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# Gastrointestinal Cancer

Foreword by James L. Abbruzzese, MD,
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With 61 Illustrations

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# FOREWORD

Cancers of the gastrointestinal tract remain a major challenge for oncologists and other cancer specialists in the United States and worldwide. This volume on the evaluation and treatment of patients with gastrointestinal malignancies represents an important milestone in the M. D. Anderson Cancer Center Series on the multidisciplinary management of cancer. Gastrointestinal cancers exemplify the importance of multidisciplinary management in modern oncologic care. Contributors to the management of patients with the spectrum of diseases that emanate from the gastrointestinal tract include pathologists, radiologists, surgical oncologists, radiation oncologists, medical oncologists, and others. It is the close interaction and interplay between these highly trained specialists that result in the improving care of patients with these challenging diseases. In the following chapters, gastrointestinal oncology specialists at M. D. Anderson Cancer Center describe the state of the art in the multidisciplinary management of diseases developing from all parts of the gastrointestinal tract.

Increasingly, we are recognizing that many gastrointestinal malignancies have a strong inherited component. In many cases, the early recognition of patients at high risk for specific preneoplastic processes involving the gastrointestinal tract—such as Barrett's esophagus and colonic polyposis—represents an important opportunity to prevent the emergence of neoplasia. Optimizing prevention strategies remains our best hope for eradicating gastrointestinal cancers as an important cause of cancer-related deaths in the United States.

Each of the malignancies discussed in the 20 chapters of this monograph has specific highly unique features. Tailored to the unique natural history of each malignancy, the management of these diseases varies considerably. Despite the progress being made, a great deal of work remains to be done to understand the basic molecular biology of gastrointestinal malignancies. It is this knowledge that will be crucial for the development of new therapeutics and new opportunities for screening and early diagnosis for gastrointestinal cancers. We believe that readers of this volume will be impressed at the dramatic improvements that are being made with these difficult cancers.

*James L. Abbruzzese, MD*
*Raphael E. Pollock, MD, PhD*

# Series Preface

As a group, gastrointestinal-tract cancers are the second most common cancers among males and females in the United States. The most dominant is colorectal cancer; remarkably, only a small proportion of people nationwide receive adequate screening for this malignancy. Patients with gastrointestinal-tract cancers are benefiting from a multidisciplinary treatment approach. For example, multidisciplinary collaboration has enabled sphincter preservation in rectal cancer. The interdisciplinary approach is also yielding favorable results for the more difficult tumors, such as pancreatic cancer and liver cancer. We are seeing the advantages of early systemic therapy as an adjunct to surgery in colorectal cancer, and novel agents are showing improved results in advanced disease. Increased utilization of adjuvant therapy in early disease could very well change the natural history of gastrointestinal-tract malignancies such as colorectal cancer.

Much effort has been put into this 20-chapter volume. We would like to thank the volume editors, Drs. Jaffer Ajani, Steven Curley, Nora Janjan, and Patrick Lynch, for their steadfast efforts in bringing this book to fruition. Also, sincere thanks to Mariann Crapanzano, Stephanie Deming, Ginny Norris, Michael Worley, and Chris Yeager of the Department of Scientific Publications for editing and compiling this volume.

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# 1 Staging of Gastrointestinal Malignancies

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## Chapter Overview

Clinical and pathologic staging of gastrointestinal malignancies is critically important in the planning of neoadjuvant, adjuvant, and multidisciplinary treatment programs. This chapter describes the approach at M. D. Anderson Cancer Center to the clinical staging of cancers arising in the stomach, liver, biliary system, pancreas, colon, and rectum. Emphasis is placed on our use of state-of-the-art diagnostic modalities, including endoscopic ultrasonography, computed tomography, and magnetic resonance imaging. Accurate staging in patients with gastrointestinal malignancies assists us in identifying patients who are most likely to benefit from multimodality therapy.

## Introduction

Gastrointestinal (GI) malignancies are a heterogeneous group of diseases that must be segregated by organ of origin, histologic type, and stage at presentation when the clinician considers appropriate treatment modalities. Despite impressive advances in the equipment and software used in diagnostic radiology and the development of improved diagnostic

imaging modalities, a complete history and physical examination are still critical in the evaluation and follow-up staging of GI malignancies. Taken as a group, GI malignancies are the most common type of human solid cancer worldwide. However, the incidence varies dramatically from organ to organ within the GI system. Even within a single organ site in the GI system, the incidence can be highly variable because of population, geographic, and environmental differences. Complete clinical staging of GI malignancies is the first important step in assessing new patients, developing a treatment plan, and designing new protocol-based therapies at M. D. Anderson Cancer Center.

## Gastric Cancer

Gastric adenocarcinoma is one of the most common human solid tumors worldwide. In the United States, approximately 25,000 people are diagnosed annually with gastric adenocarcinoma. We see approximately 300 patients with newly diagnosed gastric cancer yearly at M. D. Anderson.

The symptoms related to gastric cancer are typically vague and long-standing in many patients. Thus, advanced-stage disease is diagnosed in a significant proportion of patients. Esophagogastroduodenoscopy is considered the standard of care in the evaluation of patients with new or worsening symptoms of epigastric pain, gastroesophageal reflux, early satiety, or unremitting nausea and vomiting. A Clo test is performed on gastric aspirates to determine the presence of *Helicobacter pylori* infection. Any suspicious mass lesion, areas of inflammation, or edges of ulcers are biopsied to assess for the presence of malignant disease.

The history obtained from a new gastric cancer patient includes symptoms, risk factors, and family history. During the physical examination, evidence of advanced-stage disease can be found in the form of a palpable epigastric mass or a nodule located in the periumbilical region (Sister Mary Joseph's node) or supraclavicular region (Virchow's node) or on digital rectal examination (Blummer's shelf). Lymphatic regions in the neck, supraclavicular, and infraclavicular regions are thoroughly examined, and suspicious lymph nodes are biopsied by fine-needle aspiration.

At M. D. Anderson, the diagnostic evaluation includes initial laboratory tests, including a complete blood cell count (CBC), liver function studies, and measurement of serum electrolytes. Baseline serum tumor markers, carcinoembryonic antigen and carcinoma antigen 125, are measured and then followed serially during treatment and follow-up. Standard 2-view chest radiographs are evaluated for the presence of pulmonary metastasis. Chest computed tomography (CT) is performed only in patients with abnormal results on standard chest radiography or with gastroesophageal junction tumors to assess extent of disease. Helical

CT of the abdomen and pelvis is performed in all patients to evaluate the stomach, regional lymph nodes, liver, and peritoneal cavity.

Esophagogastroduodenoscopy with endoscopic ultrasonography (EUS) is now a routine component of our staging in new patients with gastric cancer. At M. D. Anderson, we follow the American Joint Committee on Cancer (AJCC) staging guidelines (Table 1–1). EUS is extremely useful in determining the T classification of the tumor and may be helpful in assessing the presence of regional lymph node metastases. State-of-the-art EUS endoscopes are equipped with biopsy channels that can be used to perform needle aspiration biopsies of the stomach wall or of lymph nodes adjacent to the stomach.

Subclinical peritoneal spread (carcinomatosis) of gastric adenocarcinoma may not be diagnosed by high-quality CT or EUS. Because of this limitation, surgeons at M. D. Anderson routinely employ staging laparoscopic evaluation in patients with potentially resectable gastric carcinoma. Staging laparoscopy is generally the final staging procedure in gastric cancer patients who are thought to be surgical candidates with stage II or III disease. A finding of peritoneal carcinomatosis diagnoses stage IV disease, and the patient is considered for systemic rather than surgical therapy.

## Hepatobiliary Malignancies

Physicians and physician assistants in the GI Tumor Center at M. D. Anderson evaluated more than 900 new patients with primary or metastatic hepatobiliary tumors in 2002. Patients with primary liver cancer include those with hepatocellular carcinoma (HCC), gallbladder cancer, and intrahepatic or extrahepatic cholangiocarcinoma. Patients with liver metastases from other organ sites, most commonly colorectal adenocarcinoma, and with disease confined to the liver may be considered for surgery, tumor ablation, regional chemotherapy, or systemic chemotherapy. The initial screening evaluation of new patients includes a thorough review of outside medical records, pathologic assessment of any surgical or needle-biopsy specimens, and review of prior diagnostic CT scans and plain radiographs. Once again, a thorough history and physical examination are mandatory. In patients with liver metastases, recent assessment of the primary site of disease, such as colonoscopy for colorectal cancer, is critical to exclude local recurrence. The history also includes an evaluation of risk factors, such as chronic hepatitis B or C virus infection in patients with HCC, and a family history. While family history is not a component of staging of malignant disease, it is an important component of the mission at M. D. Anderson to evaluate and diagnose early-stage, treatable malignant disease. The physical examination focuses on assessment of accessible lymph node basins, cardiopulmonary examination to determine

**Table 1–1. Stage Grouping for Gastric Cancer**

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage 1A | T1 | N0 | M0 |
| Stage 1B | T1 | N1 | M0 |
| | T2a/b | N0 | M0 |
| Stage II | T1 | N2 | M0 |
| | T2a/b | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T2a/b | N2 | M0 |
| | T3 | N1 | M0 |
| | T4 | N0 | M0 |
| Stage IIIB | T3 | N2 | M0 |
| Stage IV | T4 | N1–3 | M0 |
| | T1–3 | N3 | M0 |
| | Any T | Any N | M1 |

**Definition of TNM**

***Primary Tumor (T)***

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ*: intraepithelial tumor without invasion of the lamina propria |
| T1 | Tumor invades lamina propria or submucosa |
| T2 | Tumor invades muscularis propria or subserosa* |
| T2a | Tumor invades muscularis propria |
| T2b | Tumor invades subserosa |
| T3 | Tumor penetrates serosa (visceral peritoneum) without invasion of adjacent structures**, *** |
| T4 | Tumor invades adjacent structures**, *** |

* *Note:* A tumor may penetrate the muscularis propria with extension into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures. In this case, the tumor is classified T2. If there is perforation of the visceral peritoneum covering the gastric ligaments or the omentum, the tumor should be classified T3.

** *Note:* The adjacent structures of the stomach include the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, and retroperitoneum.

*** *Note:* Intramural extension to the duodenum or esophagus is classified by the depth of the greatest invasion in any of these sites, including the stomach.

***Regional Lymph Nodes (N)***

| | |
|---|---|
| NX | Regional lymph node(s) cannot be assessed |
| N0 | No regional lymph node metastasis* |
| N1 | Metastasis in 1 to 6 regional lymph nodes |
| N2 | Metastasis in 7 to 15 regional lymph nodes |
| N3 | Metastasis in more than 15 regional lymph nodes |

* *Note:* A designation of pN0 should be used if all examined lymph nodes are negative, regardless of the total number removed and examined.

***Distant Metastasis (M)***

| | |
|---|---|
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

suitability for surgery and cytotoxic chemotherapy, an abdominal examination to measure palpable organomegaly or extrahepatic masses, a rectal examination for gross or occult blood, and an evaluation for clinical stigmata of chronic liver disease.

Laboratory evaluation includes a CBC, coagulation profile, liver function tests, electrolytes, and serum tumor markers when appropriate. Serum carcinoembryonic antigen levels are measured in patients with colorectal cancer liver metastases, serum alpha fetoprotein levels are measured in HCC patients, carcinoma antigen 19-9 levels are measured in patients with gallbladder cancer and cholangiocarcinoma, and serum hormone or urinary metabolite levels are measured in patients with neuroendocrine-tumor liver metastases. A 2-view chest radiograph is obtained to evaluate for pulmonary metastasis, with chest CT reserved for patients with abnormal findings on chest radiographs. Helical 3-phase liver protocol CT has become our standard to accurately measure the number, size, and intrahepatic site of primary and metastatic hepatic tumors. The advantage of this type of CT is the speed of information acquisition (less than 45 seconds). The 3 phases of the scan are an early arterial phase after a bolus intravenous administration of iodinated contrast, a portal venous phase, and a delayed phase. Hypervascular lesions, such as HCC or neuroendocrine metastases, are demonstrated nicely in the arterial phase because of the vascular enhancement of the tumor with minimal hepatic parenchymal enhancement. Less vascular lesions, such as metastatic adenocarcinoma or cholangiocarcinoma, are more distinct during the portal phase of the CT scan, as the contrast enhancement of the normal hepatic parenchyma is greater than that of the tumor tissue. The high resolution of this helical high-speed scan also permits 3-dimensional reconstruction of intrahepatic biliary and vascular structures, volumetric determination of tumor volume and of the volume of liver that would remain after hepatic resection, and assessment of regional lymph node involvement by tumor.

By definition, patients with liver metastases from other organs have stage IV disease, and their assessment focuses on determining suitability of surgical or regionally directed therapies. Patients with liver metastases and extrahepatic malignant disease are treated with suitable systemic or protocol-based therapy. The AJCC staging system is employed for patients with HCC (Table 1–2), gallbladder cancer (Table 1–3), and bile duct cancer (cholangiocarcinoma, Table 1–4). The sequence and timing of surgical, medical, and radiation treatment modalities are based on the stage of disease and the severity of any coexistent chronic hepatic dysfunction.

**Table 1–2. Stage Grouping for Hepatocellular Cancer**

| | | | |
|---|---|---|---|
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage IIIA | T3 | N0 | M0 |
| IIIB | T4 | N0 | M0 |
| IIIC | Any T | N1 | M0 |
| Stage IV | Any T | Any N | M1 |

**Definition of TNM**

***Primary Tumor (T)***

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Solitary tumor without vascular invasion |
| T2 | Solitary tumor with vascular invasion or multiple tumors none more than 5 cm |
| T3 | Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s) |
| T4 | Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum |

***Regional Lymph Node(s)***

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

***Distant Metastasis (M)***

| | |
|---|---|
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |



## Pancreatic Cancer

Cancer of the pancreas is the fifth leading cause of cancer death in the United States. Almost 30,000 new patients will be diagnosed with pancreatic cancer in 2003, and at least 28,000 of these individuals will die of the disease. Because there are no proven or standardized laboratory or radiologic diagnostic tests for pancreatic carcinoma, most patients present with locally advanced or metastatic disease. The patients with the highest probability of long-term survival are those who present with AJCC early-stage disease (Table 1–5). This translates into cancer localized to the pancreas that can be resected completely, with no regional nodal, peritoneal, or liver metastases. Unfortunately, fewer than 10% of patients diagnosed with pancreatic adenocarcinoma present with surgically treatable disease.

The rapid onset of jaundice is the most frequent complaint of patients with pancreatic-head cancers. Patients with tumors originating in the body or tail of the pancreas may present with abdominal or back pain or with upper GI bleeding from splenic vein thrombosis and resultant gastric

**Table 1–3. Stage Grouping for Gallbladder Cancer**

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage 1A | T1 | N0 | M0 |
| Stage 1B | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage III | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

**Definition of TNM**

***Primary Tumor (T)***

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor invades lamina propria or muscle layer |
| T1a | Tumor invades lamina propria |
| T1b | Tumor invades muscle layer |
| T2 | Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver |
| T3 | Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, or pancreas, omentum or extrahepatic bile ducts |
| T4 | Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures |

***Regional Lymph Nodes (N)***

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

***Distant Metastasis (M)***

| | |
|---|---|
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |



varices. Patients with locally advanced pancreatic-head tumors may also present with symptoms of gastric outlet obstruction or upper GI bleeding from tumor invasion into the duodenum. Once again, clinical staging at M. D. Anderson begins with a thorough history and physical examination. A routine 2-view chest radiograph and laboratory tests including a CBC, coagulation profile, liver function tests, and serum electrolytes are obtained. A helical, thin-section CT scan is obtained; a multiphase study is performed to obtain arterial contrast phase, venous contrast phase, and delayed-phase images. Pancreatic adenocarcinoma appears as a hypodense mass within the pancreas compared with the normally perfused pancreatic parenchyma. The more uncommon pancreatic islet cell tumors

**Table 1–4. Stage Grouping for Extrahepatic Bile Duct Cancer**

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage 1A | T1 | N0 | M0 |
| Stage 1B | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage IIII | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |
| | T4 | N0 | M0 |

**Definition of TNM**

***Primary Tumor (T)***

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ* |
| T1 | Tumor confined to the bile duct histologically |
| T2 | Tumor invades beyond the wall of the bile duct |
| T3 | Tumor invades the liver, gallbladder, pancreas, and/or unilateral branches of the portal vein (right or left) or hepatic artery (right or left) |
| T4 | Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall |

***Regional Lymph Nodes (N)***

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

***Distant Metastasis (M)***

| | |
|---|---|
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |



are hypervascular lesions that appear as enhancing tumors within the pancreas on the initial arterial phase that is obtained immediately after bolus intravenous administration of iodinated contrast. The high-resolution CT scan is critical for evaluating the local extent of tumor with invasion into the superior mesenteric or portal vein, the superior mesenteric artery, the base of the mesentery, or the duodenum and for evaluating evidence of lymph node, peritoneal, or liver metastases.

EUS has become a standard part of our staging evaluation in patients who are considered possible surgical candidates. Pancreatic adenocarcinomas and islet cell tumors can be visualized ultrasonographically in most patients, and the tumor association with the common bile duct, portal

**Table 1–5. Stage Grouping for Exocrine Pancreatic Cancer**

| | | | |
|---|---|---|---|
| Stage 0 | Tis | N0 | M0 |
| Stage 1A | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T3 | N0 | M0 |
| Stage IIB | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N1 | M0 |
| Stage III | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

**Definition of TNM**

***Primary Tumor (T)***

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma *in situ** |
| T1 | Tumor limited to the pancreas, 2 cm or less in greatest dimension |
| T2 | Tumor limited to the pancreas, more than 2 cm in greatest dimension |
| T3 | Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery |
| T4 | Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor) |

***Regional Lymph Nodes (N)***

| | |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |

***Distant Metastasis (M)***

| | |
|---|---|
| MX | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |



vein, and superior mesenteric artery can be assessed. As in cases of gastric cancer, suspicious peripancreatic lymph nodes can be visualized with EUS and biopsied under ultrasonographic guidance using the fine-needle aspiration biopsy channel of the endoscope.

In the past at M. D. Anderson, patients who were considered candidates for resection had their disease staged laparoscopically prior to initiation of neoadjuvant chemoradiation therapy. This served to exclude the presence of subclinical carcinomatosis and to stage the liver with laparoscopic ultrasonography. It was also possible to place a feeding jejunostomy tube with laparoscopic guidance to provide nutritional support for patients during chemoradiation therapy. However, current protocols for neoadjuvant chemoradiation therapy for potentially resectable pancreatic adenocarcinoma at M. D. Anderson use a shorter course of 2–3 weeks of

treatment, and laparoscopy is reserved for selected patients with suspicious findings on CT scans. The Pancreatic Cancer Treatment Group at M. D. Anderson has demonstrated that state-of-the-art preoperative imaging studies can accurately predict the local extent of disease and identify patients who will be candidates for a margin-negative resection.

Patients with pancreatic islet cell tumors have their disease staged with helical pancreas protocol CT scans and EUS. CT- or EUS-guided biopsy of the pancreatic tumor is critical in distinguishing a neuroendocrine from a pancreatic exocrine tumor. A thorough clinical history is obtained to determine symptoms possibly related to excess hormone secretion, and the physical examination focuses on signs related to endocrine syndromes. A family history to detect familial neuroendocrine tumor syndromes, such as multiple endocrine neoplasia or Von Hippel-Lindau syndrome, is obtained. Serum levels of pancreatic peptides, including glucagon, insulin, gastrin, vasoactive intestinal peptide, and somatostatin, may be obtained as baseline measurements in these patients. A helical 3-phase liver protocol CT scan may also be obtained, as the liver is the most common site of distant organ metastasis.

## Colorectal Cancer

Colorectal adenocarcinoma is the second most common cause of cancer death in the United States, and patients with colon and rectal cancer form the largest single group of GI cancer patients seen at M. D. Anderson.

Presenting complaints in patients with colorectal cancer may include rectal bleeding, fatigue related to anemia, change in bowel habits, or the development of abdominal pain. A significant number of patients referred to M. D. Anderson are asymptomatic but have positive findings on a Hemoccult test on stool specimens. Complete colonoscopy is essential during the staging process to document the location of the primary tumor and to exclude the presence of synchronous premalignant polyps or additional malignant lesions. Physical examination consists of an assessment of lymph node basins, particularly the inguinal lymph nodes in patients with rectal tumors; assessment of cardiopulmonary findings; abdominal examination; and digital rectal examination. Patients with rectal tumors may also undergo rigid proctoscopy at the initial evaluation to determine the location and extent of tumor within the rectum, degree of luminal compromise by the tumor, and evidence of tumor invasion or fixation to pelvic structures.

Most patients referred to M. D. Anderson with colorectal cancer have already undergone CT of the abdomen and pelvis or magnetic resonance (MR) imaging after the diagnosis. Patients with colon cancer may not require a preoperative CT scan, although it can be useful in demonstrating a locally advanced (T4) tumor in the ascending, transverse, or sigmoid colon that involves adjacent structures or organs (Table 1–6). Patients with

**Table 1–6. Stage Grouping for Colon and Rectal Cancer**

| *Stage* | *T* | *N* | *M* | *Dukes** |
|---|---|---|---|---|
| Stage 0 | Tis | N0 | M0 | — |
| Stage I | T1 | N0 | M0 | A |
| | T2 | N0 | M0 | A |
| Stage IIA | T3 | N0 | M0 | B |
| Stage IIB | T4 | N0 | M0 | B |
| Stage IIIA | T1–T2 | N1 | M0 | C |
| Stage IIIB | T3–T4 | N1 | M0 | C |
| Stage IIIC | Any T | N2 | M0 | C |
| Stage IV | Any T | Any N | M1 | — |

* Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any T N1 M0 and Any T N2 M0).

**Definition of TNM**

***Primary Tumor (T)***

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*: intraepithelial or invasion of lamina propria*
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissues
T4 Tumor directly invades other organs or structures, and/or perforates visceral peritoneum**, ***

* *Note:* Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.
** *Note:* Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum.
*** Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

***Regional Lymph Nodes (N)***

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

*Note:* A tumor nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

***Distant Metastasis (M)***

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

## KEY PRACTICE POINTS

- Esophagogastroduodenoscopy is considered the standard of care in the evaluation of patients with new or worsening symptoms of epigastric pain, gastroesophageal reflux, early satiety, or unremitting nausea and vomiting.
- In patients with gastric cancer, EUS is extremely useful in determining the T classification of the tumor and may be helpful in assessing the presence of regional lymph node metastases.
- Subclinical peritoneal spread of gastric adenocarcinoma may not be diagnosed by high-quality CT or EUS. Because of this limitation, surgeons at M. D. Anderson routinely employ staging laparoscopic evaluation in patients with potentially resectable gastric carcinoma.
- In patients with liver metastases from other organ sites, assessment of the primary tumor site—such as colonoscopy for colorectal cancer—is critical to exclude local recurrence prior to any liver-directed therapy.
- In patients with pancreatic cancer, high-resolution CT is critical for evaluating the local extent of tumor with invasion into the superior mesenteric or portal vein, the superior mesenteric artery, the base of the mesentery, or the duodenum and for evaluating evidence of lymph node, peritoneal, or liver metastases.
- In patients with colorectal cancer, complete colonoscopy is essential during the staging process to document the location of the primary tumor and to exclude the presence of synchronous premalignant polyps or additional malignant lesions.
- Evaluation of the local extent of disease is particularly important in rectal cancer patients as local disease extent is one of the factors that determines whether sphincter-preserving surgery may be possible.

locally advanced colon cancer at these sites can still be treated with curative surgical intent if an en bloc resection of the primary tumor and involved organs can be performed. Patients with rectal cancer routinely undergo CT of the abdomen and pelvis to assess local extent of tumor and to check for extension of tumor into adjacent pelvic structures. The abdominal CT scan in colorectal cancer patients can also help detect liver and regional lymph node metastases and occasionally provides evidence of peritoneal spread of disease. A 2-view chest radiograph is standard, with a CT of the chest limited to those patients with abnormal findings on the standard chest x-ray. Patients undergo routine laboratory evaluation with a CBC, liver function tests, serum electrolytes, and serum carcinoembryonic antigen measurement; a urinalysis is added in patients with rectosigmoid tumors.

EUS is a standard component of staging in rectal cancer patients treated at M. D. Anderson. With EUS, the ultrasonographic T classification of the tumor and extent of local invasion into the perirectal fat or adjacent structures can be assessed. Enlarged or suspicious-appearing lymph nodes (N classification) can be identified in the mesorectum and biopsied through the biopsy channel of the EUS scope. The evaluation of local extent of disease (T and N classifications) is particularly important in rectal cancer patients. A significant proportion of rectal cancer patients evaluated at M. D. Anderson undergo preoperative chemoradiation therapy. Thus, presenting T classification and tumor location within the rectum are crucial factors in decisions regarding the appropriate definitive surgical procedure, including sphincter-preserving operations, in patients who may achieve marked local tumor downsizing following pelvic chemoradiation therapy.

Patients referred to M. D. Anderson for evaluation and treatment of a pelvic recurrence of rectal adenocarcinoma undergo MR imaging of the pelvis in addition to CT and laboratory assessment to exclude distant metastatic disease. MR imaging permits detailed axial, sagittal, and coronal views of pelvic organs in relation to recurrent tumor and more accurately delineates postsurgical and postirradiation scarring from local tumor recurrence. Emphasis is placed on MR-imaging-based evidence of contiguous organ, sciatic nerve, blood vessel, and sacral involvement in order to assess resectability and to inform the patient of the nature of a potential resection.

# 2 Recent Advances in Histopathology of Gastrointestinal Cancers: Prognostic and Therapeutic Assessment of Colorectal Cancers

*Asif Rashid*



## Chapter Overview

The genetics and molecular biology, precursor lesions and predisposing conditions, and hereditary syndromes of gastrointestinal cancers, especially colorectal cancers, are well characterized. Fifteen to twenty percent

of sporadic colorectal carcinomas have microsatellite instability (MSI; replication-error phenotype), characterized by defective DNA repair resulting in alterations of short tandem repeat sequences, including mononucleotide, dinucleotide, and tetranucleotide repeats. This is due to alteration of mismatch repair enzymes. Patients with colorectal cancers with MSI have a better prognosis than do those without. In contrast, about 50% to 60% of colorectal cancers have loss of the long arm (q) of chromosome 18, the chromosomal location of the *deleted in colorectal cancer*, *SMAD4*, and *SMAD2* genes. Chromosome 18q loss has been associated with poor outcome in patients with colorectal cancer. Growth factors and growth factor receptors play a major role in the development and progression of cancer. Gastrointestinal cancers express epidermal growth factor receptor (EGFR) and related receptors that activate intrinsic tyrosine kinase activity and result in signals of cell proliferation. This activity can be modulated by a variety of therapeutic options, including monoclonal antibody against EGFR or related receptors and selective inhibition of tyrosine kinase activity. Immunohistochemical analysis for EGFR can select patients who have EGFR-overexpressing gastrointestinal cancer and thus are potential candidates for anti-EGFR therapy.

## Introduction

Among the most important recent advances in the field of gastrointestinal cancer are elucidation of the genetics of these cancers and characterization of the molecular pathways utilized by these neoplasms. This work has revolutionized many aspects of patient care, including prevention, screening, and treatment. The goal now is to identify new therapeutic targets that can be utilized for therapy and for increasing our understanding of prognosis. In cases of gastrointestinal cancer, histopathologic analysis typically provides diagnosis of predisposing conditions, information necessary for the surveillance of such conditions, and diagnosis of the type, grade, and stage of cancer. The evaluation of molecular predictors of prognosis and therapeutic response is a recent development in histopathology.

## Histopathologic Features of Gastrointestinal Cancers

Malignancies of the gastrointestinal tract can be classified histopathologically as epithelial tumors, endocrine or mesenchymal tumors, or lymphomas (Table 2–1; Hamilton and Aaltonen, 2001). Epithelial tumors can be subclassified as adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, small cell carcinoma, carcinoid tumor, or other.

**Table 2–1. Histopathologic Classification of Primary Malignant Neoplasms of the Esophagus, Stomach, and Colon and Rectum**

| *Histopathologic Classification* | *Histopathologic Subtype by Anatomic Location* | | | |
|---|---|---|---|---|
| | *Esophagus* | *Stomach* | *Small Intestine* | *Colon and Rectum* |
| Epithelial | Squamous cell carcinoma<br>Verrucous (squamous) carcinoma<br>Basaloid squamous carcinoma<br>Spindle cell (squamous) carcinoma<br>Adenocarcinoma<br>Adenosquamous carcinoma<br>Mucoepidermoid carcinoma<br>Adenoid cystic carcinoma<br>Small cell carcinoma<br>Undifferentiated carcinoma<br>Other | Adenocarcinoma<br>Intestinal type<br>Diffuse type<br>Papillary adenocarcinoma<br>Tubular adenocarcinoma<br>Mucinous adenocarcinoma<br>Signet-ring-cell adenocarcinoma<br>Adenosquamous carcinoma<br>Squamous cell carcinoma<br>Small cell carcinoma<br>Undifferentiated carcinoma<br>Other | Adenocarcinoma<br>Mucinous adenocarcinoma<br>Signet-ring-cell adenocarcinoma<br>Adenosquamous carcinoma<br>Squamous cell carcinoma<br>Small cell carcinoma<br>Medullary carcinoma<br>Undifferentiated carcinoma<br>Other | Adenocarcinoma<br>Mucinous adenocarcinoma<br>Signet-ring-cell adenocarcinoma<br>Adenosquamous carcinoma<br>Squamous cell carcinoma<br>Small cell carcinoma<br>Medullary carcinoma<br>Undifferentiated carcinoma<br>Other |
| Endocrine | Carcinoid tumor (well-differentiated endocrine neoplasm) | Carcinoid tumor (well-differentiated endocrine neoplasm)<br>Mixed carcinoid-adenocarcinoma | Carcinoid tumor (well-differentiated endocrine neoplasm)<br>Mixed carcinoid-adenocarcinoma | Carcinoid tumor (well-differentiated endocrine neoplasm)<br>Mixed carcinoid-adenocarcinoma |

| | | | | |
|---|---|---|---|---|
| Nonepithelial Mesenchymal | Gastrointestinal stromal tumor<br>Leiomyosarcoma<br>Rhabdomyosarcoma<br>Kaposi's sarcoma<br>Malignant melanoma<br>Other | Gastrointestinal stromal tumor<br>Leiomyosarcoma<br>Kaposi's sarcoma<br>Other | Gastrointestinal stromal tumor<br>Leiomyosarcoma<br>Angiosarcoma<br>Kaposi's sarcoma<br>Other | Gastrointestinal stromal tumor<br>Leiomyosarcoma<br>Angiosarcoma<br>Kaposi's sarcoma<br>Other |
| Malignant Lymphomas | | Marginal zone B-cell lymphoma of MALT type<br>Mantle cell lymphoma<br>Diffuse large B-cell lymphoma | Immunoproliferative small intestinal disease (includes α-heavy-chain disease)<br>Marginal zone B-cell lymphoma of MALT type<br>Mantle cell lymphoma<br>Diffuse large B-cell lymphoma<br>Burkitt's lymphoma<br>Burkitt's-like/atypical Burkitt's lymphoma<br>Enteropathy-associated T-cell lymphoma<br>Other | Marginal zone B-cell lymphoma of MALT type<br>Mantle cell lymphoma<br>Diffuse large B-cell lymphoma<br>Burkitt's lymphoma<br>Burkitt's-like/atypical Burkitt's lymphoma<br>Other |

Adenocarcinoma can be further subclassified as adenocarcinoma, not otherwise specified, or intestinal, signet-ring-cell, or mucinous (colloid) adenocarcinoma.

Tumor stage at the time of diagnosis is the most important factor in determining prognosis. Current TNM staging systems for gastrointestinal cancer are shown in chapter 1 (Tables 1–1 through 1–6) and chapter 15 (Tables 15–1 and 15–2). The 5-year survival rates for patients with gastrointestinal cancer differ by anatomic site and histologic subtype of cancer.

## Metastatic Carcinoma of Unknown Primary Origin

In most patients, the site of origin of a metastatic carcinoma of unknown primary origin cannot be reliably determined by light microscopy (Hammar, 1998). Almost 60% of metastatic carcinomas of unknown primary origin are adenocarcinomas. Some metastatic adenocarcinomas (e.g., colonic adenocarcinomas) have distinctive histologic features that allow for determination of their site of origin. For most other metastatic adenocarcinomas of unknown primary origin, immunohistochemical analysis can help to identify the primary site. Immunophenotyping for cytokeratin 7, cytokeratin 20 (Chu et al, 2000), and other antigens used in conjunction with histologic analysis is effective in narrowing the potential primary site of origin of adenocarcinomas (Table 2–2), although these and other antigens are not absolutely site specific and cannot be reliably used to determine the site of origin. Other antigens that help determine the site of origin are thyroglobulin for thyroid, prostate-specific antigen and prostatic alkaline phosphatase for prostate, estrogen receptor for breast, and thyroid transcription factor 1 for lung and thyroid. Thyroglobulin, prostate-specific antigen, and prostatic alkaline phosphatase are site specific. Ultrastructural details of neoplastic cells can be studied by electron microscopy and may help determine the tumor type and site of origin of poorly differentiated cancers.

## Genetic Alterations of Colorectal Cancer

The molecular genetic alterations in colorectal carcinoma are among the best understood in human cancer and involve abnormalities in multiple dominant-acting oncogenes and tumor-suppressor genes (Kinzler and Vogelstein, 1996; Fearon and Dang, 1999). Various pathways of colorectal carcinogenesis are evident in sporadic, familial, and inflammatory bowel disease–associated neoplasms. The somatic alterations in sporadic colo-

**Table 2–2. Immunophenotype of Various Adenocarcinomas**

| *Immunophenotype* | | |
|---|---|---|
| *Cytokeratin 7* | *Cytokeratin 20* | *Tumors by Site and Type* |
| Positive | Positive | 93% of ovarian mucinous carcinomas |
| | | 62% of pancreatic adenocarcinomas |
| | | 43% of cholangiocarcinomas |
| | | 25% of bladder transitional cell carcinomas |
| | | 13% of gastric adenocarcinomas |
| Positive | Negative | 100% of salivary gland carcinomas |
| | | 98% of thyroid carcinomas |
| | | 96% of breast carcinomas |
| | | 96% of ovarian endometrioid, serous, and clear cell carcinomas |
| | | 80% of endometrial endometrioid carcinomas |
| | | 72% of lung carcinomas |
| | | 65% of malignant mesotheliomas |
| Negative | Positive | 95% of colorectal carcinomas |
| | | 78% of Merkel cell tumors of skin |
| | | 37% of gastric carcinomas |
| Negative | Negative | 100% of prostatic carcinomas |
| | | 89% of renal cell carcinomas |
| | | 81% of hepatocellular carcinomas |
| | | 79% of pulmonary and gastrointestinal carcinoid tumors |

rectal carcinoma include truncating mutations or deletions of the *adenomatous polyposis coli* (*APC*) gene on chromosome 5q and mutations of the *β-catenin* gene. Point mutations of the K-*ras* proto-oncogene, loss of the *deleted in colorectal cancer* gene and nearby *SMAD2* and *SMAD4* genes on chromosome 18q, and mutations and deletions of the *p53* gene on chromosome 17p are also common. Familial adenomatous polyposis is an autosomal-dominant inherited syndrome characterized morphologically by more than 100 colorectal adenomas and is due to a germline mutation in the *APC* gene. The tumors have somatic alterations similar to those of sporadic cancers.

In a second pathway to colorectal neoplasia, microsatellite instability (MSI; also termed DNA replication errors and ubiquitous somatic mutations) is caused by the alteration of a nucleotide mismatch repair gene, including *hMSH2*, *hMLH1*, *PMS1*, *PMS2*, or *GTBP*. MSI is characterized by additions and deletions of nucleotides in numerous repeated nucleotide sequences (microsatellites). Germline mutation of a mismatch repair gene causes hereditary nonpolyposis colorectal cancer (HNPCC), an autosomal-dominant syndrome characterized by early-onset, right-