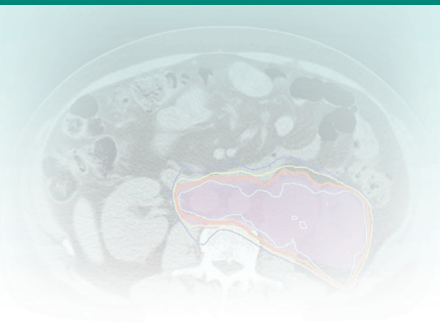
Overview



Joel E. Tepper and Leonard L. Gunderson

Gastrointestinal (GI) cancer continues to be a common health problem. Approximately 290,200 new cases of GI malignant disease were estimated to occur in the United States in 2013.[1] Although colorectal tumors account for almost 50% of the cases in the United States (142,720), cancers of the esophagus, stomach, liver, and pancreas continue to occur with regularity and have high mortality rates, and the incidence of hepatoma is increasing rapidly. Although the death rate from colon and rectal cancer is gradually decreasing, and that from gastric cancer has been decreasing for a century, there has been a marked increase in the incidence of tumors arising at the gastroesophageal junction and of primary liver cancers. Pancreatic cancer also continues to gradually increase in incidence and there has been little improvement in overall survival rates. Gastric and hepatic cancers are two of the most common causes of cancer incidence and death worldwide. Hereditary factors play a role in the etiology of GI cancer, and environmental toxins are causative agents in certain diseases. Because these are a diverse group of tumors, the etiology, epidemiology, diagnosis, and treatment vary enormously between diseases and are discussed in the respective chapters.

A significant problem with many GI cancers relates to a delay in clinical presentation. Signs that give early warning of other types of cancer (e.g., pain or palpation of a mass) do not occur early in most patients with GI cancers. For example, the severe back pain that can occur with pancreatic cancer is usually a manifestation of unresectability because of posterior tumor extension. Patients with alimentary tract GI cancers often present with symptoms of bleeding and occasionally bowel obstruction that may be associated with a large primary tumor, a high risk of metastasis, and a low chance of cure.

Physicians should be aware of the early signs and symptoms of GI cancer and educate their patients to be aware of certain symptoms to make earlier diagnoses, and to perform screening procedures (especially for colorectal cancer), as indicated. In general, the early warning signs include vague abdominal discomfort, evidence of GI bleeding, unexplained weight loss, change in bowel habits, or new onset of anemia. Routine colonoscopy or sigmoidoscopy and stool testing for occult blood are recommended screening procedures for colorectal cancer, and virtual colonoscopy may be a viable alternative. With these procedures, survival rates are affected because cancers are found at an early stage and benign polyps are removed before they have had a chance to progress to invasive cancers. Colorectal cancer is one of the few cancer types that can often be prevented, in this case by removing benign polyps before progression to malignancy. Other tests such as routine contrast radiography, upper endoscopy, or cytologic analysis have yet to demonstrate cost effectiveness in the United States as general screening procedures for upper GI malignant diseases, but they may be appropriate for select high-risk populations. There is a major controversy regarding aggressive screening procedures for patients with Barrett's esophagus because although these patients have a significant risk of neoplastic progression, the annual progression rate is quite low. There is substantial interest in innovative approaches of screening, such as molecular analyses of stool or bile for changes such as *RAS* mutations, that could be important in the future. There is also hope that advances in proteomics may lead to development of a blood assay for identifying patients with early cancers; but at the present time this is more a hope than reality.

This overview discusses conceptual issues pertinent to a variety of GI cancers, with site-specific details covered in the disease site chapters. Topics covered here include epidemiology and prevention, biology, anatomy and pathway of tumor spread, staging, prognostic factors and patterns of relapse, treatment issues of surgery alone versus primary chemoradiation or trimodality treatment (surgery, radiation therapy, and chemotherapy), and tolerance of organs and structures that limit the radiation dose in the treatment of abdominopelvic GI cancers.

EPIDEMIOLOGY AND PREVENTION

It has long been known that colon and rectal cancers are related to dietary factors, and these tumors have therefore been used as a model for cancer epidemiology. There is a strong association of colorectal tumors with high-fat and low-fiber diets.[2] It has been argued as to whether high fat or low fiber is most important in the process of cancer development, or whether there are other nutrients associated with these diets that are most important. However, data now suggest that neither high fat nor low fiber is critical but rather that high-fat/low-fiber diets tend to be low in nutrients such as folate.[3,4] Confirmation of this is critical in designing prevention strategies because dietary supplementation is far easier to implement than is a major change in the eating habits of the population. Other environmental factors, specifically exercise, are important in colorectal carcinogenesis, perhaps related to alterations in insulin-like growth factors. It is fortunate that a lifestyle that is healthy for the heart is also beneficial in decreasing colorectal cancer incidence. The same strong dietary correlate with cancer formation is unfortunately not present for most other GI tract tumors. Smoking is a major risk factor primarily for esophageal cancer and, to a lesser extent, for pancreatic cancer.

Along with the dietary factors just described, there have been major epidemiologic changes in geographic location and histopathologic findings for tumors of the esophagus, stomach, colon, and rectum over the last half-century, although the

reason for these changes is largely unknown. The primary histopathologic type of esophageal cancer has changed rapidly from squamous cell carcinoma of the proximal and midesophagus to adenocarcinomas of the distal esophagus, gastroesophageal junction, and proximal stomach. At many U.S. institutions, three fourths of all patients with esophageal cancer have distal esophageal/gastroesophageal junction adenocarcinomas, although this was a relatively rare entity only 20 to 30 years ago. The reasons for these changes are uncertain but are likely related to the increased incidence of Barrett's esophagus and esophageal reflux.[5] One theory is that the increased use of H_2-receptor blockers has relieved the symptoms of reflux but has not decreased the inflammatory response in the distal esophageal mucosa, so that Barrett's lesions continue to form and undergo metaplastic changes to become esophageal cancers. The concomitant substantial increase in the incidence of proximal (cardia) gastric cancers suggests that a similar etiology is present for both cardia and gastroesophageal junction carcinomas and that the increased incidence of esophageal cancers is not simply a misclassification of proximal gastric cancers as esophageal adenocarcinomas.[6]

At the same time that there has been an increased incidence of proximal gastric adenocarcinomas, the overall incidence of gastric cancers is decreasing. At the beginning of the 20th century, gastric cancer was the most common malignant disease in the United States. Although gastric cancer is still a common cause of death, it has decreased in incidence so much that it is now only the 11th-most common cause of death from cancer in the United States.[1] The change has been attributed to dietary modifications, although the exact cause is unknown. The incidence of gastric cancer worldwide is much higher than in the United States.

In the large bowel, there has been a more gradual epidemiologic change. Previously, the majority of colorectal cancers were located in the rectum, but now most are located in the right colon. Although screening for, and removal of, precancerous polyps in the rectum and sigmoid colon with sigmoidoscopy could be producing some of these changes, it is unlikely to be a major factor. Dietary changes are suspected, but unproved, as a cause.

There has also been a major increase in the incidence of hepatocellular carcinoma (HCC) in the United States, although it is not nearly as high as the incidence worldwide. Some of the reasons for this are known, such as the strong association of HCC with hepatitis B and C virus infection. Improved prevention and treatment of hepatitis B and C infections should decrease the incidence of these diseases over the long term.

A major emphasis in the future will be to determine ways to prevent tumor formation or to find tumors early enough so that the risk of tumor mortality is minimized. Data strongly suggest that prevention strategies can be used to decrease the incidence of colorectal cancers. Screening for and removal of polyps before they become malignant interferes with the polyp-to-cancer sequence that occurs in the majority of colon and rectal cancers. Studies of patients screened with flexible sigmoidoscopy have demonstrated a markedly decreased incidence of cancers in areas within reach of the sigmoidoscope but no decrease in areas that could not be effectively screened.[7,8] Convincing data demonstrate the value of regular screening and stool guaiac studies in decreasing colorectal cancer mortality rates.[9,10] However, neither of these interventions is used widely enough to decrease markedly the overall incidence of these diseases. Virtual colonoscopy, a computed tomography (CT)-based radiographic examination, has generated a great deal of interest as a screening tool. However, the data do not yet support its widespread use and patients currently still need to do what many consider to be the worst part of an endoscopic procedure, the bowel preparation. Controlled studies are being performed to determine whether the bowel preparation is necessary or whether electronic deletion techniques can be used to exclude stool from the images.

Screening approaches have also been considered for tumors of other sites in the GI tract, but cost-effective strategies have not been defined. The incidence of gastric cancer in the United States and many Western countries is not high enough to justify the cost and morbidity of screening endoscopy for gastric or esophageal cancer, and radiographic studies such as CT scans are not sensitive. If it were possible to define a high-risk group of patients, then perhaps screening could be used successfully. Although controversial, the one other situation in the upper GI tract in which screening may be useful at the present time is in patients with Barrett's esophagus, where the incidence of esophageal cancer is high and regular endoscopy or elective surgery may be justified, at least for high-grade dysplastic lesions.

Prevention strategies have been studied extensively, especially for colon and rectal cancers. There are a variety of agents that have substantial potential as preventive agents for people at high risk. These include aspirin[11,12] and other nonsteroidal anti-inflammatory drugs (NSAIDs) and calcium.[13,14] The data are now quite convincing that the incidence of polyps can be decreased with the use of NSAIDs, presumably reflecting their activity as inhibitors of cyclo-oxygenase-2 (COX-2).[15] The finding of increased cardiovascular events in patients taking selective COX-2 inhibitors will have a major impact on the use of these agents for cancer prevention, but aspirin use is advocated by some.

BIOLOGY OF GASTROINTESTINAL CANCERS

Over the past decade, an enormous amount of information has been gathered regarding the molecular correlates of GI carcinomas. As is true for other anatomic sites, there are a large number of molecular changes in most of these tumors, but most of the changes occur in only a relatively small subset of tumors. A wide spectrum of molecular abnormalities has been found that likely define the genetic characteristics of the tumor. The specific molecular abnormalities probably have a major effect on both the pace of disease progression and the response of the tumor to therapy, but the relationship is clearly complex. Colorectal cancer is one of the best-studied adult solid tumors in this regard and illustrates the type of information that we are likely to obtain about other solid tumors. The detailed molecular changes associated with GI tumors and the general issues related to carcinogenesis are beyond the scope of this introduction but are covered elsewhere in this book, as well as in multiple reviews.[16]

Although there are a large number of molecular changes observed in colorectal cancer, a few are most common. These include altered promoter methylation, mutations of the *RAS* oncogene, mutations in the *TP53* tumor suppressor gene, mutations of a gene on the short arm of chromosome 18 (in an area referred to as the *DCC* gene [deleted in colon cancer]), and mutations in chromosome 5 in a region associated with the familial polyposis syndrome (FAP). Although there is clearly no orderly progression from one molecular change to another, there is a tendency for certain of these changes to occur early in the oncogenesis pathway. For example, changes in the *FAP* gene and altered methylation tend to occur early, whereas *TP53* mutations tend to occur late.[17]

As one probes deeply into the genome, a large number of abnormalities are being found, but many of these may be secondary to a generalized chromosomal instability. The significance of some types of molecular abnormalities is now

better understood. For example, microsatellite instability in colon cancer is associated with right-sided colon tumors but with an improved prognosis compared with those with no microsatellite instability. These tumors may also have altered (i.e., less) chemosensitivity, especially to 5-FU, compared with tumors without microsatellite instability. There is also awareness that changes in miRNA (and other nonprotein-coding RNAs) can have major importance in defining outcomes and perhaps response to therapy. Some investigators now classify colorectal cancer into three categories: those that have microsatellite instability (MIS), characterized clinically as right colon lesions with a relatively good prognosis (10% to 20% of tumors); those of the CpG island methylator phenotype (CIMP), which have a poor prognosis and relatively poor responsiveness to standard chemotherapy (10% to 30% of tumors); and those with chromosomal instability (CIN; 50% to 70% of tumors). This classification may help in the understanding, subclassification, and management of these diseases. More recently work of the The Cancer Genome Atlas (TCGA), sponsored by the National Cancer Institute (NCI), has compiled a comprehensive analysis of molecular changes in these tumors,[18] including not only mutational analysis, but also methylation, copy number variation, and miRNA changes.

An area of interest is the correlation of the known epidemiologic factors for cancer formation and the molecular abnormalities. For example, it is unknown how dietary changes are related to observed molecular alterations. Determining which dietary factors are of true importance and which dietary factors produce which molecular changes, and the mechanisms by which they do so, may be critical in designing effective prevention strategies.

For other tumors of the GI tract, the molecular correlates are not nearly as well established. Pancreatic cancer is unusual because approximately 90% of these tumors have a mutation in the *K-RAS* oncogene,[18] and mutations in the *P16, TP53*, and *MADH4* genes are common. This has been emphasized by the results of sequencing of pancreatic cancers, where a relatively small number of common mutational events were found, and most of the findings were unexpected from previous data. The finding of abnormalities that are present in most cancers of a certain type produces exciting possibilities for detection, prevention, and therapy because it suggests that these mutational events may be required for cancer formation. In addition, even when a specific mutation is not present, an abnormality in the same pathway may be present and produce the cancer of interest. However, the abnormality may be produced by one of many mutational events or even by gene silencing through altered methylation.

There is a major effort to develop pharmaceuticals that will block the function of critical pathways and thereby either inhibit tumor growth or kill the tumor. Many of the drugs that have been developed as pure molecular inhibitors for primary therapy do not seem to be effective when used alone. However, most of these agents (e.g., endothelial growth factor receptor [EGFR] or vascular endothelial growth factor [VEGF] inhibitors) have substantial radiation sensitization properties and may be useful adjuncts to standard radiation therapy (see Chapter 5).

A great deal of interest exists in using molecular analysis techniques to improve prognostication and to better define which tumors would be best treated with which modalities. These include whole genome sequencing, sequencing of the transcriptome, expression array analyses, epigenetic analyses (such as methylation), and so on. These studies are still in their early phases and require much additional work before routine clinical application. The further work of TCGA may provide additional information on the molecular characteristics of these tumors.

ANATOMY AND PATHWAYS OF TUMOR SPREAD

Upper GI (i.e., stomach, pancreas, and biliary tract) and colorectal cancers have anatomic similarities that lead to common patterns or pathways of tumor spread. The four common mechanisms of tumor spread for these sites include direct extension, lymphatic spread, blood-borne hematogenous metastases, and peritoneal seeding. Esophageal and anal cancers have no risk for peritoneal seeding because of their anatomic location, unless they extend to involve organs with access to the peritoneal cavity (e.g., stomach or upper rectum).

Direct extension of tumor that may lead to surgical unresectability because of fixation to or involvement of surrounding organs or structures is more common with upper GI cancers than with lower GI cancers. Within the triad of upper GI cancers, gastric cancers are most likely to be resectable at the time of diagnosis.

Lymphatic spread and nodal involvement are common at all GI sites. For the alimentary sites (i.e., esophagus, stomach, colorectum, and anus), the risk is minimal for lesions limited to the mucosa. The risk increases with direct extension into the submucosa in view of the presence of submucosal lymphatics, which are especially prominent in the stomach and esophagus. The mechanism of tumor spread within submucosal and subserosal lymphatics can also lead to subclinical tumor spread 5 cm to 10 cm or more from the margin of the gross tumor for both esophageal and gastric cancers. For colorectal cancers, it is unusual to have subclinical tumor extension in the bowel wall for more than 1 cm to 1.5 cm beyond the gross tumor, but nodal spread can occur at more distant locations.

Hematogenous dissemination from GI cancers is usually to the liver or lungs. With esophageal, anal, and rectal cancers, both sites are at risk. Gastric, colon, or pancreas cancers that do not extend beyond the wall or organ to involve other organs or structures have venous drainage via the portal circulation, placing the liver at primary risk for blood-borne metastases.

Peritoneal seeding can theoretically occur when a tumor extends to a free peritoneal surface. The finding of peritoneal seeding at initial surgical exploration is highest for gallbladder and pancreatic cancers, is rare with low rectal cancers, and can sometimes be found with gastric, colon, bile duct, and upper (with or without mid) rectal cancers.

STAGING

The current TNM (tumor, lymph nodes, metastasis) staging system of the American Joint Committee on Cancer (AJCC) is the accepted staging system for GI cancers.[19] However, because of either lesser nodal dissections or incomplete pathology, the pathologic examination of 10 to 15 nodes in gastric cancer does not always occur, and this can decrease the value of the N classification (N1, metastases in 1 to 2 regional lymph nodes; N2, metastases in 3 to 6 regional nodes; and N3, metastases in 7 or more regional nodes [N3a, 7 to 15 regional nodes; N3b, 16 or more regional nodes]). However, for both gastric and colorectal tumors, the aggressiveness of lymph node staging is of enormous prognostic importance. The prognosis is much inferior for "N0" tumors when few lymph nodes have been evaluated compared with these tumors when large numbers of nodes have been studied.[20] The ratio of positive lymph nodes to the total number of lymph nodes in a specimen is also becoming a more widely used measure because it partially compensates for inadequate nodal sampling. These variations in nodal count result in both understaging and stage migration, which make it difficult to compare results by

series. Some individuals have used the lymph node ratio (percentage of nodes that are involved with tumor) as an alternative to lessen the problem of poor nodal sampling.

Colorectal Cancers

The TNM system applies to both clinical and pathologic staging, defines the degree of primary tumor extension for lesions confined to and extending beyond the bowel wall, and defines node involvement by the number of nodes involved (N1, three or fewer nodes; N2, four or more nodes). The updated 2010 AJCC/UICC (Union for International Cancer Control) TNM classification should be used as the standard staging system (see Table D-1).

Considerable improvements in TNM staging for colon and rectal cancer have been achieved as a result of both the sixth and seventh editions of the AJCC staging manual.[21,22] Through the fifth edition of the manual, substaging was not used despite marked differences in outcomes by TN category of disease for patients with stages II and III disease. In both the sixth and seventh editions of the manual, substaging, based on available outcomes data, has been used to account for those differences in survival.[20-28]

Before making substantive changes in the AJCC seventh edition for colon and rectal cancer, the AJCC hindgut task force sought population-based validation that depth of invasion and nodal status interact to affect survival rates. Surveillance Epidemiology and End Results (SEER) survival data were obtained for patients with invasive colon and rectal cancer and evaluable TN category of disease (35,829 patients with rectal cancer and 109,953 patients with colon cancer).[27,28] T4N0 category cancers were stratified by "tumors that perforate visceral peritoneum" (T4a) versus "tumors that invade or are adherent to adjacent organs or structures" (T4b). N1 and N2 categories were stratified according to the number of involved nodes (N+): N1a and N1b (one node versus two to three nodes), and N2a and N2b (four to six nodes versus seven or more nodes). The 5-year observed and relative survival data were obtained for each TN category. The analyses indicated the following information: Survival times are better for patients with T1-2N0 cancers than for those with T3N0 cancers; survival times are better for patients with T3N0 tumors than for those with T4N0 tumors; and survival times are better for patients with T1-2N2 tumors than for those with T3-4N2 tumors. Survival times for patients with T4bN1 tumors are similar to those for T4N2 tumors.

In addition, patients with T4a lesions have better survival times than patients with T4b tumors by N category, and the number of positive nodes affects survival times for each T category. The SEER population-based colon and rectal cancer analyses supported subdividing T4 into T4a and T4b, N1 into N1a and N1b, and N2 into N2a and N2b, and supported revised substaging of II and III (shift of T1-2N2 lesions from IIIC to IIIA or IIIB and T4bN1 lesions from IIIB to IIIC).

Other Gastrointestinal Cancers

Staging of pancreatic, biliary, and esophageal cancers is less useful. The major factors defining therapy are whether the tumor is resectable, borderline resectable, or locally unresectable and whether distant metastatic disease is present. As therapy becomes more sophisticated and treatment outcomes improve, we will likely be better able to use more precise staging information. The ability to evaluate stage more effectively preoperatively through positron emission tomography (PET) scans (especially in esophageal and anal cancer but also in colorectal cancers) and endoscopic ultrasound (in esophageal and gastric cancers) should be of benefit over the long term with regard to choice of treatment (single-modality versus bimodality or trimodality treatment) and sequencing of various modalities (preoperative or postoperative, or both). HCC is generally not staged in the usual manner, but both patient and tumor factors are important in determining therapy and outcome.

TABLE D-1 Comparison of Staging Systems for Colorectal Adenocarcinoma

AJCC TNM Stage*	T	N	M	Dukes Stage	Modified Astler-Coller Stage
0	Tis	N0	M0	—	—
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1-2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3-4a	N1/N1c	M0	C	C2
	T2-3	N2a	M0	C	C1/C2
	T1-2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-4a	N2b	M0	C	C2
	T4b	N1-2	M0	C	C3

From Edge SB, Byrd DR, Compton CC, et al, editors: AJCC cancer staging handbook, ed 7, New York, 2010, Springer.

*Tis, *Carcinoma in situ;* T1, *tumor invades submucosa;* T2, *tumor invades muscularis propria;* T3, *tumor invades through the muscularis propria into pericolorectal tissues;* T4a, *tumor penetrates to the surface of the visceral peritoneum; T4b, tumor directly invades or is adherent to other organs or structures (surgical/pathologic definition).*

N0, *no regional lymph node metastases;* N1, *metastasis in one to three regional lymph nodes; (*N1a, *one regional node; N1b, two to three regional nodes);* N2, *metastasis in more than four regional lymph nodes; (*N2a, *four to six regional nodes;* N2b, *seven or more regional nodes);* M0, *no distant metastasis;* M1, *distant metastasis;*

Lymph nodes beyond those encompassed by standard resection of the primary tumor and regional lymphatics (e.g., retroperitoneal nodes) are considered distant metastases.

PROGNOSTIC FACTORS AND PATTERNS OF RELAPSE

Adjuvant Colorectal Cancer

Survival and disease relapse after surgery with or without adjuvant treatment for colon and rectal cancer are a function of both degree of bowel wall penetration of the primary lesion and nodal status. Nodal involvement is not the only important pathologic factor determining survival and relapse.

Impact of TN Category on Relapse and Survival

In the sixth edition of the AJCC staging manual, stage II was subdivided into IIA (T3N0) and IIB (T4N0) and stage III was subdivided into IIIA (T1-2N1M0), IIIB (T3-4N1M0), and IIIC (any TN2M0), based on improved outcomes for patients with stage IIA versus IIB disease and for those with stage IIIA versus IIIB cancers.[21] The placement of all patients in the TN2 category into stage IIIC, however, was not based on in-depth outcomes analyses because the prognostic impact of the depth of bowel wall invasion (T category) in N2 patients had not been evaluated in detail.

TABLE D-2 Pooled Rectal Analyses: Impact of NT Category on Survival

NT Category	Overall Survival (5-year)* No. Patients	%	*p* Value	Disease-Free Survival (5-year)* No. Patients	%	*p* Value
N0T3	668	74	0.046	664	66	0.05
T4	95	65		95	54	
N1T1-2	225	81	<0.001	225	74	<0.001
T3	544	61		536	50	
T4	59	33		59	30	
N2T1-2	180	69	<0.001	180	62	<0.001
T3	663	48		659	39	
T4	84	38		84	30	

From Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer. A pooled analysis. Int J Radiat Oncol Biol Phys 54:390, 2002.
**Unadjusted Kaplan-Meier estimates.*

TABLE D-3 Pooled Rectal Analyses: Impact of NT Category on Disease Relapse

NT Category	Local Recurrence (5-year)* No. Pts	%	*p* Value	Distant Metastasis (5-year)* %	*p* Value
N0T3	664	8	0.04	19	0.04
T4	95	15		28	
N1T1-2	225	6	0.002	15	<0.001
T3	536	11		34	
T4	59	22		39	
N2T1-2	180	8	0.14	26	<0.001
T3	659	15		45	
T4	84	19		50	

From Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer. A pooled analysis. Int J Radiat Oncol Biol Phys 54:390, 2002.
**Cumulative incidence rates.*

Rectal Cancer Pooled Analyses

Rectal cancer pooled analyses subsequently demonstrated the independent prognostic significance of each TN and NT category of resected rectal cancer with regard to both disease relapse and survival rates[23,24] (Tables D-2 to D-4). Patients with T1-2N1-2 disease had a more favorable prognosis than previously thought, and those with T4N1 lesions (stage IIIB in the AJCC sixth edition, along with T3N1 lesions) had a prognosis more akin to that of patients with T3-4N2 lesions (stage IIIC in the sixth edition). For patients with N2 disease, data from the rectal cancer pooled analyses showed that N2 disease does not by itself confer a poor prognosis (see Tables D-2 and D-3). Substaging by T category influenced both the 5-year overall survival (N2T1-2, 67%; N2T3, 44%; and N2T4, 37%; $p < 0.001$) and the 5-year disease-free survival (58% versus 36% and 30%; $p < 0.001$). Placement of all N2 patients within AJCC substage IIIC in the sixth edition did not reflect the markedly different prognosis of patients who were N2 found in the two rectal cancer pooled analyses.[23,24] Outcomes data from the pooled analyses supported revised substaging of stage III because of improved survival rates for patients with T1-2N2 cancers versus T3-4N2 cancers, and survival rates for those with T4N1 lesions were more similar to those of T3-4N2 tumors than T3N1 tumors.

SEER Colon and Rectal Analyses

As shown in Table D-5, data in the large SEER population-based colon and rectal cancer analyses were highly consistent with those of the rectal cancer pooled analyses with regard to the more favorable prognosis of patients with T1-2N1-2 category lesions (stage IIIC, AJCC sixth edition) and the less favorable prognosis of patients with T4N1 category cancers (IIIB, sixth edition).[27,28] Data from the SEER colon and rectal analyses and the rectal pooled analyses supported shifting T1-2N2 lesions from IIIC to an earlier stage of disease (stage IIIA or IIIB) and shifting T4N1 lesions from stage IIIB to IIIC (see Table D-5).

SEER colon and rectal cancer outcomes data (see Table D-5) supported the substaging of T4, N1, and N2 tumors.[27,28] Patients with T4a cancers (penetration to the surface of the visceral peritoneum [revised definition in the AJCC seventh edition]) have a better prognosis than those with T4b cancers (direct invasion of or adherent to other organs or structures) for each N category of disease (N0, N1, N2). For patients with N0T4a versus T4b lesions, there is a 15% to 20% improvement in absolute 5-year relative and overall survival rates, and for N1T4a versus T4b and N2T4a versus T4b disease, there is a 15% to 25% improvement in 5-year survival rates. Earlier analyses with much smaller data sets had suggested that patients with perforated T4 lesions may have a worse prognosis than those with invasion of or adherence to other organs or structures. However, as has been shown in the large SEER colon and rectal cancer datasets, patients with T4 lesions that penetrate to the surface of the visceral peritoneum have a more favorable prognosis than those with lesions that invade or adhere to other organs or structures.[27,28]

As shown in the SEER colon and rectal cancer analyses and prior series, both the number of positive nodes and the number of nodes examined had prognostic significance.[20,27,28] In the large SEER colon and rectal cancer analyses, patients with one positive node (N1a) have a 5% to 13% better 5-year survival rate than those with two to three positive nodes (N1b) by T category, with improved survival rates for all TN categories. Patients with four to five positive nodes (N2a) have a 5-year survival that is 5% to 19% better than those with more than seven positive nodes (N2b) by T category, with improved survival rates for all TN categories except T1N1a versus T1N1b.

These data in total suggest that both the extent of the primary tumor and the extent of the nodal disease are independent prognostic factors for patients with colorectal cancer. Both must be taken into consideration in designing appropriate therapy.

TABLE D-4 Rectal Cancer Pooled Analyses: Survival and Relapse Rates by Stage or TN Category of Disease

Risk for Relapse*	Stage: TN Category	Stage: Modified Astler-Coller	Survival Rate (5 year)†: Overall (%)	Survival Rate (5 year)†: Disease-Free (%)	Relapse Rate: Local (%)	Relapse Rate: Distant (%)	Stage: Dukes	Stage: TNM (6th ed)
Low‡	T1-2N0	A, B1	~90	~90	≤5	~10	A	I
Intermediate	T1-2N1	C1	81	74	7	15	C	IIIA
	T3N0	B2	74	66	9	20	B	IIA
Moderately high	T1-2N2	C1	69	62	8	31	C	IIIC
	T4N0	B3	65	54	13	28	B	IIB
	T3N1	C2	61	50	12	37	C	IIIB
High	T3N2	C2	48	39	14	47	C	IIIC
	T4N1	C3	33	30	23	39	C	IIIB
	T4N2	C3	38	30	17	53	C	IIIC

From Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N substage on survival and disease relapse in adjuvant rectal cancer. A pooled analysis. Int J Radiat Oncol Biol Phys 54:393, 2002.

**Data from rectal cancer pooled analyses in AJCC Hindgut Taskforce: Colon and rectum. In Greene FL, Page DL, Fleming ID, et al, editors: AJCC cancer staging manual, ed 6, New York, 2002, Springer, pp 113–124.*

†Survival rates based on unadjusted Kaplan-Meier estimates.

‡Data are derived from prior publications because patients who were low-risk were not eligible for the five Phase III trials in the rectal cancer pooled analyses.

TABLE D-5 Changes in Substaging of AJCC Stages II and III Colorectal Cancer Based on Rectal Cancer Pooled Analyses and SEER Rectal and Colon Cancer Analyses

TN Category	Rectal Pooled Analyses* (5-yr OS): No. Patients	Rectal Pooled Analyses* (5-yr OS): %	AJCC TNM Stage (6th ed)	AJCC TNM Stage (7th ed)	SEER Rectal Analyses† (5-year Observed Survival): No. Patients	SEER Rectal Analyses† (5-year Observed Survival): %	SEER Rectal Analyses† (5-year Observed Survival): SE	SEER, Colon Analyses‡ (5-year Observed Survival): No. Patients	SEER, Colon Analyses‡ (5-year Observed Survival): %	SEER, Colon Analyses‡ (5-year Observed Survival): SE
T1-2N0	—	—	I	I	9,961	77.6	0.5	23,861	76.3	0.3
T1N0	—	—	I	I	3,348	81.4	0.8	10,930	78.7	0.5
T2N0	—	—	I	I	6,613	75.7	0.6	12,931	74.3	0.3
T3N0	1060	77	IIA	IIA	10,615	64.0	0.5	40,338	66.7	0.3
T4N0	111	65	IIB	T4a, IIB	818	55.7	1.9	5,020	60.6	0.8
				T4b, IIC	769	44.7	2.1	3,088	45.7	1.0
T1-2N1	355	79	IIIA	IIIA	2,008	72.1	1.2	3,134	71.1	1.0
T1-2N2	226	67	IIIC	IIIA/IIIB§	508	56.1	2.6	499	61.5	2.6
T3N1	887	60	IIIB	IIIB	5,787	52.4	0.8	17,866	54.9	0.4
T4N1	62	35	IIIB	T4a, IIIB	480	48.2	2.5	2,771	47.0	1.1
				T4b, IIIC	423	24.3	2.5	1,774	27.9	1.2
T3N2	935	44	IIIC	T3N2a, IIIB	1,964	42.5	1.3	5,331	42.8	0.8
				T3N2b, IIIC	1,791	32.0	1.3	3,235	30.4	0.9
T4N2	108	37	IIIC	T4a, IIIC	397	34.3	2.7	1,653	26.6	1.2
				T4b, IIIC	308	15.6	2.5	1,383	15.8	1.1

OS, Overall survival; SE, standard error.

**Modified from Gunderson LL, Sargent DJ, Tepper JE, et al: Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer. A pooled analysis. J Clin Oncol 22:1785–1796, 2004.*

†Modified from Gunderson LL, Jessup JM, Sargent DJ, et al: Revised TN categorization for rectal cancer based on SEER and rectal pooled analysis outcomes. J Clin Oncol 28:256–263, 2010.

‡Modified from Gunderson LL, Jessup JM, Sargent DJ, et al: Revised TN categorization for colon cancer based on national survival outcomes data. J Clin Oncol 28:264–271, 2010.

§IIIA–T1N2a; IIIB–T2N2a, T1-2N2b, T3N2a.

Adjuvant Gastric Cancer

As with other alimentary tract cancers, the two most important prognostic features are depth of invasion and extent of lymph node involvement. Nodal involvement reduces survival times, and the number of positive nodes is of prognostic importance. However, if the primary lesion is confined to the gastric wall (T1 or T2) when nodes are involved, the prognosis at 5 years (40% survival rate) is similar to that of patients with T2N0 or T3N0 lesions (~50% 5-year survival rate; see Chapter 45).

SINGLE-MODALITY VERSUS COMBINED-MODALITY TREATMENT

Radiation therapy has a role as a component of primary therapy in most cancers of the GI tract. It is used as part of the

initial management for patients with locally advanced cancers of the esophagus, stomach, pancreas, colon, rectum, and anus in most U.S. institutions and for hepatobiliary cancer in some institutions.

Chemoradiation: 5-Fluorouracil–Based

Although combined-modality therapy with chemotherapy and external beam radiation therapy (EBRT) is of great importance in many adult solid tumors, its use in the treatment of GI tumors is substantial and of long duration. 5-fluorouracil (5-FU) has been used as an anticancer therapy since the 1950s, and since the late 1960s, it has been used in combination with radiation therapy for GI tumors (concomitant with or without maintenance) (Figure D-1). Early studies of the combination were reported from the Mayo Clinic in the treatment of locally advanced pancreatic, gastric, and large bowel cancers.[29] Although modifications of this therapy have been developed, the use of concomitant 5-FU–based chemotherapy plus radiotherapy has remained a standard therapy for treatment of selected patients with tumors at almost all sites in the GI tract.

Although drugs such as cisplatin or mitomycin C are used in combination with 5-FU in a number of these anatomic sites (especially, the esophagus and anus), they have not replaced 5-FU but are used in conjunction with 5-FU and irradiation. There is now routine use of oral 5-FU analogs (e.g., capecitabine), with the hope that the oral formulation will make this treatment more acceptable to patients while maintaining similar efficacy; however, it has not markedly changed the toxicity profile although tumor efficacy appears as good as 5-FU infusional approaches.

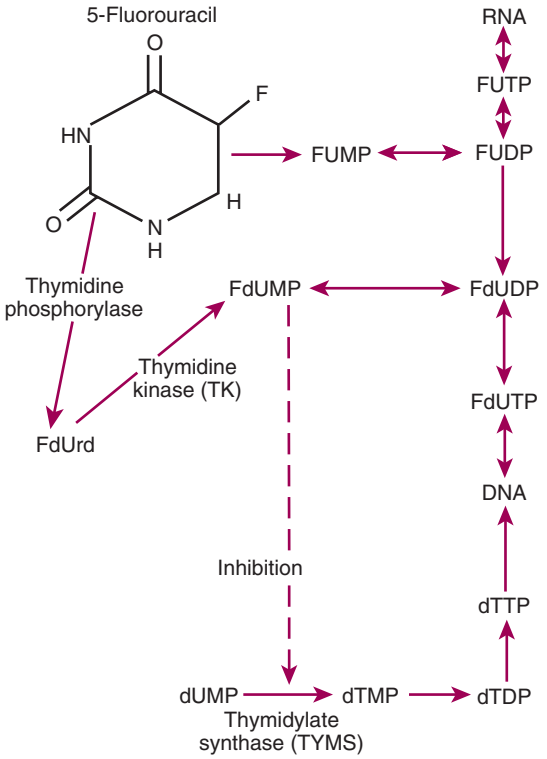


Figure D-1 The agent 5-fluorouracil (5-FU) has, as its primary mode of action, conversion into fluorodeoxyuridine monophosphate (F-dUMP), which acts to inhibit the enzyme thymidylate synthase, which is necessary for production of DNA. 5-FU can also be converted into fluorouracil triphosphate (FUTP) and incorporated into RNA or into fluorodeoxyuridine triphosphate (FdUTP) and incorporated into DNA. *FUMP*, Fluorouridine monophosphate.

For decades, 5-FU was essentially the only drug useful in colorectal and pancreatic cancer. Gemcitabine has now displaced 5-FU as the primary adjuvant drug treatment for pancreatic cancer, but other more aggressive combinations are being used for fit patients with metastatic disease. The combination of 5-FU or capecitabine and oxaliplatin or irinotecan is routinely used in the chemotherapeutic management of colorectal cancer. All of these agents have substantial radiation-sensitizing properties, and their use in rectal cancer has been extensively explored. The Phase III studies of oxaliplatin plus EBRT and 5-FU in rectal cancer have caused increased toxicity with no improvements in disease outcomes,[30] and irinotecan has not been as well studied because of additive toxicity (diarrhea) with radiation plus fluoropyrimidine. As mentioned, the use of EGFR or VEGF inhibitors as radiation sensitizers in a variety of sites in the GI tract, especially rectum, has generated substantial interest, but have not yet produced encouraging results beyond demonstration of tolerability.

Although surgery remains the primary mode of curative treatment for gastric, pancreatic, and large bowel cancers, combined chemotherapy plus irradiation has become the primary treatment for anal cancer and may offer an equivalent option to surgery alone for some patients with esophageal cancer. Although surgical techniques have continued to evolve, most prominently with the use of total mesorectal excision for rectal cancer, therapy with surgery alone is unlikely to significantly improve the survival rates for gastric, pancreatic, esophageal, and large bowel cancers. Adjuvant and neoadjuvant radiation therapy or chemotherapy, or both, offer the best prospect for improving cure rates.

A large number of studies have been performed using the aforementioned strategies. With unresected esophageal cancers, combined chemotherapy plus irradiation has clearly improved rates of disease control and 5-year survival over irradiation alone in Phase III randomized trials.[31] In an important Phase III trial from the Netherlands preoperative chemoradiation, using carboplatin and paclitaxel as the chemotherapy, improved survival rates compared with surgery alone in patients with resectable esophageal/gastroesophageal junction cancer.[32] For resected high-risk rectal cancers, postoperative chemoradiation has improved rates of local and distant disease control, disease-free survival, and overall survival compared with surgery alone or adjuvant irradiation.[33,34] Preoperative irradiation has demonstrated improved local control and survival when compared with surgery alone for resectable rectal cancer in a large randomized trial in Sweden,[35] and a large German trial[36] has shown the superiority of preoperative chemoradiation over the same therapy delivered postoperatively. Adjuvant postoperative chemoradiation has resulted in improved local control and survival in some Phase II and Phase III trials for resected pancreatic cancer.[37-40] Postoperative chemoradiation has also improved local control and survival rates when compared with surgery alone in patients with resected high-risk gastric cancers in a Phase III U.S. GI intergroup trial.[41]

For resected node-positive colon cancers, adjuvant chemotherapy has produced improved disease-free survival and overall survival compared with surgery alone. Postoperative chemoradiation has been evaluated in patients with resected high-risk colon cancers,[42] and although it has not been shown to be of value for the typical patient, it may be of value in selected clinical situations, as when microscopic residual disease remains (although this is not truly an adjuvant setting). A preferred approach would be to use imaging to identify patients who would likely have marginal resection if surgery were the initial component of treatment (e.g., a T4 lesion with adherence to a surgically unresectable structure). In such patients, preoperative chemoradiation would preferably

precede surgical resection. Finally, chemoradiation has replaced surgical resection as the primary treatment for anal carcinomas, with surgical resection being reserved for salvage therapy. Although these positive trials are exciting and encouraging, refinements in multimodality therapy will necessitate continued enrollment of patients in clinical trials to help develop the most effective combined-modality treatment strategies for the future.

Chemoradiation: New Chemotherapy Drugs

For the first time in many years, there are a variety of new drugs that may supplement or supplant 5-FU when used in combination with radiation therapy in the treatment of GI cancers. These new cytotoxic drugs include gemcitabine, irinotecan, oxaliplatin, and oral 5-FU compounds.

Gemcitabine is the first drug developed in many years with single-drug activity against pancreatic cancer.[43] Reliable data demonstrate that gemcitabine has substantial radiation-sensitizing properties,[44] and clinical studies are continuing with this drug used in combination with radiation therapy for patients with both locally advanced and resected pancreatic cancer.[45] Because gemcitabine is a potent radiation sensitizer, it needs to be used cautiously. In view of positive survival outcomes for gemcitabine plus nab-paxitaxal (Abraxane) versus gemcitabine alone for patients with metastatic pancreas cancer[46] it may be of interest to determine if both drugs can be given during concurrent EBRT. Although the combination of gemcitabine and irradiation may be effective in other sites in the GI tract, the fact that gemcitabine lacks substantial activity when it is used alone in colon and rectal cancer makes its use for these diseases unlikely.

A number of other drugs have substantial activity in colon and rectal cancer, including the topoisomerase inhibitor irinotecan (CPT-11) and the platinum compound oxaliplatin. Data exist to demonstrate radiation sensitization with irinotecan[45] and oxaliplatin.[47] Both of these drugs have been tested in combination with radiation therapy for patients with rectal cancer. Although preliminary Phase II data suggested that they appeared to increase the rates of pathologic complete response when used with 5-FU and irradiation in the preoperative setting, subsequent larger studies have suggested that this may not be true.[48-50]

Another group of important drugs are oral analogs of 5-FU, although they may behave slightly differently than the infusional approaches. Some of these agents are 5-FU prodrugs, and some act to inhibit the degradation of 5-FU, either by direct or indirect inhibition of the degradation pathway. Others attempt to increase tumor selectivity, and yet others act as specific inhibitors of thymidylate synthase (in contrast to the nonspecific action of 5-FU).[51] The major potential advantages of these compounds are the convenience for patients and the elimination of the continuous infusion pumps needed for 5-FU. The toxicity spectrum of these agents does not differ substantially from that of 5-FU given by conventional infusion.

Capecitabine is an agent that has entered routine clinical use both as a single-modality chemotherapeutic agent and used in combination with irradiation.[52] Capecitabine is delivered twice daily, and although serum levels are much flatter than after a 5-FU bolus, major variations in serum levels do exist. Therefore, the timing of irradiation and capecitabine may still be important. The recommendation is to take capecitabine approximately 1 hour before the delivery of radiation therapy to maximize radiation sensitization. Capecitabine doses used with concurrent radiation are less than doses of the drug used alone (typically, 1650 mg/m^2/day delivered in two doses) and investigators vary on whether the drug should be delivered 7 days per week or Monday to Friday with EBRT.

IRRADIATION TECHNIQUE AND TOLERANCE

Irradiation Field Definition

Because treatment tolerance to irradiation is usually a function of both dose and volume, proper definition of tumor and target volumes is of utmost importance. If patients are referred for primary or preoperative EBRT, the radiation oncologist can obtain the necessary imaging studies to define both the primary tumor and the nodal areas at risk. If the patient is referred after complete resection, however, the radiation oncologist is dependent on the availability of pertinent preoperative imaging studies or placement of surgical clips at sites of tumor adherence or microscopic residual disease.

For unresected alimentary tract cancers (e.g., esophageal, stomach, colorectal, anal cancers), the primary lesions and nodal areas at risk are best defined with CT scanning. The chest plus the abdomen are imaged for esophageal cancers, the abdomen and generally the chest for gastric cancers, and the chest, abdomen, and pelvis for colorectal and anal cancers. PET/CT scans are preferable for esophageal and anal cancers because these tumors are usually PET avid and the primary tumors are often not well seen on conventional CT scan. Endoscopic ultrasound (EUS) can also be used in esophageal, gastric, and rectal tumors to determine both the depth of invasion in the wall and the presence of nodal involvement. The ability to biopsy suspicious areas is an advantage for endoscopic evaluation. None of these tests adequately define longitudinal disease extension in esophageal cancer, however. EUS is the best widely used imaging technique for determining the T category of disease for esophageal, gastric, and rectal cancers before resection, but it is most useful in rectal cancer for defining the patients who need preoperative therapy. MRI is considered by many to be superior to EUS in rectal cancer because of its ability to assess the adequacy of the surgical mesorectal excision. The use of endoscopy to both define lesions and obtain biopsies has essentially eliminated the use of preoperative contrast radiographs, so the preoperative CT, PET, or MRI imaging is essential to construct proper irradiation fields if patients are referred after resection. However, some important structures (such as the anal verge) are not well defined with cross-sectional imaging unless markers are placed at the site of interest.

For unresected biliary tract cancers, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTHC), and MRI or magnetic resonance cholangiopancreatography (MRCP) demonstrate the distal and proximal extent of disease most precisely. If transhepatic catheters have been placed at the time of PTHC imaging, the radiation oncologist can reinject the catheter with contrast medium to reconstruct the ductal system and define target volumes. If stents have been placed at ERCP, the relationship of the stent to ductal involvement as demonstrated on ERCP imaging can be used to define tumor and target volumes. MRI can also effectively reveal these tumors and is commonly used. The medial and lateral disease extent is best distinguished with MRI/MRCP or PET/CT imaging.

With unresected pancreatic cancers, abdominal CT or MRI best demonstrates tumor and nodal target volumes, and PET/CT is used by some to better define the primary lesion and rule out early metastatic disease. If the tumor has been resected, postoperative CT or MRI scans of the abdomen can help rule out liver metastases and define postoperative nodal volumes, and the preoperative CT scan and surgical clips can be used to define the tumor bed.

Conformal three-dimensional radiation therapy with CT-based treatment planning is recommended for the

treatment of most, if not all, patients with GI cancer, and intensity-modulated radiation therapy (IMRT) is appropriate for some GI cancer sites, especially anal canal cancers. For patients with esophageal and gastroesophageal junction cancers, CT-based planning is useful in defining the medial-lateral and anteroposterior extent of tumor, but it should be combined with contrast radiographs, endoscopic information, and PET/CT imaging to determine the proximal and distal extent of the primary lesion. In patients with gastric cancer, the proximal stomach or gastric remnant is best defined by oral contrast images plus CT scanning because CT imaging alone may underestimate the anatomic location. With CT scanning for rectal cancer treatment planning, the precise location of the anal sphincter should be defined by placing BB markers or another type of metal marker at the anal verge. The anorectal margin is not visualized on a CT scan without contrast medium in the rectum. Fusion of PET/CT images may be helpful in defining the gross tumor extent for both rectal and anal lesions.

Definition of irradiation fields can be difficult in hepatic irradiation. It is critical to use high-quality CT or MR imaging and to have control over the liver position during the breathing cycle. Diagnostic images often need to be fused with treatment planning scans, and placement of fiducial markers can be useful for some radiation techniques, including stereotactic body irradiation (SBRT). Typically, these tumors do not have a large degree of extension into the hepatic parenchyma, but margins for uncertainty and breathing are critical.

Normal Tissue Tolerance

When irradiating the abdomen and pelvis, there are numerous normal structures that can be dose limiting and must be considered in treatment planning. These include the stomach, small intestine, spinal cord, large intestine, liver, and kidneys, in addition to the soft tissue in the abdomen. A full discussion of the tolerance of these structures is beyond the scope of this overview, but a brief review is given here.

Upper Gastrointestinal and Extrapelvic Colon Cancers

The tolerance of the liver is dose limiting when a substantial portion of the liver is included in the radiation field. The hepatic parenchyma is relatively sensitive to radiation, with total organ tolerance doses in the range of 30 Gy, using conventional fractionation (1.5 Gy to 2.0 Gy), being near tolerance. The ability to tolerate higher doses to portions of the liver is primarily dependent on the volume of liver receiving high doses because recovery of the hepatic parenchyma is dependent on hypertrophy of the unirradiated liver. In an individual with normal baseline hepatic function, it is possible to irradiate approximately 50% to 60% of the liver to high doses without undue problems if the remainder of the liver remains untreated (see Chapter 49). If hepatic function is compromised, less parenchyma can be safely treated, although an exact determination of the safe amount is not defined. Because it is possible to totally irradiate and destroy a portion of the liver without danger to the patient, there is essentially no limit to the dose that can be given to small portions of the liver, although biliary obstruction may be produced after high doses to the major biliary radicals. Dawson et al[53] have conducted a series of elegant clinical trials that define hepatic tolerance better than has been done for most other organs.

Hepatic tolerance is becoming a major issue with the increased interest in irradiating hepatocellular carcinomas and liver metastases. Although radiation oncologists have historically not had a major role in treatment of hepatocellular cancers, improvements in technology has allowed for better radiation dose delivery and a greater use of radiation in selected clinical situations, especially for localized but unresectable hepatocellular carcinomas. Preliminary data suggest that radiosurgical or fractionated SBRT approaches will be effective complements to surgical resection and radiofrequency ablative approaches.

The tolerance of the kidney is conceptually similar to that of the liver in that irradiation of a portion of the kidney to a high dose is well tolerated if the baseline renal function is good and if a significant portion of the remaining kidney is unirradiated to allow for hypertrophy (e.g., only 20% to 30% of the kidney receives more than 20 Gy). It is important to be certain that the baseline renal function is adequate (by measuring creatinine clearance or by estimating the clearance based on the creatinine level, age, gender, and weight of the patient, using the Cockcroft formula) and that the contralateral kidney is functioning properly so that it can take over the renal function. The latter is best done with a functional renal scan (such as a dimercaptosuccinic acid [DMSA] scan) that can provide the percentage of function from each kidney. Although the data on renal tolerance are fairly old, even moderate doses (in the range of 25 Gy) can produce substantial renal injury. Doses higher than 30 Gy are likely to produce major renal parenchymal injury. Studies suggest that clinically significant sequelae are unlikely after conventional abdominal irradiation if the preceding factors are taken into consideration.[54] Although it is possible to produce severe kidney injury with secondary renovascular hypertension, this is an uncommon event.

The stomach has generally been considered to be a radiation-sensitive structure, with ulcer formation occurring after doses greater than 45 Gy to 50 Gy (1.8-Gy to 2-Gy fractions), but precise gastric tolerance has not been well established. Although a large number of patients have received moderate to high doses of radiation therapy to the upper abdomen, this has usually been done for tumors that have a poor cure rate and for patients where survival of longer than 2 years is relatively unusual. The experience in the treatment of Hodgkin's disease clearly demonstrates gastric tolerance to doses of 45 Gy. When irradiating a portion of the stomach in the treatment of upper GI cancers, one must minimize both the volume and the dose to the stomach. It is of interest, however, that there are few recent data describing gastric ulceration, suggesting that some of the old tolerance data may not be reliable. Mayo Clinic data on the treatment of bile duct cancers suggest that gastroduodenal tolerance is best if doses of 54 Gy or less (in 1.8-Gy fractions) are used. With EBRT plus 5-FU, the rate of grade-3 or higher GI intolerance is 10% with doses of 54 Gy or less and 30% to 40% with doses of more than 54 Gy.[55]

Tolerance of the pancreas to radiation therapy is not often discussed, but there is anecdotal evidence that both exocrine and endocrine dysfunction can result, although analyses are complicated by the effects of the tumor and of surgery. It is appropriate for the radiation oncologist to consider the possibility of pancreatic dysfunction during patient follow-up. Pancreatic enzymes are commonly needed during and after therapy, and insulin is required at times.

Pelvic Gastrointestinal Cancers

The small bowel is the organ that has produced the most clinical problems after conventional radiation therapy in the pelvis. Moderate doses to the small bowel (50 Gy in 1.8-Gy to 2-Gy fractions) will begin to cause clinically significant problems. It has been suggested that risk factors for injury include diabetes and hypertension as well as prior surgery, but this finding has not been well substantiated. It is clear that the volume of irradiated small bowel is also important, but it has not been well quantified as to how much bowel can be treated safely. When

larger volumes are treated, small bowel obstruction is the most likely complication.[56] The obstructive episodes can be recurrent, and 50% or more of patients may require laparotomy for resolution. At surgery, it is often not possible to resect the damaged small bowel, which is usually enveloped in a fibrotic mass, and a surgical bypass may be the treatment of choice. However, if the damaged bowel can be resected with low morbidity, that approach is optimal. Dissection of irradiated bowel in an attempt to free up all adhesions may result in enterotomy and subsequent fistula. Small bowel complications are most common with irradiation of the pelvis, an area that has commonly been exposed to extensive surgery with associated adhesions and small bowel fixation. Although complications are less likely in the upper abdomen, they can still occur, and efforts should be made to minimize the volume of irradiated small bowel.

There are a number of manipulations that the radiation oncologist can use to minimize the amount of small bowel in a pelvic irradiation field, including the use of IMRT or three-dimensional conformal irradiation techniques. The first action is to determine the location of the small bowel. This can be done by giving oral small bowel contrast medium at least 45 minutes before a radiographic imaging study, either by conventional simulation or CT scanning. With this information, the radiation oncologist can design fields that will minimize the volume of small bowel irradiated. It is also helpful to work with a surgeon who can perform surgical manipulations to move the small bowel out of the pelvis. A number of techniques have been tried, including reperitonealization of the pelvic floor after abdominoperineal resection, using a vascularized omental sling or pedicle to displace small bowel out of the pelvis, retroverting the uterus to act as a space-occupying device, and putting mesentery or a foreign body into the pelvis for the same purpose. In addition, during simulation, one can use bladder distention or displacement devices to shift small bowel out of the pelvis. Having the patient lay in the prone position on a false tabletop located at or superior to the radiation field (9-cm × 12-cm opening) is one technique that has been effective for many patients. These techniques work to a varying extent on individual patients.[57] Small bowel being fixed in the pelvis is much less of a problem when patients are receiving preoperative radiation therapy for rectal cancer, the standard of care at this time. Whichever approach is taken, the treating physician must pay attention to the location of the small bowel and dose to the organ or risk significant complications.

There is less information on the tolerance of the large bowel (colon and rectum) to high radiation doses, and much of the information available comes from irradiation of non-GI tumors, especially those of the prostate and cervix. There is little information on the tolerance of the colon, partially because there has been little high-dose irradiation of the intraperitoneal or retroperitoneal colon. Rarely is the colon a dose-limiting structure. The rectum or portions of it have been treated to doses of 65 Gy to 70 Gy or higher for cervical, prostate, and anal cancers and for localized treatment of rectal cancers. It is clear that portions of the rectum can be treated to high doses with minimal late effects. The most obvious example of this is in the use of endocavitary radiation therapy of small rectal cancers. In this technique, doses of approximately 90 Gy to 120 Gy have been delivered in four fractions. Although the rectal muscular wall receives a low dose from the first two fractions because of rapid dose fall-off, it receives a full dose for the last one to two fractions. Late complications such as bleeding and ulceration occur in 10% to 15% of patients, and only an occasional temporary diverting colostomy is needed, likely because the rectal mucosa can be repopulated from surrounding normal tissue and because the area of scarring is not large enough to cause stricture formation.

However, when high doses of radiation are given to a substantial portion of the rectal circumference (i.e., more than half), the tolerance is much less. With circumferential irradiation, the dose to a 10-cm length of rectum is preferably limited to 60 Gy or less in 2-Gy fractions to prevent problems with bleeding, ulceration, and narrowing of the rectum. Even with partial organ radiation therapy, there have been significant problems with bleeding (10% to 15% incidence) reported at doses of approximately 72 Gy. Although conservative treatment with bulk agents and steroid preparations can alleviate most situations, laser therapy at the time of endoscopy may be necessary to control bleeding. Difficult management problems are rare but at the extreme can require surgical correction, usually a temporary diverting colostomy.

There is even less information available on anal tolerance. However, it is generally thought that doses higher than 55 Gy to 60 Gy to the whole anal canal in conjunction with chemotherapy, as used in the treatment of anal cancer, have a risk of stricture formation or poor anal sphincter function. In the treatment of rectal cancer, one should try to minimize the amount of anus in the radiation field because anal irradiation produces a large amount of acute morbidity, occasional stricture formation, or poor late functioning of the anus. There is clearly a significant risk of late morbidity in anorectal function that can cause clustering and frequency of bowel movements with suboptimal control and intolerance to certain foods.[58] These effects are likely the result, at least partially, of anal dysfunction as well as poor rectal capacity from surgery or irradiation. Minimizing the radiation dose and volume and careful surgical techniques need to be used to minimize the risk of late complications.

Irradiation Boost Techniques

For completely resected, margin-negative GI cancers, adjuvant doses of irradiation (50 Gy to 54 Gy) plus concomitant 5-FU–based chemotherapy are adequate to achieve local control in 85% to 90% of patients. For margin-positive or unresected GI cancers, the dose of irradiation required to achieve adequate local control would usually exceed the normal tissue tolerance (e.g., >70 Gy in 1.8-Gy to 2-Gy fractions). Therefore, the use of brachytherapy or intraoperative electron irradiation (IOERT) as a supplement to EBRT and chemotherapy after resection may improve local control rates in the treatment of locally advanced GI cancers.

The use of IOERT as a component of treatment for a variety of disease sites is discussed in Chapter 17 and for GI malignant diseases in Chapters 47, 48, 50, and 51. IOERT plus EBRT (with or without 5-FU) and maximal resection appear to improve rates of both local control and survival for locally unresectable and locally recurrent colorectal cancers.[59-61] With unresectable pancreatic cancers, the addition of IOERT to EBRT with or without 5-FU improves local control rates but has no apparent impact on survival rates in view of the high rates of relapse in the liver and peritoneal cavity.[62-64]

Brachytherapy has been used as a supplement to EBRT with biliary tract cancers.[65,66] There is a suggestion of improved survival rates in patients treated with both EBRT and brachytherapy compared with either alone (see Chapter 49), but Phase III trials are unlikely in view of small patient numbers.

SUMMARY

Radiation therapy is now a part of the therapeutic approach for many patients with cancers of the GI tract, although mostly for patients with moderately advanced locoregional disease. In most of these sites, the combination of radiation therapy

and 5-FU–based chemotherapy is standard therapy, although cisplatin or mitomycin is used with 5-FU in tumors of the esophagus and anus. In many GI cancer sites, chemoradiation is used as an adjuvant to surgical resection because of the propensity of GI rumors to recur locally and the difficulty in obtaining a wide resection margin, usually relating to the anatomic site. Careful attention to radiation therapy technique and respect for normal tissue tolerance are essential if local control is to be obtained without producing unacceptable normal tissue morbidity.

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