen include:
 - Sporadic Juvenile (or "Retention") Polyps:** Inflammatory or hamartomatous polyps, usually single, which can occur in children and in adults (about 1/3 of cases). Majority (80%) of polyps are in the sigmoid or rectum. Chief symptoms are rectal bleeding of modest degree, and prolapse of the polyp. Treatment by excision. Rare incidence of dysplasia.
 - Juvenile Polyposis:** Multiple polyps in colon and rectum; often in stomach and small intestine as well. Autosomal dominant inheritance; not clear whether inflammatory or hamartomatous in nature. Slight increase in incidence of associated carcinoma.
- Hamartomatous Polyps** are abnormal proliferation of normal indigenous tissue elements, resulting in disorganization of mucosal elements with interspersed bands of smooth muscle. May occur in isolation, or as part of *Peutz-Jeghers Syndrome*. Major features of the syndrome are:
 - Autosomal dominant genetic transmission
 - Increased melanin pigmentation in face, oral mucous membranes, and digits
 - Hamartomatous gastrointestinal polyps: Polyps may be present throughout the GI tract, are generally small (0.2-2.0 cm) and smooth contoured. Major clinical symptoms are abdominal pain, related to intussusception, and rectal bleeding, due to polyp ulceration. Therapy consists of conservative local excision of symptomatic polyps, and of polyps showing X-ray evidence of increasing size. There is a small increase in incidence of carcinoma of small and large intestines in this syndrome.
- Hyperplastic Polyps** are the most common polyps in human colon and rectum, probably affect all age groups, and are almost invariably present in the colon. They are thought to result from excessive maturation of non-neoplastic colonic epithelium. Grossly, they are minute hemispheric 1-3 mm protrusions; sessile; smooth contoured; often multiple. Microscopically, there is excessive cytoplasm of superficial colonic enterocytes resulting in "scalloped" papillary projections; irregular mucin production; and basally-oriented benign nuclei. Pathogenesis is unknown. Large hyperplastic polyps (1 cm or greater) are rare; and such polyps should be evaluated for coexisting adenomatous change. Hyperplastic polyps are asymptomatic, usually incidental, with virtually no malignant

potential of association.

Hyperplastic polyps are also the most common epithelial polyp in the stomach, representing more than 90% of benign gastric polyps. Gastric hyperplastic polyps are typically found in the antrum and are less than 1.5 cm in maximum dimension. Histologically, they are composed of non-dysplastic epithelial elements with dilated glands, variable inflammation, and fibrosis. Keep in mind that unlike colonic polyps, gastric polyps are relatively uncommon (overall prevalence of ~1%) and are often found incidentally on work-up for other reasons.

4. **Benign Lymphoid Polyps** are exuberant mucosal lymphoid follicles, and may be misinterpreted grossly as epithelial polyps. Histological differentiation is easily made.

B. ADENOMAS

Adenomas are benign epithelial neoplasms of the gastrointestinal tract. Adenomas are common lesions occurring in 25-50% of people over 60 years of age, with a male:female ratio of 2:1. Most adenomas (~90%) are colonic, but they can also occur in the stomach and small intestine. The majority of colonic adenomas are in the rectosigmoid, which is readily accessible to sigmoidoscopic examination. Adenomas are usually single, but may be multiple in up to 25% of cases. They are usually discovered incidentally or during screening, but may clinically present with blood in stools.

Adenomas are divided into three types based on their architectural growth pattern. *Tubular adenomas* are the most common type, and are characterized by a flat contour in which tubular crypts are randomly organized (reminiscent of normal colonic mucosal architecture). *Villous adenomas* are characterized by the presence of papillary fronds at the surface (reminiscent of small intestinal mucosal architecture). *Tubulovillous adenomas* contain a mixture of the two patterns. Small tubular adenomas (measuring only a few millimeters) are typically sessile, but almost all develop a stalk as they become larger (measuring several millimeters to centimeters). Pure villous adenomas are rare (~1% of all adenomas), almost always sessile, and can be quite large (several centimeters) at the time of detection. Tubulovillous adenomas are intermediate in frequency and histopathology between tubular and villous adenomas. It is important to note that these three types of adenoma appear to be *histologic variants of the same neoplastic process*. All adenomas are considered to be pre-malignant lesions with an increasing frequency of invasive carcinoma with increasing size. Foci of carcinoma are thought to be present in up to 50% of adenomas larger than 2 cm.

Dysplasia, the histological hallmark of adenomas, is a morphological diagnosis based on the presence of a variable combination of the following architectural and cytologic abnormalities:

1. Nuclear enlargement and increased N/C ratio
2. Hyperchromasia (excessively dark staining of the nuclear chromatin)
3. Irregularity of the nuclear contour
4. Loss of cytological polarity
5. Increased mitoses
6. Absence of epithelial maturation toward the surface
7. Loss of cytoplasmic mucin
8. Abnormal glandular architecture (branching, budding, back-to-back glands)

Based on the severity of the abnormal cytological and architectural features, dysplasia may be classified into low-grade and high-grade in a two-tier system, or mild, moderate, and severe in a three-tier system. *When the dysplastic epithelium extends (or "invades") beyond the basement membrane of the glands within which it arose, it becomes a carcinoma.* Carcinomas are further graded based on the level of invasion and the degree of differentiation (see below). Removal by polypectomy is curative only if the carcinoma is limited to the superficial mucosa and is completely excised.

Although the majority of adenomas represent sporadic polyps, adenomas are also the characteristic lesion of several important adenomatous polyposis syndromes:

Familial Adenomatous Polyposis (FAP) is an autosomal dominant disease with almost complete penetrance, characterized by the progressive development of hundreds of adenomatous colonic polyps. The incidence of FAP is approximately 1 in 10,000 live births, approximately 80% of which are inherited. The average age of patients with grossly detectable adenomas is 15 years, and the average age of colorectal cancer development in patients who have not had a prophylactic colectomy is about 35 years. FAP patients who have had a prophylactic colectomy will eventually face the development of upper gastrointestinal adenomas and adenocarcinomas. Extraintestinal manifestations of FAP are common, and include the classical triad of sebaceous cysts, osteomas, and desmoid tumors in **Gardner's Syndrome**, and malignant brain tumors (glioblastomas and medulloblastomas) in **Turcot's Syndrome**.

FAP is associated with mutations in the **Adenomatous Polyposis Coli (APC) gene** on chromosome 5q21. The normal APC protein is localized to the basolateral membrane of epithelial cells, and functions as a tumor suppressor presumably through its interaction with β -catenin, a cytoskeletal protein that can exert a suppressive effect on cellular proliferation through the Wnt signaling pathway. So far, more than 300 different mutations have been described in the APC gene, and there appears to be specific APC genotype-FAP phenotype associations. For instance, mutations in exons 3 and 4 (close to the 5' end) and mutations beyond codon 1578 in exon 15 are associated with Attenuated FAP (also known as Flat Adenoma Syndrome) which is characterized by fewer than 100 polyps (many of which are "flat") and a 10-15 year later onset of colorectal cancer. In contrast, patients with mutations in codon 1309 in exon 15 develop thousands of adenomas and colorectal carcinomas by their early teens. There is also some association between specific mutations and the extracolonic manifestations of FAP. For instance, there is a strong association between mutations in the distal portion of exon 15 (close to the 3' end) and desmoid tumors and Gardner's Syndrome. Somatic mutations of the APC gene are also critical in sporadic colorectal carcinogenesis.

Hereditary Nonpolyposis Colorectal Cancer (HNPCC) is an autosomal dominant disease that also predisposes to the development of colorectal polyps and cancer at an early age (typically 40- to 45-years-old). HNPCC is classically characterized by right-sided colonic polyps (few to less than 100) and cancer, with increased risk of synchronous and metachronous colorectal cancer, as well as extracolonic cancers in the genitourinary tract, ovaries, upper gastrointestinal tract, and the hepatobiliary system. HNPCC has been associated in 20-90% of reported cases with germline mutations in five different **DNA mismatch repair (MMR) genes**, with up to 90% of which involve *hMSH2* on chromosome 2p and *hMLH1* on chromosome 3p. Tumors of *hMSH2* and *hMLH1* mutation carriers exhibit **microsatellite instability (MSI)**, characterized by expansion or contraction of short repeat sequences of DNA at multiple loci (also see the discussion below under molecular biology of colorectal cancer). There is no general consensus on the diagnostic criteria for HNPCC, and several guidelines have been proposed (Table 1).

Table 1. Proposed Clinical Criteria for HNPCC

Original International Collaborative Group criteria (the Amsterdam Criteria)	<ol style="list-style-type: none"> 1. Three relatives with colorectal cancer (CRC), one a first-degree relative of the other two 2. CRC involving at least 2 generations 3. ≥ 1 CRC diagnosed before the age of 50y
Modified Amsterdam Criteria	<ul style="list-style-type: none"> • In very small families: <ol style="list-style-type: none"> 1. Two CRC's in first-degree relatives 2. CRC involving at least 2 generations 3. ≥ 1 CRC diagnosed before the age of 50y • In families with 2 first-degree relatives affected by CRC, the presence of a third relative with an unusually early onset of CRC or endometrial cancer

NCI Workshop (Bethesda Guidelines)	<ul style="list-style-type: none"> • Cancer in families that fulfill Amsterdam criteria • Two HNPCC-related cancers • CRC or endometrial cancer before the age of 45 • CRC and a first-degree relative with CRC and/or HNPCC-related cancer and/or colorectal adenoma; one of the cancers before the age of 45 and adenoma before the age of 40 • Right-sided CRC with "undifferentiated" histology before the age of 45 • Signet-ring-cell-type CRC before the age of 45 • Adenomas before the age of 40
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C. ADENOCARCINOMA OF THE COLON AND RECTUM

Epidemiology

In 1999, colorectal adenocarcinoma (CRC) was the third most common carcinoma, and the third leading cause of death from cancer in the United States. Between 1990 and 1995, there were more than 130,000 new cases of CRC with an estimated incidence of approximately 16 new cases/100,000 for American Indians (lowest incidence rate) to 51/100,000 for African Americans (highest incidence rate). Over the same time period, mortality from CRC was estimated at approximately 10/100,000 (American Indians) to 23/100,000 (African Americans). There has been a statistically significant increase in 5-year survival rate for CRC between 1974 (48-50%) and 1994 (61-63%), perhaps due to better diagnostic procedures and improvements in treatment.

There is an increasing incidence of CRC with increasing age; it is rare before the age of 40 (except in hereditary cases), and the male:female ratio is approximately 1:1. There is a higher incidence of CRC in countries with a high degree of economic development (USA and Western Europe); and it is rare in populations such as the native African population. There may be a possible role for diet in this difference; a highly refined, low-residue diet is thought to be important in the pathogenesis of this disease, due to (1) increased transit time leading to prolonged contact of concentrated stool contents with colonic mucosa, and (2) excessively refined carbohydrates leading to altered bacterial content and metabolism of bile salts and other substances to carcinogens. However, the role of diet in the development and progression of adenomas and carcinomas remains somewhat controversial.

Molecular Biology

The adenoma-carcinoma sequence: The current concept about the development of CRC is that essentially all carcinomas evolve through malignant transformation of adenomas (which may be flat or polypoid). This concept is generally supported by such facts as:

- Demonstration of *in situ* and invasive carcinoma in polyps, especially those over 1.0 cm in diameter.
- Extreme rarity of documented small carcinomas (0.5 to 1.0 cm in diameter) occurring in "flat" non-adenomatous mucosa.
- Familial adenomatous polyposis syndromes and their striking correlation with eventual development of carcinoma.
- Geographic association between colorectal adenomas and CRC, with a slight delay in peak age incidence of the latter (58 vs 62 years, respectively).

Perhaps the strongest evidence in support of the adenoma-carcinoma sequence of CRC development has been the development and refinement of the Vogelstein model of CRC. In 1990, Fearon and Vogelstein proposed a multistage model for the development of adenomas and progression to

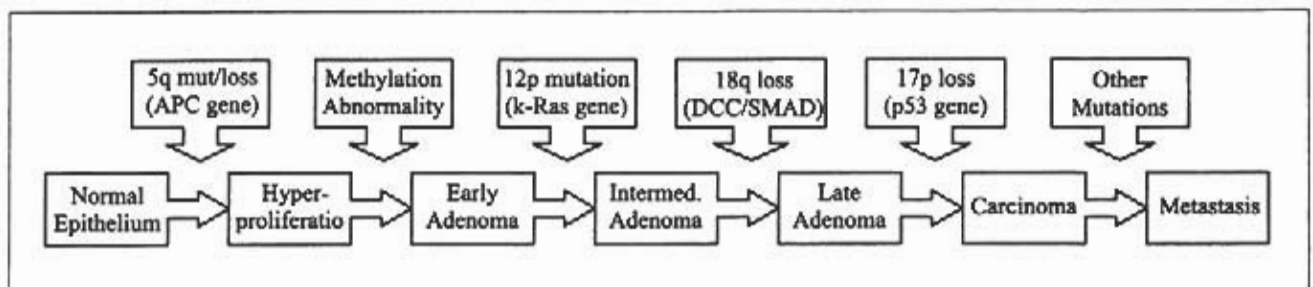


Figure 1. The classical ("Vogelstein") genetic model for colorectal tumorigenesis (modified from Fearon and Vogelstein, *Cell* 1990; 61:759). See the review article by Arends for an updated and complete review.

carcinoma in which a number of genes were involved (Figure 1). Although the original Vogelstein model has been somewhat modified in the past ten years, the fundamental concepts and steps required to progress from normal epithelium to carcinoma in both sporadic CRC and in FAP have proven to be an excellent paradigm for multi-step tumorigenesis.

The idea that most cancers, including CRC, arise as a result of accumulation of genetic alterations over time is now commonly accepted. However, the rate of random mutations alone cannot account for the number of genetic alterations found in most cancers in humans. It has therefore been suggested that destabilization of the genome must be a prerequisite for carcinogenesis. This destabilization is best understood in CRC, in which two distinct pathways are thought to lead to an accelerated rate of genetic alterations. The more common of these "mutator phenotype" pathways is characterized by *chromosomal instability* as manifested in allelic losses (or *loss of heterozygosity*), translocations, etc.,

in key regulatory proteins. Chromosomal instability currently accounts for the majority of the cases of CRC. In the second mutational instability pathway, cancers display increased rates of intragenic mutations, characterized by generalized instability of short, tandemly repeated DNA sequences known as microsatellites. This so-called *microsatellite instability* (defined by some as instability in at least 40% of microsatellite loci) has a high prevalence in patients who meet the criteria for HNPCC (see above), but is also found in approximately 15 percent of sporadic cases of CRC. Mismatches of nucleotides that "normally" occur when DNA polymerase inserts the wrong bases in newly synthesized DNA are typically repaired by mismatch-repair enzymes. Defects in the process of mismatch repair lead to microsatellite instability. Inherited germ-line mutations of mismatch-repair genes have been found in approximately 50 percent of patients who fulfill the Amsterdam criteria for HNPCC. In particular, alterations of the *MSH2* and *MLH1* mismatch-repair genes account for more than 90 percent of these cases. In addition, acquired alterations of the *MLH1* occur in most sporadic cases of colorectal cancer with microsatellite instability.

Pathological Considerations

Colonic adenocarcinomas are most common in rectum and sigmoid (75%), while transverse colon is the least frequent site. Grossly, tumors may be of any size, but are usually over 2-3 cm when detected and have overgrown the adenomas from which they presumably arose. Tumors may rarely be polypoid, but most are sessile and firm with central ulceration ("fungating"). Patterns of growth vary somewhat according to location (and possibly the "mutator phenotype"). In the right colon the carcinomas tend to be sessile, bulky masses that outgrow their blood supply, leading to ischemia, necrosis, and ulceration with bleeding. Obstruction is uncommon. In the left colon (rectum and sigmoid) the carcinomas tend to grow in an annular encircling fashion, creating so-called "napkin-ring" constriction of bowel wall with partial or complete obstruction of fecal flow. Microscopically, the majority of CRCs are moderately- to well-differentiated, with gland formation and variable mucin production. The usual architectural and cytologic features of dysplasia (see above) are present. Occasional tumors (10-20%) form large amounts of mucin ("mucinous adenocarcinomas") and present at later stages than their non-mucinous counterparts (hence the impression of "poorer prognosis" for mucinous tumors). Exuberant fibroblastic stromal response to invasive tumor produces firm fibrous ("scirrhous") tissue containing invasive cancer. This tissue response is usually called *desmoplastic response*. Colorectal carcinomas invade through the wall of the colon into the pericolonic tissue, with lymphatic and venous spread to local and distant sites. Diffuse peritoneal spread may be seen in mucinous tumors. Several different systems have been proposed for staging of CRC. For decades, Dukes' classification scheme which was originally introduced in 1932, was the standard. Currently, the TNM (Tumor, Nodes, Metastases) system adopted by the American Joint Commission on Cancer and modification of Dukes' scheme are in common use. Essentially all of these staging systems are meant to be predictive of survival, and all are based on (1) depth of tumor invasion into the wall, (2) status of lymph nodes, and (3) metastases. The Astler-Coller modification of Dukes' is in common use, and is presented here as an example (Table 2).

Symptoms and signs of colonic adenocarcinoma include bleeding (occult or gross red blood), anemia, obstruction, and less commonly symptoms from extracolonic spread. Diagnosis is confirmed by radiology, colonoscopy, and biopsies. Serological test for carcinoembryonic antigen (CEA) may be of use as a screening test for *recurrence* of colon adenocarcinoma in patients whose tumors was originally accompanied by elevated CEA levels. False positives occur in patients with hepatic cirrhosis and renal failure, and in some patients with non-colonic carcinomas (e.g., ovarian).

Table 2: Astler-Coller Staging of Colorectal Adenocarcinomas*

Stage	Definition	% 5-year Survival
A	Tumor limited to mucosa	100
B1	Tumor extending into muscularis propria but not penetrating it; negative lymph nodes.	67
B2	Tumor penetrating through muscularis propria; negative lymph nodes.	54
C1	Tumor extending into muscularis propria but not penetrating it; positive lymph nodes.	43
C2	Tumor penetrating through muscularis propria; positive lymph nodes.	23

Therapy for CRC is radical surgery with removal of draining lymph nodes. Adjuvant radiation and chemotherapy may be used depending on the stage and resectability of the tumors. Best prognosis is for low-stage tumors that are confined to the colonic wall (up to 80% five-year survival).

D. GASTRIC ADENOCARCINOMA

In the US, incidence of gastric carcinoma has been steadily decreasing for the past 50 years. The decline is probably due to environmental (dietary) factors. The incidence in the US seems to have leveled off at the present. On the contrary, in Japan, Chile and the Scandinavian countries, this tumor is very common, with an incidence 4-5x that in this country. Gastric carcinomas are rare in Africa.

Until recently in the US, males were more often affected than females (approximately 2 males:1 female), tumor has been rarely detected before age 50, with a peak incidence of 50-70 years. This pattern has been recently changing, with more tumors being detected in females, at younger age, and of poor differentiation. This change possibly is the consequence of the decline of other better-differentiated types of gastric carcinomas.

Etiologic factors for gastric carcinoma include:

- a. *Dietary carcinogens*: The role of high dietary levels of polycyclic hydrocarbons is under question. These compounds have been used experimentally to induce gastric carcinomas, and are present in large amounts in smoked meat and fish, foods extensively consumed in many of the countries with a high incidence of gastric carcinoma.
- b. *Familial tendency*: Relatives of patients with gastric carcinoma have up to a 4x greater risk of developing gastric cancer than relatives in non-cancer families. It is unclear if this tendency is genetic or environmental (same dietary exposures).
- c. *Chronic inflammatory lesions* possibly or probably associated with gastric carcinoma:
 - Gastric atrophy-intestinal metaplasia-pernicious anemia
 - Menetrier's disease in adults (probability based on retrospective data only)
 - Recurrent hyperplastic polyps (cancers elsewhere in stomach)
 - Adenomas (cancers elsewhere in stomach and within adenomas)
 - Chronic enterogastric reflux in gastroenteric anastomoses (Billroth procedures)

The majority of gastric tumors are presumably derived from the neck mucous cells, the regenerative population of the gastric epithelium. Tumors may arise *de novo* or be associated with intestinal

metaplasia. The most common microscopic classification (Lauren classification) divides tumors into two major categories:

1. **Intestinal type**, with gland formation and precursor stage of dysplasia; arises from metaplastic mucosa; is the type with declining incidence in Western countries.
2. **Diffuse type**, with single tumor cells often in a *signet ring* form; arises directly from surface-foveolar cells, and is not associated with known environmental factors. This type is more common in females, and presents at younger ages, frequently in the distal stomach.

Grossly, the majority of gastric carcinomas occur in the antral-pyloric region (>50%); followed by lesser curvature (12-25%); cardia (10-30%); and diffuse (7%). Tumor size and gross appearance is extremely variable. Tumors may be polypoid and superficial; ulcerating; or diffusely infiltrating ("linitis plastica" type; usually transmural and poorly-differentiated with signet ring cells).

Gastric adenocarcinomas are highly aggressive lesions with potential for widespread extension in the following forms:

- Direct spread from stomach to pancreas, liver, esophagus (mucosal and subserosal), and duodenum (subserosal)
- Lymphatic spread to regional and more distant nodes in 70 to 90% (may involve left supraclavicular lymph nodes via thoracic duct spread (Virchow's node))
- Venous spread to liver (35%). Other metastatic sites: lungs, adrenal, bone
- Peritoneal involvement with pelvic nodules
- Metastases into ovaries, with a desmoplastic ovarian response (These lesions called *Krukenberg tumors* of the ovary; were originally described in association with gastric tumors, but now documented to occur with other GI tract malignancies. Activation of ovarian stromal cells may result in endocrine dysfunction.)

Symptoms related to the primary tumor include pain; bleeding; and features of gastric obstruction (with pyloric lesions). However, the primary may be "silent," and symptoms may develop late and be related to metastatic disease including abnormal liver function, ovarian masses, palpable lymph nodes, and weight loss.

Diagnosis is based on x-ray studies; biopsy of lesions; and gastric cytology (brushings of lesions). The mainstay of therapy is surgical excision, but prognosis is poor because so many tumors are discovered in an advanced state of spread. Tumors are not very responsive to radiation therapy or current chemotherapy regimens.

Prognosis is poor. At initial evaluation, only about 40% of patients are potentially resectable for cure. Overall 5-year survival is about 15%. The more extensive the carcinoma, the worse the prognosis. Medical goal is to detect more early carcinomas and thereby improve prognosis. So called "*early gastric carcinoma*" is confined to mucosa and submucosa, with a much improved prognosis (approximately 90% 5-year survival). It accounts for 1/3 of gastric cancers in Japan (related to high frequency of tumor and high index of suspicion, resulting in widespread screening programs).

E. ESOPHAGEAL ADENOCARCINOMA

Adenocarcinoma is the second major form of esophageal carcinoma. The overall incidence of adenocarcinoma is less than squamous cell carcinoma worldwide, but in the distal esophagus adenocarcinoma approaches 50% of esophageal carcinomas in some reports, with an alarming rate of increase in its incidence in the United States in the past few decades.

Primary adenocarcinoma of the esophagus arises mostly from Barrett's mucosa, which is a complication of chronic reflux esophagitis. Of interest, it has been suggested that adenocarcinomas arising in Barrett's mucosa and in the proximal stomach may have similar pathogenesis. In fact, the latter group may include tumors arising from "short-segment" Barrett's, i.e., Barrett's involving <0.5-2 cm of the distal esophagus, and therefore obliterated by the developing tumor.

Microscopically, esophageal adenocarcinomas are similar to adenocarcinomas arising in other sites, and are comprised of invasive gland-forming/mucin-producing neoplastic cells. Macroscopic features, mode of invasion, clinical features and outcome similar to squamous tumors. To detect lesions at an earlier and curable phase, it has been recommended that patients at high risk (such as those with Barrett's esophagus) have periodic surveillance with endoscopy and mucosal biopsy.

F. ESOPHAGEAL SQUAMOUS CELL CARCINOMA

About 8000 new cases of esophageal carcinoma occur each year in USA, accounting for 6% of all GI malignancies. Diagnosis carries a high mortality rate. Squamous cell tumors represent approximately 50% of carcinomas of the distal esophagus, and over 90% of those in the rest of the esophagus. There is a much greater incidence of squamous carcinoma in parts of Africa, Iran and China.

Over two-thirds of the squamous carcinomas occur in the mid- and distal parts of the esophagus. The M:F ratio is 4:1, and peak age of diagnosis 55-65 years. Predisposing factors include alcohol and tobacco abuse, corrosive esophagitis and stricture, and achalasia. Tumors in the post-cricoid region (proximal esophagus) have distinctly different epidemiologic factors with sex ratio of 1 male/10 females, and peak age of onset 40-50 years. A predisposing factor is Plummer-Vinson Syndrome (iron deficiency anemia, hypochlorhydria, esophageal webs).

Grossly, these tumors form polypoid or ulcerative (more common) masses. Histologic differentiation is highly variable and of no prognostic significance. Prognosis depends on stage, i.e., degree of mural invasion and nodal or distant metastasis.

Initial presenting symptoms are GI bleeding and dysphagia; later, there is progressive weight loss and emaciation. Diagnosis is by x-ray and endoscopy with biopsy and/or cytology. When symptoms appear, most patients have advanced tumors, and survival rate is less than 10% at 5 years. Therefore, patients with predisposing conditions should receive periodic examination to detect earlier lesions of dysplasia or superficial carcinoma. This has proven a successful strategy in high incidence areas such as China.

G. NEUROENDOCRINE TUMORS (CARCINOID TUMOR)

Neuroendocrine tumors arise from neuroendocrine cells of the gastrointestinal mucosa, and may be found throughout the digestive tract or in its embryological derivatives, such as the tracheobronchial tree or the gallbladder. It takes years for malignant behavior to be expressed, and so these tumors have been described as "malignancies in slow motion," hence the term "carcinoma-like" or "carcinoid." However, carcinoids can behave like and histologically resemble more aggressive GI adenocarcinomas, so firm conclusions about biologic behavior cannot be drawn.

Neuroendocrine tumors are relatively uncommon compared to other mucosal tumors, and there are no known predisposing factors. The most common sites of occurrence are appendix (35%) and ileum (20%). Appendiceal carcinoids are generally small nodules 1-2 cm in diameter. Extra-appendiceal carcinoids usually appear as small, round or plaque-like submucosal elevations 4-5 cm in diameter with generally intact overlying epithelium. Multiple primaries are found in 20-30% of patients. Nodules are yellow-gray on cut surface. Appendiceal carcinoids rarely metastasize, whereas extra-appendiceal carcinoids may be biologically malignant with distant metastases (about 20% of ileal tumors).

Microscopically, both benign and malignant tumors have similar appearances: solid nests and/or trabecular cords of regular cells with finely granular ("salt & peppery") nuclear chromatin. Biologic aggressiveness is determined by evidence of mural invasion, and lymphatic or vascular spread. Tumors show variable positive staining by silver salts (hence the term "argentaffinomas"). Appendiceal tumors are frequently incidental findings at appendectomy, although tumors may present with occult blood loss. Clinical work-up includes radiological studies (BE, UGI with SBFT) and colonoscopy, as well as urine chemical tests (see below).

Carcinoid Syndrome develops with malignant carcinoids that have liver metastases. Tumors produce 5-hydroxy-tryptamine (serotonin) which is secreted in the urine as 5-hydroxyindole acetic acid (5-HIAA). Tumors may also produce histamine, kinins, etc. These substances are normally detoxified in the liver, but with extensive hepatic metastases there is (1) direct entrance of these metabolites into the hepatic veins from the tumor, and (2) loss of functioning hepatic cells for detoxification. Clinical features of the syndrome, which may be caused by serotonin or by other metabolites, include:

- Flushing of the skin: spontaneous or induced by exertion or motion
- Diarrhea
- Bronchoconstriction
- Fibrous thickening of right heart endocardial surfaces, especially of the pulmonary and tricuspid valves. This will result in right heart failure primarily due to pulmonic stenosis and tricuspid insufficiency. The left heart is normally protected because metabolites are detoxified by passage through the lungs.

II. NON-EPITHELIAL TUMORS

A. LYMPHOMAS

Lymphomas are neoplasms of lymphoid tissue that arise in lymph nodes (nodal lymphomas) or in other sites (extra-nodal lymphomas) such as the gastrointestinal tract. Two broad categories of lymphoma are *Hodgkin's Disease (HD)* and *Non-Hodgkin's Lymphoma (NHL)*. Gastrointestinal involvement by HD is rare, and will not be discussed here. The GI tract may be secondarily involved in up to 70% of patients who die of primary nodal NHL. In the Western countries, primary GI NHL has an incidence of approximately 1 in 100,000 people, and accounts for 4-20% of all NHLs and 30-45% of extra-nodal NHLs. The median age at presentation is ~50 years, and approximately 25% of cases occur in patients older than 60 years of age. Symptoms are related to hemorrhage (ulceration through surface mucosa), obstruction, and/or perforation. Overall 5-year survival is about 60%.

Stomach is the most common site of involvement (50% of cases), followed by the small intestine (40%) and colon (10%). Essentially all primary GI lymphomas are B cell type, with the important exception of Enteropathy-Associated T Cell Lymphoma which is seen as a complication of long-standing celiac disease. The other distinctive type of gastrointestinal lymphoma is the *Mucosa-Associated Lymphoid Tissue Lymphoma* (or MALToma). MALTomas can develop anywhere in the GI tract, but the most common are gastric MALTomas in the setting of longstanding *Helicobacter pylori* infection. Low-grade

gastric MALTomas can potentially be treated simply by eradication of *H. pylori* infection, but high-grade neoplasms require chemotherapy.

B. GASTROINTESTINAL STROMAL TUMORS

Gastrointestinal Stromal Tumors (GISTs) are spindle-cell neoplasms that are thought to arise from the intrinsic pacemaker cells of the gastrointestinal wall, the interstitial cells of Cajal. Small GISTs are usually benign. Larger stromal tumors may behave in a malignant fashion despite their benign cytologic features. It is best to regard any stromal tumor larger than ~5 cm (in any part of the GI tract) as "potentially" malignant. Other histopathological features that favor malignancy in a stromal tumor include increased mitoses and areas of hemorrhage/necrosis within the tumor mass.

Benign smooth muscle tumors, or leiomyomas, may occur at any level of the GI tract but are most common in the esophagus, stomach, and rectum. They may project into the lumen causing overlying mucosal ulceration and hemorrhage, or obstruction if located in narrowed zone such as cardia or pylorus.

III. OTHER TUMORS

Adenocarcinomas of small intestines are very uncommon and difficult to detect early, and thus have typically penetrated bowel wall, invaded mesentery or other bowel segments, spread to regional lymph nodes or sometimes metastasized more widely at the time of diagnosis. "En bloc" excision offers best chance for cure. Subgroup of adenocarcinomas or adenomas of ampulla of Vater require pancreatectomy (Whipple's procedure) for removal.

Tumors of the Anal Canal include benign inflammatory polyps (skin tags); rare but aggressive squamous cell carcinomas that show early spread to inguinal lymph nodes; and rare adenocarcinomas arising from the anal glands.

Tumors of Appendix include carcinoids (see above) and adenocarcinomas. Adenocarcinomas are rare, but often diagnosed late due to hidden location. Tumor may rupture through appendiceal wall and extensively seed the peritoneal cavity. Adenocarcinomas must be distinguished from benign mucoceles of the appendix, mucosal hyperplasia and benign mucosal adenomas.

Lipomas are submucosal; chiefly in colon and ileum near ileocecal valve; benign but may cause bleeding or obstruction; usually incidental.

Vascular tumors include *angiodysplasia* which constitutes an apparently acquired non-neoplastic vascular ectasia, generally occurring in ileum and right colon. It consists of dilated racemose mucosal and submucosal vessels and arterio-venous communications. Common in elderly, and may represent a common cause of lower GI bleeding in patients over age 60.

Mesotheliomas are malignant proliferation of mesothelial lining of peritoneal serosal surfaces, which may occur in four histological forms: solid, fibrous, glandular, or diffuse. Approximately 50% of patients with peritoneal mesothelioma have history of asbestos exposure and pulmonary fibrosis. Intestinal involvement frequently leads to death from intestinal obstruction.

Kaposi's sarcoma is a malignant proliferation of endothelial cells with an associated inflammatory component. Usually presents as multiple blue-red skin nodules with occasional visceral spread, but may present as GI primary, with blue-red mucosal or submucosal nodules which bleed easily. Once extremely rare, now seen more frequently in association with acquired immunodeficiency syndrome.

Selected Additional Reading:

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5. Ransohoff DF, Sandler RS. Screening for colorectal cancer. *N Engl J Med* 2002;346:40-44.
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9. Haggitt RC. Adenocarcinoma in Barrett's esophagus: a new epidemic? *Hum Pathol* 1992; 23:475-476.
10. Allen JW, Richardson JD, Edwards MJ. Squamous cell carcinoma of the esophagus: a review and update. *Surg Oncol* 1997; 6:193-200.
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12. Isaacson PG. Gastrointestinal lymphoma. *Hum Pathol* 1994; 25:1020-1029
13. Harris NL et al. A Revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994; 84:1361-1392.