Gastrointestinal and Hepatobiliary Toxicities of Cancer Treatments

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Author's disclosures of potential conflicts of interest are found at the end of this article.

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Abstract

Individuals undergoing multimodality treatments for cancer are at risk for treatment toxicities that can negatively impact the entire gastrointestinal (GI) tract and the liver. These toxicities can be short term or they can linger for years after completion of treatment. Early assessment and recognition of patient symptoms allows for early intervention and management of toxicities. Some of the toxicities that impact patients include xerostomia, trismus, malabsorption, neutropenic typhlitis, nonalcoholic fatty liver disease, veno-occlusive disease, and anterior resection syndrome. Symptoms affecting the GI tract are often underreported because of the social stigma of bowel problems. Accurate assessment is critical to optimal clinical management of toxicities. The treatment challenge is to prevent or manage these GI tract toxicities so that patient function is optimized and quality of life is maintained.

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The combined modalities of oncologic treatment can impact multiple body systems. Chemotherapy, radiotherapy, and targeted therapies all present challenges to the balance of efficacy and toxicity. Individuals undergoing cancer treatments demonstrate these effects of treatment both at the initiation of treatment and also commonly long after therapy has ended. These treatment toxicities can adversely affect any portion of the gastrointestinal (GI) tract. Adverse events include oral complications, esophagitis, gastroparesis, pancreatitis, malabsorption, hepatotoxicity, and diarrhea. Long-term effects of treatment also impact cancer survivors' GI tract function and quality of life (QOL).

Oral Complications

Oral toxicities from cancer treatments include mucositis, xerostomia, dysgeusia, periodontal disease, caries, and trismus. Oral mucositis is notoriously characterized in the hematologic transplant setting where patients receive high-dose, myeloablative chemotherapy. This toxicity is also frequently seen in patients receiving other chemotherapies for a variety of solid malignancies. Oral mucositis usually begins 5 to 10 days after the start of chemotherapy. Dryness progresses to erythema with subsequent

erosions and/or ulcerations in the friable epithelium of the buccal mucosa, floor of the mouth, tonsillar folds, and tongue. If mucositis extends into the pharynx, then this adds to pain, difficulty maintaining oral nutrition, and problems with speech and swallowing. Mucosal ulceration offers an entry point for local bacterial, fungal, and viral infections or gram-negative, anaerobic septicemia. *Herpes simplex* virus, Epstein Barr virus, and cytomegalovirus are all possibilities for oral infection, especially in the setting of neutropenic mucositis (Walsh, 2010). Primary treatment of oropharyngeal candidiasis includes clotrimazole 10 mg five times daily or nystatin suspension four times daily. Fluconazole 100–200 mg is recommended for moderate to severe candidiasis, and 7 to 14 days of topical therapy is recommended for mild cases (Pappas et al., 2009).

Mucositis prevention strategies include dental evaluations and care prior to initiation of treatment, meticulous oral hygiene with frequent changes of soft toothbrushes, and salt and baking soda mouth rinses. Cryotherapy, or sucking on ice chips, is a cost-effective recommendation for high-dose melphalan or bolus fluorouracil (5-FU) oral mucositis prevention (Keefe et al., 2007). Palifermin (Kepivance), a recombinant human keratinocyte growth factor that stimulates epithelial cell growth, is approved for use in hematologic stem-cell transplantation for prevention of severe mucositis (Hensley et al., 2009). One randomized, double-blind trial (Vadhan-Raj et al., 2010) evaluated palifermin given as a single dose before each cycle of doxorubicin-based chemotherapy in sarcoma patients. Forty-eight patients were randomized in a 2:1 ratio to receive palifermin or placebo. Palifermin reduced the cumulative incidence of moderate to severe mucositis (44% vs. 88%; $p < .001$) and severe mucositis (13% vs. 51%; $p = .002$).

Xerostomia and dysgeusia are additional early or late treatment-related toxicities that can greatly impact QOL. Decreased saliva negatively affects speech and swallowing and hastens the development of dental caries. External beam radiotherapy to the head and neck can have adverse lifelong effects on QOL, but chemotherapy-induced xerostomia more often occurs only during the course of treatment. Oral mucosal lubricants and saliva substitutes have been found to be beneficial but only for a short time (Jensen et al., 2010).

Acupuncture is a safe intervention for radiation-induced xerostomia with some residual functioning of the salivary glands. It is a safe, supportive modality to stimulate salivary gland secretion after delivery of radiation therapy to the head and neck. Efficacy was demonstrated in a pilot study (N = 19) of patients with squamous cell carcinoma of the head and neck treated with radiation to a mean dose of 68.2 Gy. Median time from completion of radiation to the beginning of acupuncture was 2.35 years. Acupuncture was given twice a week for 4 weeks, and response to acupuncture treatment was measured 1 month later. The partial response rate was 55.6%. Additionally, QOL measurements were significantly better at weeks 4 and 8 compared to baseline (Garcia et al., 2009). Although the number of patients in this study was small, the positive results warrant further trials to explore the efficacy of this therapy.

Intensity-modulated radiotherapy is conformal radiotherapy that may be designed to spare the major salivary glands. In head and neck cancer, irradiation to the salivary glands is reduced to help prevent radiation-induced xerostomia and thus afford quicker recovery of salivary secretions (Nutting et al., 2011).

Head and neck patients who undergo surgery and chemoradiation are at risk for development of trismus, or limited mouth opening. Trismus contributes to swallowing dysfunction, eating, drinking, and voice and speech difficulties. Trismus, defined as a condition in which the mouth can open less than 30 to 40 mm, is directly related to the dose of radiation administration (Dijkstra, Huisman, & Roodenburg, 2006; Teguh et al., 2008). The extent to which function is lost and the decrease in range of mandibular opening appear related to damage and fibrosis of the mastication muscles (Wang et al., 2005). Rehabilitation therapy for trismus includes tongue spatulas, the TheraBite Jaw Motion Rehabilitation System,

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Use your smartphone to access the CDC's guidelines for medical management of patients with chronic hepatitis B virus infection.

and physical and speech therapy (Garnett, Nohl, & Barclay, 2008).

Esophagitis

Patients who have undergone esophagectomy can experience reflux esophagitis or pharyngolaryngeal reflux depending on tumor location, surgical approach, and reconstructive technique employed. In the case of a cervical esophagogastrostomy, esophageal reconstruction is performed utilizing a gastric conduit. Gastric secretions then can reflux into the pharynx and larynx. If bile acids reflux into the stomach a more severe reflux pharyngolaryngitis can occur (Nishimura et al., 2010a). Reflux esophagitis and columnar-lined esophagus can develop after esophagectomy depending on the time and reconstructive technique performed.

The incidence of reflux esophagitis post-esophagectomy ranges from 44% to 71.9% (da Rocha, Ribeiro, Sallum, Szachnowicz, & Cecconello, 2008; O'Riordan et al., 2004; Yamamoto et al., 2007). Reflux esophagitis with subsequent development of columnar-lined esophagus is a risk factor for esophageal adenocarcinoma. Reported incidence rates of reflux after esophagectomy range from 11% at 1 year after surgery to 40% at 2 years after surgery (da Rocha et al., 2008; Nishimura et al., 2010b). Acid suppression using proton pump inhibitors or H2 blockers is typically utilized if reflux symptoms develop. Endoscopic evaluation and surveillance is warranted for post-esophagectomy patients, particularly if painful swallowing or dysphagia develops.

Malabsorption

Malabsorption can manifest in a variety of circumstances as a result of all cancer treatments. Gastrointestinal bacteria metabolize bilirubin, pancreatic enzymes, fatty and bile acids, cholesterol, and steroid hormones. Nutritional processing, control of intestinal angiogenesis, and immune functions are additional functions of the GI bacteria (Dai & Walker, 1999; Gorbach, 1971; Rhee, Sethupathi, Driks, Lanning, & Knight, 2004). The duodenum and jejunum contain fewer bacteria than the stomach or large colon, and these bacteria are more similar to those in the stomach. Normal peristalsis and motility are the main defenses against bacterial overgrowth in the small intestine (Heller & Duchmann, 2003; Stringer, Gibson, Bowen, & Keefe, 2009). Surgeries including gastrectomy, pancreaticoduodenectomy, and intestinal bypass for obstruction can create blind loops of bowel (Bustillo, Larson, & Saif, 2009; Paik et al., 2011). External beam radiotherapy, used in treatment of rectal, anal, endometrial, cervical, and prostate malignancies, can also contribute to small intestinal bacterial overgrowth (SIBO) and lactose intolerance (Wedlake, Thomas, McGough, & Andreyev, 2008).

Bacterial overgrowth can result in diarrhea, bloating, gassiness, and abdominal pain. Steatorrhea, megaloblastic anemia, and nutritional macro- and micronutrient malabsorption can be present. The glucose hydrogen breath test helps diagnose SIBO. Antibiotic therapy coverage for both aerobic and anaerobic bacteria are recommended (Singh & Toskes, 2004). Optimal nutritional intake and repletion with correction of any nutrient deficiencies is part of treatment for SIBO.

Pancreatic exocrine insufficiency is another factor that can contribute to intestinal malabsorption. It can occur with pancreatic, ampullary, or other upper GI surgeries as well as with chemoradiotherapy. While it is rare, pancreatic insufficiency has also been diagnosed in patients with chronic graft-vs.-host disease after hematopoietic stem cell transplantation (Akpek, Valladares, Lee, Margolis, & Vogelsang, 2001). Fat malabsorption with steatorrhea and high fecal fat load is common. This is because lipase is the most "unstable" pancreatic enzyme during gastrointestinal transit. This is thought to be due to the deactivation of pancreatic lipase in acidic pH. Intestinal secretions, which are normally alkaline, can turn acidic in the proximal small bowel (duodenum and jejunum) due to low pancreatic bicarbonate secretion (Dominguez-Munoz, 2007). Other hallmark symptoms of pancreatic insufficiency include diarrhea, indigestion, postprandial cramping, floating stools, and weight loss. Pancreatic enzyme repletion is indicated to correct pancreatic insufficiencies in protein, carbohydrate, and fat digestion and metabolism.

Pancreatic enzymes currently approved by the US Food and Drug Administration (FDA) include Creon, Pancreaze, and Zenpep. Brands still under review include Pancrecarb, Ultrase, and Viokase. It is generally recommended to take one enzyme tablet at the beginning of a meal or snack. For a regular-sized meal, one enzyme

tablet should also be taken halfway through the meal (only one tablet is recommended with snacks). The recommended brand and number of pancreatic enzymes is individualized and may change over time. Constipation can result from overuse of pancreatic enzymes. Other side effects may include nausea, abdominal cramps, or diarrhea.

Pancreatitis

Acute pancreatitis is rare with chemotherapeutic agents but has been seen in association with paclitaxel, ifosfamide, cisplatin, and cytarabine. Other causes of pancreatitis such as gallstones, pancreatic duct stricture, and obstruction are also possible. Preventative antiemetic drugs including steroids and 5-hydroxytryptamine-3 receptor ($5\text{-}HT_3$) antagonists have been identified as having causality in cases of pancreatitis. Other drugs known to cause acute pancreatitis include tamoxifen, metronidazole, and furosemide (Runzi & Layer, 1996). Nausea, vomiting, and abdominal pain are common symptoms of pancreatitis. Diagnosis is made in the presence of elevated amylase and lipase, usually three times the upper limit of normal. Abdominal CT scan should be performed to look for pancreatic inflammation and edema. Medical management, including IV hydration, analgesia, and bowel rest, is usually sufficient to correct and quiet chemotherapy-induced pancreatitis (Morgan, Tillett, Braybrooke, & Ajithkumar, 2011).

Diarrhea

Cancer-related diarrhea is usually treatment related and can develop with surgery, chemotherapy, targeted therapies, radiation therapy, and hematologic transplants. Causes of acute diarrhea can include antibiotic therapy or infectious etiology such as bacterial, viral, parasitic, or fungal infections. *Clostridium difficile* is commonly responsible for pseudomembranous colitis and is the most common nosocomial infection of the GI tract (DuPont, 1997; Kelly, Pothoulakis, & LaMont, 1994). Diarrhea is defined as an abnormal increase in the quantity, frequency, or wateriness of stool and is associated with urgency, perianal discomfort, and incontinence (Basch, 1987). Postoperative reconstructive techniques of GI surgeries may contribute to diarrhea because of increased transit time, fluid and electrolyte imbalance, gastroparesis, and dumping syndrome (Grant, Chapman, & Russell, 1996).

Chemotherapy-induced diarrhea (CID) is thought to be due to the toxicity of rapidly dividing crypt cells of the intestinal epithelium and the effect of intestinal enzymes. The balance between absorptive and secretory capacities is disrupted. Osmotic gradients in the gut are distorted, which results in higher volumes of fluids and electrolytes in the stool (Richardson & Dobish, 2007; Viele, 2003). Some chemotherapeutic agents such as irinotecan, 5-FU, and capecitabine (Xeloda) are systemic chemotherapies notorious for acute damage to intestinal mucosal epithelium and considerable diarrhea (Benson et al., 2004b). Bone marrow transplantation and graft-vs.-host disease after bone marrow or stem cell transplant can result in diarrhea.

Diarrhea is common in patients being treated with small-molecule epidermal growth factor receptor tyrosine kinase inhibitors, and is seen in up to 55% of patients receiving erlotinib and in about 34% of patients receiving sorafenib (Nexavar), a small-molecule inhibitor (Perez-Soler et al., 2004; Strumberg et al., 2007).

Patients should be assessed and categorized as having either complicated or uncomplicated diarrhea. See Table 1 for common causes of diarrhea, which should be ruled out as causative or contributing factors. It is crucial to accurately assess the patient for hemodynamic compromise; specific areas to cover include the presence or absence of orthostatic symptoms, weakness, cramping, fever,

Table 1. Nonchemotherapeutic Causes of Diarrhea

Drugs: antibiotics, magnesium supplements, laxatives, sorbitol-containing chewing gum and candy
Comorbidities: diabetes, hyperthyroidism, diverticulitis, HIV/AIDS, Crohn's disease, ulcerative colitis
Infection: Bacterial—*Clostridium difficile, Shigella, Salmonella, Campylobacter jejuni* Parasitic—*Amebiasis, Giardia, Cryptosporidiosis* Viral—*Rotavirus, Adenovirus*
Malabsorption: lactose intolerance, celiac disease (sprue), hypertonic/high osmolar caloric supplements
Motility: partial bowel obstruction, constipation/impaction

Note. Information from NCI (2010).

and abdominal pain (Table 2). Uncomplicated CID includes no other complicating symptoms such as cramping, nausea and vomiting, fever, neutropenia, bleeding, or dehydration. If one or more of these symptoms is present, then complicated CID exists (Benson et al., 2004a). Uncomplicated CID is managed with loperamide and dietary adjustments. If uncomplicated CID lasts more than 24 hours, a more aggressive regimen should be initiated and a fluoroquinolone such as ciprofloxacin should be considered for infection prophylaxis (Rothenberg, Meropol, Poplin, Van Cutsem, & Wadler, 2001). Persistent uncomplicated diarrhea requires outpatient examination and evaluation including complete blood count, electrolytes, and stool for pathogens. Hospitalization for aggressive hydration and repletion of electrolytes is appropriate for complicated and grades 3/4 CID (NCI, 2010).

Table 2. National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) Version 4

Grade	Description
1	Increase of < 4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥ 7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death

Note. Information from NCI (2010).

Glutamine is an essential amino acid that serves as a fuel for the enterocyte. While glutamine may provide protection to intestinal mucosa against chemotherapy-induced damage, there has been insufficient evidence to recommend standard use (Daniele et al., 2001; Pan et al., 2005; Ziegler et al., 1998). Dietary changes for diarrhea management include avoidance of milk and diary products as well as high-fiber and gas-forming foods. Patients should be advised to increase intake of hydrating liquids such as broths, sports drinks, decaffeinated beverages, and clear liquids, up to 3 liters a day.

First-line pharmacologic management of grade 1 and 2 diarrhea starts with loperamide. This synthetic opiate derivative slows gastrointestinal peristalsis, which increases intestinal transit time and promotes fluid reabsorption. The recommended loperamide regimen is an initial dose of 4 mg followed by 2 mg every 4 hours or after every loose bowel movement up to a maximum of 16 mg. The higher-dose loperamide regimen for more severe diarrhea consists of 4 mg followed by 2 mg every 2 hours at every episode of diarrhea. Alternately, this regimen can be changed to 4 mg every 4 hours as long as diarrhea is present (Benson et al., 2004a; Cascinu et al., 2000). Despite aggressive treatment with loperamide, up to 30% of patients will not respond and may require hospitalization. Dose modifications in chemotherapy are indicated in grade 2 diarrhea once the patient has recovered (Kornblau et al., 2000).

Octreotide is a synthetic analog of the natural hormone somatostatin. It is effective in the management of hormonal diarrheal syndromes in carcinoid syndrome or other malignant hypersecretion syndromes of vasoactive intestinal peptide and gastrin. In these cases, octreotide preferentially binds to type II somatostatin receptors on the tumor cells and suppresses hormone production, which in turn limits diarrhea (Kvols et al., 1986; Saltz, 2003). Somatostatin increases GI transit time and increases intestinal water reabsorption, and thus decreases intestinal secretions and diarrhea.

Octreotide is indicated in treatment of CID. A dose of 100 to 150 µg SC 3 times a day has achieved complete resolution of CID. The dose may be increased to 500 µg 3 times a day until diarrhea is contained (Benson et al., 2004a; Richardson & Dobish, 2007). Octreotide is also available in a long-acting release (LAR) injection. The STOP trial (Sandostatin LAR Depot Trial for the Optimum Prevention of Chemotherapy-Induced Diarrhea) was designed to determine effects of 30- and 40-mg LAR dosing in the prevention of CID. Patients on the higher dose appeared to have less diarrhea and less IV supplementation, but these results were not statistically significant (Rosenoff et al., 2006).

Enteritis

Radiation therapy to the abdomen or pelvis can injure GI mucosa and result in enteritis. The severity of the gut injury depends on the radiation dose, the amount of the bowel in the radiation field, and whether concurrent chemotherapy is being administered. Intestinal enteritis is commonly seen as diarrhea, bloating, gas, and cramping. Acute enteritis can persist for many weeks after the radiation therapy is completed. Chronic radiation enteritis can develop months or even years later (Samper-Ternent, Zhang, Kuo, Hatch, & Freeman, 2011).

Enterocolitis

Neutropenic typhlitis (enterocolitis) is a severe complication that can occur in up to 5% of patients treated with high-dose chemotherapy or diagnosed with hematologic malignancies. Chemotherapeutic agents that have been associated with neutropenic typhlitis include the taxanes, cisplatin, oxaliplatin, irinotecan, and the anthracyclines (Furonaka et al., 2005; Gadducci, Gargini, Palla, Fanucchi, & Genazzani, 2005). In neutropenic typhlitis, transmural bowel inflammation and injury begin due to cytotoxics. Secondary infection follows in this neutropenic, immunocompromised situation. Bacterial translocation leading to sepsis follows and ultimately can result in bowel perforation and death. The cecum is usually affected due to its limited blood supply, but the enterocolitis can also affect the small bowel and right and left colon (Davila, 2007). Symptoms usually occur within 30 days of cytotoxic chemotherapy and generally include fever, abdominal distension and pain, vomiting, and diarrhea (Cloutier, 2010; Gomez, Martino, & Rolston, 1998; Morgan et al., 2011). Abdominal CT scan is diagnostic to detect bowel wall thickening, pericolic inflammation, pneumatosis intestinalis, and ascites (Cronin et al., 2009).

Medical management should include broad-spectrum antibiotics with anaerobic coverage, granulocyte colony-stimulating factor, and fluid resuscitation. Total parenteral nutrition is frequently administered due to prolonged bowel rest. Surgery is reserved for cases of bowel obstruction, perforation, or when conservative management is unsuccessful and the clinical situation worsens (Morgan et al., 2011).

Hepatotoxicity

Patients with preexisting liver disease are more at risk for chemotherapy and drug-induced hepatotoxicity. There are numerous causes for abnormal serum liver biochemical tests (Table 3). Chemotherapy, including monoclonal antibodies, can reactivate hepatitis B virus (HBV). Reactivation is most common in patients with hematologic malignancies but is also possible in patients with solid tumors (Dai, Wu, Shyu, Lu, & Chao, 2004; Yeo et al., 2004b; Yeo et al., 2004c). In patients with lymphoma who are positive for hepatitis B virus surface antigen, reactivation rates may reach as high as 73% when undergoing chemotherapy. Potential problems of HBV reactivation include liver damage due to resurgent hepatitis, interruptions in oncologic treatment, and a mortality rate up to 5% (Cheng et al., 2003; Liang, Lau, & Kwong, 1999). Prophylactic treatment with anti-HBV nucleoside/nucleotide analogs such as lamivudine reduces the incidence and severity of reactivation hepatitis in HBV carriers receiving cytotoxic chemotherapy (Katz, Fraser, Gafter-Gvili, Leibovici, & Tur-Kaspa, 2008; Keeffe et al., 2006; Yeo et al., 2004a).

Chronic HBV carriers may be asymptomatic and therefore without a diagnosis. The US Centers for Disease Control and Prevention have published guidelines recommending that all patients about to receive cancer chemotherapy be tested for hepatitis B serum antigen prior to initiating chemotherapy; if positive, prophylactic nucleoside/nucleotide treatment should be initiated (Lee, Vu, Bell, & Hicks, 2010; Sherman et al., 2007; Weinbaum et al., 2008). The impact of chemotherapy on hepatitis C virus reactivation is unclear. Hepatitis C virus infection appears to increase the chance of abnormal liver function tests but severe episodes of clinical hepatitis are unusual (Shafi & Bresalier, 2010).

Chemotherapy-induced acute liver failure and mortality has been documented in a few cases where gemcitabine, docetaxel, and liposomal doxorubicin were administered (Hengge, Brockmeyer, Rasshofer, & Goos, 1993; Saif, Shahrokni, & Cornfeld, 2007). Transaminitis induced by chemotherapy is common, but the patterns of liver injury can vary greatly from cholestasis to necrosis to sinusoidal obstructive syndrome, also known as veno-occlusive disease. Chemotherapy initially injures the sinusoidal endothelial cells

and erythrocytes embolize and clog, then block venous outflow. This in turn results in hepatic congestion and sinusoidal congestion. Later on, a fibrotic reaction in the sinusoids can deteriorate to obliteration of central venules and hepatic sinusoidal obstruction syndrome (Chun, Laurent, Maru, & Vauthey, 2009); see Figures 1 and 2.

This life-threatening complication is most common in high-dose chemotherapies. Up to 20% of patients can develop this toxicity after high-dose cyclophosphamide, busulfan, thiotepa, melphalan, or vincristine. Usually self-limiting, venoocclusive disease may be fatal in up to 30% of cases (de Jonge, Huitema, Beijnen, & Rodenhuis, 2006; Lee, Gooley, Bensinger, Schiffman, & McDonald, 1999; Morgan et al., 2011). Oxaliplatin, used commonly in the treatment of GI malignancies, can be implicated in up to 52% of cases of sinusoidal injury (Aloia et al., 2006; Chun, et al., 2009; Vauthey et al., 2006).

The range of steatosis and liver changes linked to fat accumulation in hepatocytes is referred to as nonalcoholic fatty liver disease (NAFLD). It is linked to insulin resistance and metabolic syndrome. NAFLD can either be indolent or progress to fibrosis and cirrhosis (Adams et al., 2005; McCullough, 2004; Salt, 2004). Chemotherapy-induced NAFLD is known to occur with 5-FU. Irinotecan and tamoxifen are well known to cause steatohepatitis, which can progress to fibrosis, cirrhosis, and liver failure. Caution is recommended if treating with irinotecan-based chemotherapies in cases of known steatosis or steatohepatitis or in individuals with risk factors for steatosis such as high body mass index, diabetes mellitus, or metabolic syndrome (Zorzi et al., 2007).

Table 3. Common Nonmalignant Causes of Abnormal Serum Liver Biochemical Tests

	Potential causes
Increased alkaline phosphatase	Paget's disease Hyperparathyroidism and increased parathyroid hormone Any reason for increased bone turnover Fracture repair Cirrhosis
Increased gamma-glutamyltransferase	Alcohol Drugs (phenytoin, barbiturates) Fatty liver or obesity Diabetes Myocardial infarction
Increased alkaline phosphatase and gamma-glutamyltransferase	Biliary duct obstruction Cholecystitis or cholelithiasis
Increased aspartate aminotransferase	Cardiac or skeletal muscle death Hemolysis Alcoholic hepatitis (commonly AST > 2 times ALT) Chronic liver disease or cirrhosis
Increased aspartate aminotransferase and alanine aminotransferase	Markers of hepatocellular damage Hepatitis Drugs (statins, amiodarone) Nonalcoholic steatohepatitis Ischemic liver damage
Increased bilirubin	Hemolysis Gilbert's syndrome Drugs (capecitabine, mitomycin)
Decreased albumin	Malnutrition Malabsorption Liver failure Nephrotic syndrome Inflammatory states Ascites
Increased INR or prothrombin time	Liver disease or cirrhosis Coagulopathy (disseminated intravascular coagulation) Vitamin K deficiency

Note. ALT = alanine aminotransferase; AST = asparate aminotransferase; INR = international normalized ratio. Adapted, with permission, from Field et al. (2008).

Liver-directed therapies are commonly employed in the treatment of metastatic colorectal and hepatocellular cancers. Transarterial chemoembolization, yttrium-90 microspheres, and stereotactic body radiation therapy (SBRT) can be performed even in some cases when liver function is compromised. Adverse events can include abdominal pain, biliary stricture, and necrosis and GI ulceration due to collateral vessels shunting to the intestine from the hepatic arterial system (Atassi

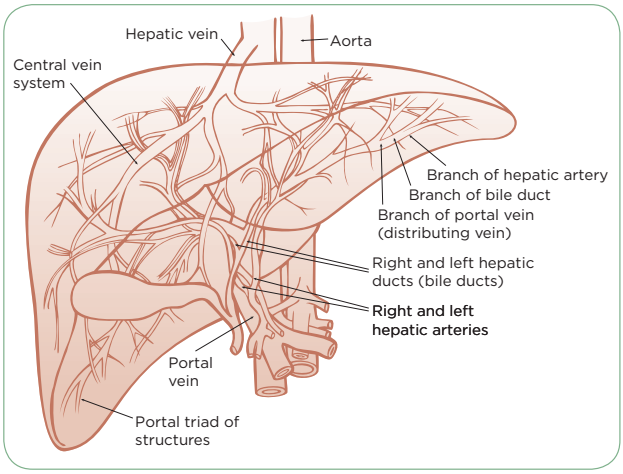

Figure 1. Internal anatomy of the liver.

et al., 2008; Hilgard et al., 2010; Khrizman, Small, Dawson, & Benson, 2010). Stereotactic body radiation therapy, originally developed from stereotactic radiosurgery of intracranial malignancies, delivers high-dose radiation with extreme accuracy to malignant targets. Toxicities related to SBRT can include nausea, anorexia, gastroparesis, and duodenal ulcers (Khrizman et al., 2010).

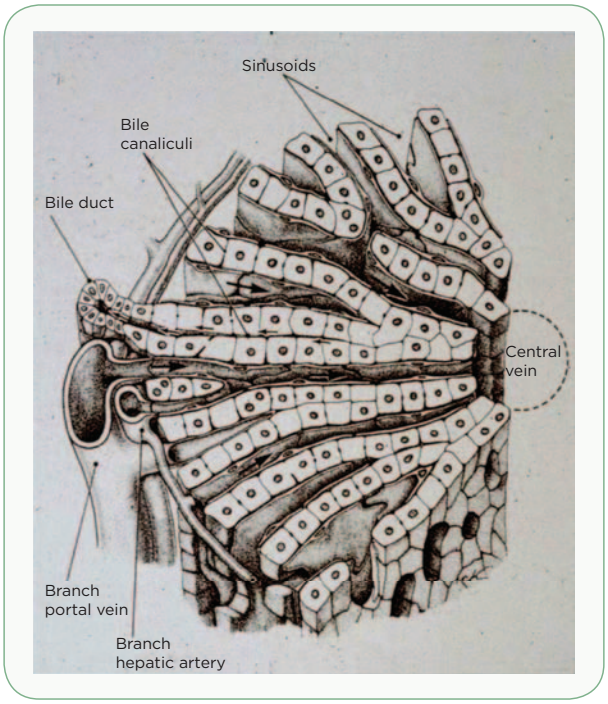

Figure 2. Summary diagram of liver hepatocyte organization in a lobule, showing the direction of the flow of bile toward the bile ducts in the portal triads.

Any abnormalities in liver function tests in a patient on chemotherapy or following liver-directed therapy need to be closely monitored and evaluated to exclude worsening preexisting liver disease, progression of hepatic metastatic disease, or toxicity from poorly metabolized drugs during liver failure. Liver ultrasound and hepatitis panels are essential components of diagnostics for patients on chemotherapy with deterioration in liver function (Morgan et al., 2011).

Long-Term Sequelae

Individuals who have undergone curative external beam radiotherapy for rectal and anal canal cancers often have chronic symptoms from their treatment. These symptoms are frequently underreported because of the social stigma of bowel problems (Arndt, Merx, Stegmaier, Ziegler, & Brenner, 2004; Desnoo & Faithfull, 2006). Pelvic radiotherapy impacts rectal elasticity. Radiation-induced fibrosis of the pelvic floor muscles and anal sphincter can occur and result in fecal incontinence (Hassan & Cima, 2007). Pelvic radiotherapy may result in increased frequency or clustering of bowel movements and occasional or frequent incontinence, which in some cases may be permanent (Lundby et al., 2005). Therapy for rectal cancer includes multimodality treatment, including surgery. Surgical technique for rectal resection has focused on sparing the sphincter and avoiding permanent ostomy. Unfortunately, however, intact colorectal continuity may result in stooling frequency, urgency, and incontinence.

Desnoo and Faithfull (2006) describe the experiences of cancer survivors with anterior resection syndrome in their quality-of-life study. Unpredictability and control of bowel function led patients to try remedies to reduce frequent bowel movements and protect clothing from soilage, to thereby achieve some sense of normalcy. Another study (Schneider et al., 2007) examined survivors of colorectal cancer 4 years out from diagnosis and found the most commonly reported symptoms were fatigue (23%), negative self-image (14%), diarrhea (13%), and constipation (7%). Thorough assessment of bowel function needs to continue long-term after the treatment concludes. Assessment of stool frequency needs to include volume and consistency because it directs recommendations for either a bulk-forming fiber agent or an antidiarrheal. Patients often re-

port frequent stooling as diarrhea when in fact, frequent small stools are a sign of constipation. Soluble-fiber–containing supplements such as Benefiber are commonly recommended for treatment of constipation. Soluble fiber assists to bulk stool, decrease stool transit time, and decrease constipation (Ternent et al., 2007). The clinical challenge becomes complete assessment of bowel function in the context of decreased rectal compliance and elasticity. These longer-term sequelae impact emotional, cognitive, and social functioning domains of quality of life and can be the greatest challenges for cancer survivors.

Conclusion

Balancing therapeutic benefit and the toxicity of treatment provides an ongoing challenge to oncologic patient care. Multimodality treatments can adversely affect the entire GI tract and liver. Accurate assessment and early recognition of symptoms is crucial to provide timely management of GI tract and hepatobiliary toxicities. Maintenance of optimal GI tract function translates into optimal patient function and quality of life.

CONFLICTS

The author has no conflicts of interest to disclose.

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