

REVIEW

Imaging of complications of oncological therapy in the gastrointestinal system

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Abstract

Treatment of cancer involves a multidisciplinary approach consisting of surgery, chemotherapy, molecular targeted therapy and radiation therapy. These therapies work on the tumor cells to result in cell stasis or cell death. The same mechanism can result in toxicity to the normal gastrointestinal tract. Radiation therapy can cause acute and chronic injury. The chronic injury results from involvement of the vascular supply of the gastrointestinal tract and by causing fibrosis. The purpose of this article is to describe the imaging of complications resulting from oncologic treatment in the gastrointestinal system.

Keywords: *Complications; oncological therapy; gastrointestinal; radiation enteritis; toxicity.*

Introduction

Oncologic therapy targets actively dividing cells such as tumor cells. However, non-malignant but actively dividing cells seen in the gastrointestinal tract can be affected by oncologic therapy. Combination therapies are currently being used as a multipronged attack to treat cancer. Traditional chemotherapy is now often combined with targeted molecular therapy. Similarly, chemotherapy and radiation therapy are often combined. The effects of the combination therapy can be additive resulting in symptomatic complications for the patient. Imaging can help identify such complications. Inflammatory changes in the entire gastrointestinal tract can be seen with chemotherapy and radiation therapy. In addition, findings such as pneumatosis, typhilitis and ischemic colitis can also be seen and are discussed in this article. Imaging of complications in the liver (such as steatohepatitis and pseudocirrhosis) and in the pancreas (such as pancreatitis) are also discussed in this article. The purpose of this article is to discuss and illustrate the imaging appearance of complications resulting from oncological therapy in an organ system based approach.

Types of therapies

Chemotherapy

Chemotherapy drugs can be divided into multiple categories based on the mechanism of action^[1]. The major categories are:

- *Alkylating agents.* Alkylating agents are the oldest and most commonly used class of chemotherapy drugs, and work by directly damaging DNA and preventing cancer cells from reproducing. They are used to treat a wide variety of cancers, but have the greatest effect on those that are slow-growing. They are cell cycle phase non-specific, meaning that they kill cancer cells in any phase of the cell cycle. Some examples of alkylating agents are carboplatin, cisplatin and oxaliplatin.
- *Antimetabolites.* Antimetabolites are chemotherapy drugs that interfere with DNA and RNA replication. They are cell cycle specific working during the S phase of the cell cycle. Some examples are methotrexate (folic acid antagonist), 5-fluorouracil

(pyrimidine antagonist) and gemcitabine (pyrimidine antagonist).

- *Anthracyclines.* Anthracyclines are anti-tumor antibiotics that interfere with DNA replication. These agents work in all phases of the cell cycle. They bind to portions of the unwound strand of nuclear DNA, halting the transcription process, which in turn prevents cell replication. Some examples of anthracyclines are doxorubicin and daunorubicin.
- *Mitotic inhibitors.* These drugs are often derived from plants or natural products. They can act by preventing mitosis or by inhibiting enzymes that are needed for protein synthesis for cell replication. They work during the M (mitotic) phase of the cell cycle, but can damage cells in all phases. Some examples of mitotic inhibitors are taxanes (paclitaxel and docetaxel) and vinca alkaloids (vinblastine and vincristine).
- *Topoisomerase inhibitors.* These drugs interfere with enzymes called topoisomerases, which help to separate the strands of DNA prior to replication. Some examples of topoisomerase I inhibitors include topotecan and irinotecan (CPT-11). Some examples of topoisomerase II inhibitors include etoposide (VP-16) and teniposide.

Targeted therapy

Therapy based on targeting critical molecular targets and pathways is being increasingly used. These are more specific than traditional chemotherapeutic agents. One of the common pathways being targeted is angiogenesis. In 1971, Dr Judah Folkman^[2] published an article describing the process of angiogenesis resulting from proangiogenic factors secreted by solid tumors. Angiogenesis is a complex pathway. One of the earliest drugs to be introduced was bevacizumab. This is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF-A) preventing it from binding to its receptor and hence from initiating angiogenesis.

Other examples of targeted therapy are imatinib (inhibits specific protein kinases such as Abl seen in leukemias and Kit, the tyrosine protein kinase, which is also the stem cell growth factor receptor) found in gastrointestinal stromal tumors), erlotinib (tyrosine kinase inhibitor which acts on the epidermal growth factor receptor) and sunitinib (multi-targeted tyrosine kinase inhibitor)^[3]. Targeted therapy can be used alone or in combination with traditional chemotherapy.

Radiation therapy

Radiation therapy uses ionizing radiation to damage the DNA of malignant cells. Malignant cells have impaired mechanisms of repairing DNA damage compared with non-malignant cells. Radiation therapy uses this concept in the local treatment of malignancies.

Photons or particle radiation can be used in treatment. Side effects from radiation therapy can occur in the acute and late settings. Acute side effects occur during and up to 8 weeks after radiation therapy. Chronic side effects can occur months to years after completion of therapy or they may begin acutely and persist after the treatment. Only 5–15% of persons treated with radiation to the abdomen develop chronic problems^[4].

The gastrointestinal tract

There is a wide range of potential gastrointestinal complications from chemotherapy and radiotherapy as summarized in Table 1.

Chemotherapy and targeted therapy complications

Stomach and duodenum

Gastritis and duodenitis are defined as inflammation with associated mucosal injury of the stomach and duodenum, respectively. Gastritis, duodenitis and gastric and duodenal ulceration can be seen in patients receiving hepatic arterial infusion chemotherapy of fluorodeoxyuridine. This has been described in the literature and is thought to be related to malpositioning of the catheter tip in the gastroduodenal artery rather than the hepatic artery^[5,6].

Gastritis and gastric ulceration can be seen on upper gastrointestinal examinations as gastric fold thickening and erosions along the gastric wall, respectively. These findings can also be seen on computed tomography (CT) examinations. Similarly duodenitis and duodenal ulceration can be seen on upper gastrointestinal examinations as duodenal fold thickening and erosions along the duodenal wall, respectively.

Table 1 Summary of potential treatment-induced gastrointestinal complications from chemotherapy and radiotherapy

	Chemotherapy/targeted therapy	Radiotherapy
Stomach and duodenum	Gastritis ± ulceration Duodenitis ± ulceration	Gastritis
Small intestine	Enteritis Ileus Pneumatosis Perforation Hemorrhage	Radiation enteritis (acute or chronic)
Large intestine	Ileus Pneumatosis Perforation Hemorrhage Typhilitis Ischemic colitis <i>Clostridium difficile</i> colitis	Radiation proctocolitis (acute or chronic)

Small intestine

Enteritis is defined as inflammation with associated mucosal injury of the small bowel.

Chemotherapy. Chemotherapy-induced enteritis is commonly seen with traditional cytotoxic chemotherapies such as 5-fluorouracil (5-FU), oral capecitabine (Xeloda), paclitaxel, irinotecan and oxaliplatin^[7,8]. When these patients are on a combination therapy such as FOLFOX (5-FU, leucovorin and oxaliplatin) or FOLFIRI (5-FU, leucovorin and irinotecan), these side effects can be additive^[9–12]. These patients can present with diarrhea, distension and generalized abdominal pain. This is believed to be related to the direct effect of chemotherapy on rapidly dividing cells in the small bowel mucosa. Involvement is usually diffuse.

On abdominal radiographs, multiple dilated small bowel loops with air–fluid levels and small bowel wall thickening can be seen. On cross-sectional imaging, the mucosa of the involved small bowel can enhance with low attenuation to the submucosa from edema resulting in a target appearance^[13–16]. However, this CT finding is non-specific and can be seen in graft versus host disease (GVHD), radiation enteritis or ischemia.

Targeted therapy. Drugs that target epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) receptor pathways such as cetuximab, erlotinib and sunitinib, sorafenib, respectively, can cause diarrhea^[17]. The drugs that target EGFR may cause a follicular acneiform rash in patients, which can help in the diagnosis^[16]. The mechanism of action for drugs that target EGFR is unknown but speculated to be related to loss of regulation of chloride secretion resulting in a secretory diarrhea. The gastrointestinal effects can be additive when treating patients with both targeted therapy and conventional chemotherapy^[18]. The typical radiological findings may not be as frequently seen as with the traditional chemotherapeutic agents.

Small and large intestine

Ileus. Ileus is defined as a temporary arrest of intestinal peristalsis resulting in a functional blockage of the intestines. Ileus has been seen with chemotherapy agents^[13] such as vincristine and vinblastine^[19]. This is seen in both the small and large bowel. Ileus is thought to be related to these agents causing neurotoxicity to the autonomic nervous system of the bowel wall. Multiple dilated small bowel and colonic loops containing air–fluid levels can be seen on abdominal radiographs and on CT. A transition point is usually not present.

Pneumatosis. Pneumatosis refers to the presence of gas within the wall of the small bowel or colon. This is a radiographic sign. Pneumatosis is associated with a wide range of etiologies^[20]. In the most benign form, this is presumed to be related to increased mucosal permeability from immunosuppression associated with chemotherapy^[21–24]. This tends to resolve when the



Figure 1 Pneumatosis: a 62-year-old woman with history of cervical cancer who presented to the emergency room with right lower abdominal pain and fever. She had just finished cycle 2 of chemotherapy consisting of bevacizumab and doxorubicin. A contrast-enhanced CT scan demonstrated pneumatosis in the right colonic wall. The pneumatosis was thought to be related to bevacizumab use and this was discontinued.

therapy is stopped. However, this can also be seen with bowel ischemia/infarction (Fig. 1) associated with chemotherapeutic agents including the more recently introduced bevacizumab^[25]. Gas within the bowel wall can be seen on abdominal radiographs and on CT. Additional CT findings seen may include bowel wall thickening, mucosal hyperenhancement, dilated bowel loops and less commonly air within the portal venous system. Air within the portal venous system usually portends a more ominous cause and is seen in ischemia/infarction. Management is based on clinical findings and is typically conservative.

Neutropenic enterocolitis. Neutropenic enterocolitis or typhilitis refers to an acute condition characterized by transmural inflammation of the cecum in patients who are severely immunosuppressed. There can be associated involvement of the ascending colon and terminal ileum. Neutropenic enterocolitis can be seen in patients with leukemias, patients undergoing chemotherapy or patients who have had stem cell transplantation. The inflammation is speculated to arise from neutropenia, mucosal injury to the small bowel or colon, ischemia and subsequent infection^[26]. The infection can cause necrosis of the bowel. Patients present with fever, neutropenia and abdominal pain. On cross-sectional imaging, the bowel wall changes are usually seen involving the cecum, ascending colon and terminal ileum^[14,27]. The bowel wall may be diffusely thickened or edematous, mucosal hyperemia, and occasionally mucosal ulceration is seen early on (Fig. 2). Pericolonic fat stranding is also seen. Transmural bowel wall involvement with necrosis, pneumatosis and less commonly perforation can also be seen later on. Prompt diagnosis with conservative treatment using antibiotics is used in patients when early diagnosis is made.

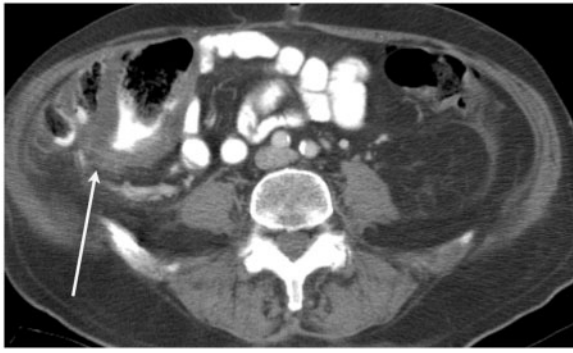


Figure 2 Typhilitis: a 70-year-old man with mantle cell lymphoma treated with systemic chemotherapy, including hyper-CVAD (cyclophosphamide, vincristine, adriamycin and dexamethasone) chemotherapy alternating with methotrexate and cytarabine. CT axial view shows diffuse thickening of the cecum with pericecal stranding, consistent with typhilitis.

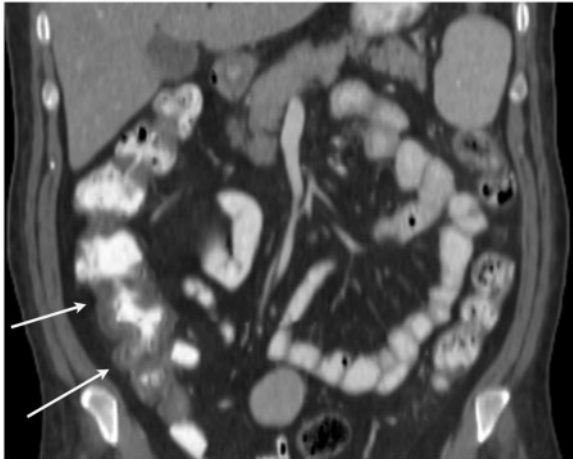


Figure 3 Ischemic colitis: a 48-year-old woman with spindle cell sarcoma presented with abdominal pain after 4 cycles of gemcitabine and docetaxel. CT scan with coronal reformats show right colonic wall thickening, consistent with colitis.

Ischemic colitis. Ischemic colitis refers to inflammation and injury of the large intestine from inadequate blood supply. This is seen in patients on treatment with docetaxel^[28,29]. The symptoms at presentation include crampy abdominal pain. The patients are all not neutropenic at presentation (Fig. 3). This typically occurs at day 4–10 following docetaxel treatment. The imaging findings on CT are of colonic wall diffuse thickening with surrounding stranding. There may be mucosal hyperemia.

Clostridium difficile associated colitis. *Clostridium difficile* colitis is defined as infection by *Clostridium difficile*, a gram-positive bacillus, causing inflammation with mucosal injury to the large intestine. This is the most common



Figure 4 *Clostridium difficile* colitis: a 40-year-old woman with a history of Hodgkin lymphoma. She presented to the emergency room on day 7 after her chemotherapy with abdominal pain and diarrhea. The coronal reformatted CT demonstrated diffuse marked colonic wall thickening suggestive of *Clostridium difficile* colitis. This was confirmed by fecal analysis. The patient was treated for this with resolution of the colonic wall thickening.

cause of diarrhea in a hospitalized patient^[30]. Patients on chemotherapy are immunosuppressed. This is associated with a high risk of *Clostridium difficile* colitis^[31–33]. In addition, many of these patients are on broad spectrum antibiotics for other infections that can predispose these patients to *Clostridium difficile* colitis. These patients typically present about 1 week after the initiation of antibiotic treatment. The patients can present with symptoms ranging from mild diarrhea to abdominal pain, fevers and colitis. In rare cases, this may progress to toxic megacolon and diffuse colitis.

On abdominal radiographs, there is diffuse thickening of the colonic wall. On CT, there is diffuse thickening of the colonic wall with surrounding fat stranding and ascites (Fig. 4). The impressive colonic wall thickening has been described as the accordion sign^[34].

Intestinal perforation. Intestinal perforation refers to full thickness erosion from the mucosa to the serosa leading to leakage of intestinal contents. Intestinal perforation is an uncommon complication of chemotherapy and has been reported with bevacizumab^[35]. While the mechanism is unknown, it is speculated that there is intestinal ischemia associated with bevacizumab causing the perforation (Fig. 5a and b). Additional theories proposed

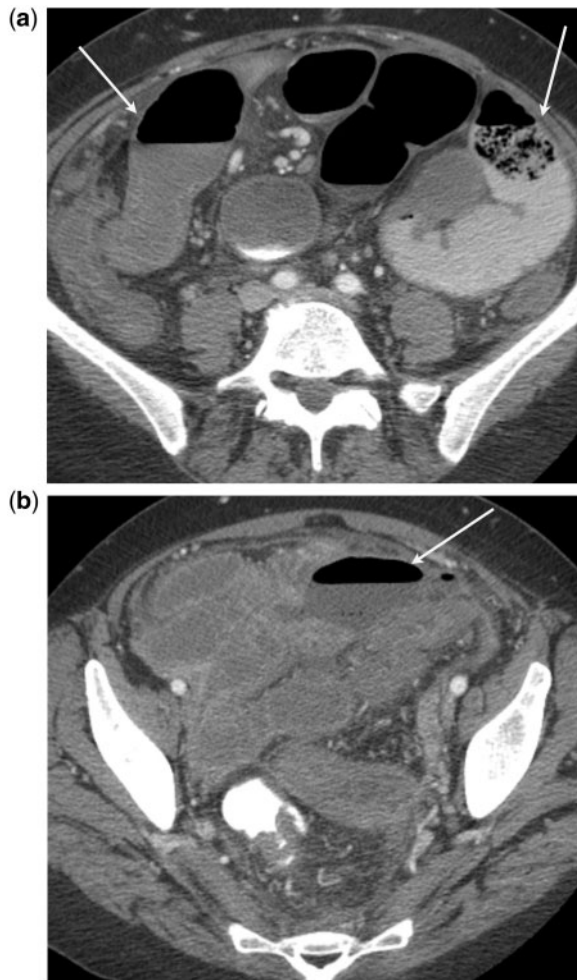


Figure 5 Intestinal perforation: a 51-year-old woman with metastatic colorectal carcinoma treated with hepatic artery infusion with oxaliplatin, followed by 13 cycles of 5-FU, leucovorin and bevacizumab. The patient presented with fever and abdominal pain. (a) CT scan shows dilation of loops of small bowel along with thickening of the large and small bowel. (b) CT scan shows diffuse thickening of small bowel loops and fluid collection with air–fluid level consistent with an abscess resulting from perforation of adjacent small bowel.

include tumor necrosis with perforation near the serosa. The incidence of perforation ranges from 1.5 to 1.7% in colon cancer^[35] to nearly 5 to 11% in patients with ovarian cancer^[36,37]. The risk factors associated with perforation include an intact primary tumor, abdominal irradiation, non-steroidal anti-inflammatory use, diverticulosis, and recent endoscopy. There can be findings of pneumoperitoneum on abdominal radiographs. This can also be seen with CT imaging. Contained perforations may result in a loculated collection of air or of air and fluid.

Gastrointestinal bleeding. Gastrointestinal bleeding is defined as bleeding from any source in the gastrointestinal tract. This has been classically reported with

gastrointestinal stromal tumors (GIST). These tumors are exophytic from the gastrointestinal tract. With targeted treatment, there can be resultant necrosis, bleeding and communication with the lumen of the gastrointestinal tract. With the bleeding into the tumor, the hemoglobin levels have been documented to decrease after the first 2 months of therapy. This has been reported to occur at a frequency of 5% in patients with GIST treated with imatinib. This is manifested by high attenuation hemorrhage or air within the GIST following treatment^[38]. Gastrointestinal bleeding can also occur in tumors such as gastrointestinal lymphomas with response to treatment^[39,40].

Radiation therapy

Stomach

Gastritis is defined as inflammation with associated mucosal injury of the stomach related to radiation therapy. Early during radiation, nausea and vomiting can occur and may be related to gastritis. Gastric ulceration can occur during or at the completion of radiation therapy^[41]. The ulcers may resolve 2 weeks after completion of therapy. Chronic gastritis can occur with radiation therapy. Concurrent chemotherapy can decrease the tolerance of the stomach to radiation therapy and is especially seen with chemotherapy such as gemcitabine and epidermal growth factor inhibitors. Acute gastritis and gastric ulceration can be seen on upper gastrointestinal examinations and can also be seen on CT examinations. These manifest with gastric wall thickening and erosions. Chronic radiation-induced gastritis may cause smoothening of the gastric folds and may sometimes be associated with stenosis of the antrum. Gastric ulceration may also occur approximately 5 months following radiation therapy.

Small intestine

Radiation enteritis is defined as inflammation of the small intestine with mucosal injury related to radiation therapy. Radiation enteritis is divided into acute and chronic phases.

Acute radiation enteritis. Acute radiation enteritis occurs in a majority of patients. They present with diarrhea, tenesmus, cramping and incontinence. Diarrhea may start as early as 3 weeks from the start of radiation treatment. These symptoms usually resolve with cessation of the radiation treatment. In the acute phase, the primary effect of radiation is on mucosal stem cells within the intestinal crypts. Radiation therapy can cause damage to these stem cells and as a result cause mucosal atrophy with intestinal inflammation and edema and decreased absorptive area. On abdominal radiographs, dilated small bowel loops with thickened walls can be seen. On CT, thickened small intestinal walls with the target sign may be seen.

Chronic radiation enteritis. Chronic radiation enteritis is typically seen at least 8–12 months after radiation



Figure 6 Radiation enteritis: a 65-year-old woman with papillary serous carcinoma of the endometrium, treated from 4/07 to 5/07 with 45 Gy to the pelvis; the patient had significant problems with diarrhea. The patient presented 11/07 with abdominal pain. CT scan shows fixed, thickened, decompressed loops of ileum in the pelvis consistent with radiation enteritis, resulting in small bowel obstruction due to radiation.

therapy. They may occur years after radiation therapy. In some cases, the symptoms of chronic enteritis can worsen with time. These patients typically present with diarrhea, malabsorption, fistulae, partial or complete small bowel obstruction. These changes are related to increased collagen deposition within the wall making it thickened and fixed. There is also injury to the blood vessels (endarteritis) with occlusion of the vessel lumen causing ischemia. Radiation changes more commonly occur in the terminal ileum which is relatively fixed in position and also in patients following surgery due to adhesions, which may render the small bowel relatively immobile. Chronic radiation enteritis can manifest on CT as small bowel wall thickening and edema, ulcerations, stricture formation, fistula and abscess formation^[42,43]. As the ulcers heal, there can be fibrosis with narrowing of the intestinal lumen and stricture formation or even obstruction (Fig. 6). Even if the intestine appears normal, patients are at risk of spontaneous perforation^[44]. Increased density in the mesentery can also be seen.

Large intestine

Radiation colitis is defined as inflammation with mucosal injury to the colon related to radiation therapy. Radiation proctitis is defined as inflammation with mucosal injury to the rectum related to radiation therapy. Radiation colitis/proctitis is divided into acute and chronic phases.

Acute radiation colitis/proctitis. Acute radiation colitis or proctitis can commonly occur during radiation therapy. They present with pain, diarrhea, tenesmus, cramping, bleeding and incontinence. These symptoms usually resolve after radiation therapy is stopped. CT performed

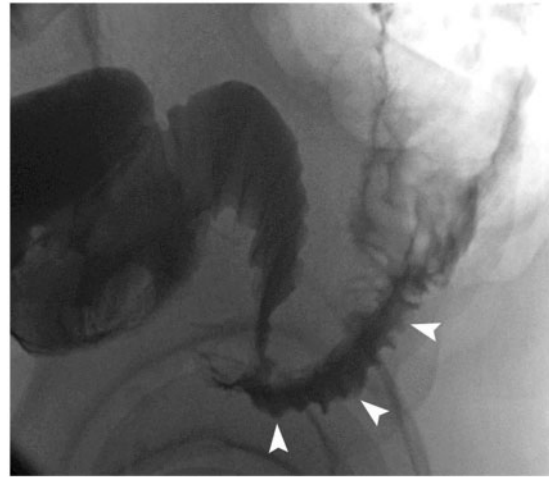


Figure 7 Radiation proctocolitis: a 61-year-old woman with endometrial cancer. The patient received whole pelvic radiation therapy of 5040 cGy, para-aortic radiation of 4350 cGy and brachytherapy. The patient presented with crampy blood-tinged diarrhea 1 year after radiotherapy. Barium enema confirmed these findings with a narrowed, fixed rectosigmoid colon with extensive mucosal abnormality (arrowheads), consistent with radiation change.

during the acute phase of radiation injury can demonstrate non-specific colonic or rectal wall thickening and inflammatory fat stranding. The colonic folds may appear to have a saw tooth appearance^[45]. There can be increased attenuation to the perirectal fat and perirectal fascial thickening seen on CT.

Chronic radiation colitis/proctitis. Chronic changes tend to occur at least 9 months after radiation therapy and can occur years after radiation therapy. The patients can present with diarrhea, rectal pain or urgency, bleeding, obstruction from stricture formation and fistulae. The sigmoid colon and rectum are the most commonly affected because radiation therapy is often given for pelvic malignancies. CT findings include colonic or rectal wall thickening, increased perirectal fat and thickening of the perirectal fascia. Colonic strictures and fistulas can occur. The strictures are areas of colonic or rectal narrowing with tapered margins. This can lead to obstruction, fistula formation and abscesses (Fig. 7). Increased presacral space can be seen on imaging. On T2-weighted images, there can be increased signal intensity to the bowel wall initially involving the submucosa and later the muscular layer^[46].

Pancreas

Chemotherapy and targeted therapy complications

Pancreatitis is defined as inflammation of the pancreas. This results in early activation of the pancreatic enzymes



Figure 8 Pancreatitis: a 53-year-old man with left renal cell carcinoma s/p resection on 2 months of pazopanib therapy for metastatic disease to the spine. The patient presented with upper abdominal pain. CT scan shows stranding anterior to the head of the pancreas, highly suspicious for pancreatitis secondary to therapy.

within the pancreas itself and leads to pancreatic damage. Chemotherapy-induced pancreatitis has been historically described with L-asparaginase therapy for acute leukemia. The time to onset is variable. Patients present with upper abdominal pain, nausea and vomiting. The CT appearance is that of pancreatic enlargement, peripancreatic stranding (Fig. 8) and loss of visualization of intrapancreatic fat clefts similar to that of acute pancreatitis from other etiologies^[47]. Pancreatitis has been described with pazopanib (Fig. 10), sunitinib and sorafenib with or without CT features of pancreatitis accompanied by clinical manifestations and lipase elevation^[48,49].

Radiation therapy complications

Chronic pancreatitis is a rare entity that can occur following radiation therapy^[50]. Radiation can cause vascular damage, edema within the pancreas and inflammation of the pancreas. These patients can present with malabsorption from chronic pancreatitis.

Liver

Chemotherapy and targeted therapy complications

Pseudocirrhosis

Pseudocirrhosis refers to a cirrhosis-like appearance seen in patients with metastatic disease characterized by irregular and lobulated liver contour with areas of hepatic capsular retraction. Pseudocirrhosis has been seen most commonly in patients who have received chemotherapy

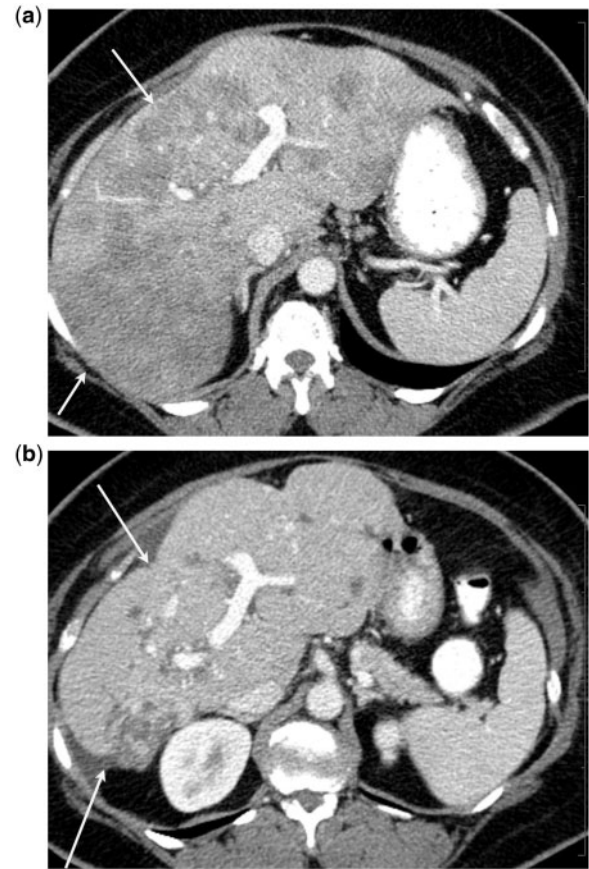


Figure 9 Hepatic pseudocirrhosis: a 59-year-old woman with history of breast cancer, s/p 1 year of therapy with navelabine and herceptin. (a) CT scan shows pre-therapy scan with multiple metastatic lesions. (b) Follow-up CT 1 year later shows post-therapy scan with capsular retraction and small volume ascites. This should not be mistaken for cirrhosis.

for breast cancer, but can also occur after treatment for carcinoid or Hodgkin lymphoma. It may occur in the presence of increasing or decreasing metastatic disease, and typically the area of retraction occurs adjacent to the metastatic disease, causing distortion of the capsule. The pathologic basis for this retraction is focal regenerative hyperplasia. On CT, there is a nodular contour to the liver, with thin bands emanating from the areas of retraction representing scarring or fibrosis (Fig. 9a and b). The patient may have other signs, such as portal hypertension, splenomegaly, and ascites. Cessation of chemotherapy may reverse the radiologic findings^[51].

Fatty liver

Fatty liver or steatosis refers to a reversible condition characterized by abnormal and excess triglyceride deposition in hepatocytes. Steatosis and steatohepatitis are side effects of chemotherapy and have been seen in patients receiving treatment for breast cancer and colorectal carcinoma. The presence of fatty liver should be

reported in patients undergoing chemotherapy, as it has the potential to change management. This is particularly true in patients undergoing pre-operative chemotherapy with irinotecan for colorectal carcinoma. Steatosis greater than 30% has been associated with higher morbidity after surgery and the presence of steatohepatitis is associated with a higher 90-day postoperative mortality^[52]. On CT and magnetic resonance imaging (MRI), fatty infiltration typically has a well-defined geometric pattern. The attenuation of the liver is lower than the spleen due to the deposition of fat within the hepatocytes, and the Hounsfield unit measurement may be less than 40. MRI with fat-suppressive and in-phase and out-of-phase techniques can be used if findings are equivocal on CT; the area of fatty deposition drops out of signal in the out-of-phase images. Findings of steatosis are reversible if chemotherapy is discontinued.

Hepatic veno-occlusive disease

Hepatic veno-occlusive disease (HVOD) refers to a non-thrombotic endothelial injury to the terminal hepatic venules and hepatic sinusoids. Hepatic veno-occlusive disease or sinusoidal obstruction syndrome (SOS) is a complication of stem cell transplantation^[53] or high-dose chemotherapy with a high morbidity and mortality. Recently, it has been observed in patients who have received oxaliplatin to treat metastatic colorectal carcinoma^[54]. Patients may present with hepatic failure, jaundice and abdominal pain. Pathologically, there is destruction of the hepatic venules with fibrosis and sinusoidal obstruction due to hepatocyte necrosis. Ultrasonography is typically used as the first line of evaluation and may show hepatomegaly, gallbladder wall thickening and ascites, with possible decrease in hepatic venous flow^[55]. CT may show ascites, periportal edema, and narrowing of the right hepatic vein^[56]. There is no specific treatment for sinusoidal obstruction syndrome, and the focus is on prevention.

Radiation therapy complications

Radiation change within the liver is typically seen within 2–8 weeks of completing radiotherapy. Radiation-induced liver disease is seen in 5–10% of patients who receive radiation to their liver in doses exceeding 30–35 Gy. Patients may present with anicteric ascites, hepatomegaly and elevated liver enzymes^[57]. Typically, findings usually resolve in 4–6 months, but a small portion of patients progress to chronic liver failure. Pathologically, the findings are very similar to veno-occlusive disease, with congestion of the lobules and injury to the endothelial cells. On CT, the area of radiation change is lower in signal (Fig. 10) due to the edema and there may be a linear demarcation known as the straight line sign. MRI findings include a low T1 signal and a high T2 signal in the area of radiation. There may be increased metabolic activity in the area of injury on [¹⁸F]fluorodeoxyglucose



Figure 10 Radiation-induced liver disease: a 21-year-old woman with lymphoma of the right anterior chest wall. The patient received 39.6 Gy to the right chest wall. CT obtained 5 weeks after the completion of radiation therapy shows a well-defined area of low attenuation in the liver with a sharp demarcation between the area of radiation and the normal liver. This is consistent with the straight-border sign of radiation change.

(FDG)-positron emission tomography (PET)/CT due to leukocyte injury. As radiation injury may occasionally present as a focal area, important attention must be paid to the radiation treatment plan to avoid mistaking radiation change for metastatic disease^[53].

Conclusion

Symptomatic complications can arise in patients from oncological treatment. It is important for the radiologist to be familiar with the clinical and treatment history and associated complications that may occur, in order to facilitate treatment changes in these patients.

References

- [1] Takimoto CH, Calvo E. Principles of oncologic pharmacotherapy. In: Pazdur R, Wagman LD, Camphausen KA, Hoskins WJ, editors. Cancer management: a multidisciplinary approach. 11th ed. P R R Inc.; 2008.
- [2] Folkman J. Tumor angiogenesis: therapeutic implications. *N Engl J Med* 1971; 285: 1182–6.
- [3] Benjamin RS, Blanke CD, Blay JY, Bonvalot S, Eisenberg B. Management of gastrointestinal stromal tumors in the imatinib era: selected case studies. *Oncologist* 2006; 11: 9–20. doi: 10.1634/theoncologist.11-1-9.
- [4] Yeoh EK, Horowitz M. Radiation enteritis. *Surg Gynecol Obstet* 1987; 165: 373–9.
- [5] Hall DA, Clouse ME, Gramm HF. Gastrointestinal ulceration after hepatic arterial infusion chemotherapy. *AJR* 1981; 136: 1216–18.
- [6] Hohn DC, Stagg RJ, Price DC, Lewis BJ. Avoidance of gastrointestinal toxicity in patients receiving hepatic arterial 5-fluoro-2'-deoxyuridine. *J Clin Oncol* 1985; 3: 1257–60.

- [7] Ikuno N, Soda H, Watanabe M, Oka M. Irinotecan (CPT-11) and characteristic mucosal changes in the mouse ileum and cecum. *J Natl Cancer Inst* 1995; 87: 1876–83.
- [8] Benson AB, 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004; 22: 2918–26. doi:10.1200/JCO.2004.04.132.
- [9] Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Eng J Med* 2000; 343: 905–14. doi:10.1056/NEJM200009283431302.
- [10] Messersmith WA, Laheru DA, Senzer NN, et al. Phase I trial of irinotecan, infusional 5-fluorouracil, and leucovorin (FOLFIRI) with erlotinib (OSI-774): early termination due to increased toxicities. *Clin Cancer Res* 2004; 10: 6522–7. doi:10.1158/1078-0432.CCR-04-0746.
- [11] Kuebler JP, Colangelo L, O'Connell MJ, et al. Severe enteropathy among patients with stage II/III colon cancer treated on a randomized trial of bolus 5-fluorouracil/leucovorin plus or minus oxaliplatin: a prospective analysis. *Cancer* 2007; 110: 1945–50. doi:10.1002/cncr.23013.
- [12] Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000; 355: 1041–7. doi:10.1016/S0140-6736(00)02034-1.
- [13] Kelvin FM, Gramm HF, Gluck WL, Lokich JJ. Radiologic manifestations of small-bowel toxicity due to floxuridine therapy. *AJR* 1986; 146: 39–43.
- [14] Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. *Radiology* 2003; 226: 668–74. doi:10.1148/radiol.2263011932.
- [15] Cronin CG, O'Connor M, Lohan DG, et al. Imaging of the gastrointestinal complications of systemic chemotherapy. *Clin Radiol* 2009; 64: 724–33. doi:10.1016/j.crad.2009.02.016.
- [16] Torrisi JM, Schwartz LH, Gollub MJ, Ginsberg MS, Bosl GJ, Hricak H. CT findings of chemotherapy-induced toxicity: what radiologists need to know about the clinical and radiologic manifestations of chemotherapy toxicity. *Radiology* 2011; 258: 41–56. doi:10.1148/radiol.10092129.
- [17] Shah NT, Kris MG, Pao W, et al. Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005; 23: 165–74. doi:10.1200/JCO.2005.04.057.
- [18] Czito BG, Willett CG, Bendell JC, et al. Increased toxicity with gefitinib, capecitabine, and radiation therapy in pancreatic and rectal cancer: phase I trial results. *J Clin Oncol* 2006; 24: 656–62. doi:10.1200/JCO.2005.04.1749.
- [19] Toghiani PJ, Burke JD. Death from paralytic ileus following vincristine therapy. *Postgraduate Med J* 1970; 46: 330–1. doi:10.1136/pgmj.46.535.330.
- [20] Pear BL. Pneumatosis intestinalis: a review. *Radiology* 1998; 207: 13–19.
- [21] Wiesner W, Mortelet KJ, Glickman JN, Ji H, Ros PR. Pneumatosis intestinalis and portomesenteric venous gas in intestinal ischemia: correlation of CT findings with severity of ischemia and clinical outcome. *AJR* 2001; 177: 1319–23.
- [22] Shanbhogue AK, Virmani V, Vikram R, et al. Spectrum of medication-induced complications in the abdomen: role of cross-sectional imaging. *AJR* 2011; 197: W286–94. doi:10.2214/AJR.10.5415.
- [23] Galm O, Fabry U, Adam G, Osieka R. Pneumatosis intestinalis following cytotoxic or immunosuppressive treatment. *Digestion* 2001; 64: 128–32. doi:10.1159/000048852.
- [24] Kung D, Ruan DT, Chan RK, Ericsson ML, Saund MS. Pneumatosis intestinalis and portal venous gas without bowel ischemia in a patient treated with irinotecan and cisplatin. *Digest Dis Sci* 2008; 53: 217–19. doi:10.1007/s10620-007-9846-9.
- [25] Asmis TR, Chung KY, Teitcher JB, Kelsen DP, Shah MA. Pneumatosis intestinalis: a variant of bevacizumab related perforation possibly associated with chemotherapy related GI toxicity. *Invest New Drugs* 2008; 26: 95–6. doi:10.1007/s10637-007-9094-z.
- [26] Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. *Cancer* 1992; 69: 17–23. doi:10.1002/1097-0142(19920101)69:1<17::AID-CNCR2820690106>3.0.CO;2-X.
- [27] Frick MP, Maile CW, Crass JR, Goldberg ME, Delaney JP. Computed tomography of neutropenic colitis. *AJR* 1984; 143: 763–5.
- [28] Ibrahim NK, Sahin AA, Dubrow RA, et al. Colitis associated with docetaxel-based chemotherapy in patients with metastatic breast cancer. *Lancet* 2000; 355: 281–3. doi:10.1016/S0140-6736(99)06195-4.
- [29] Kreis W, Petrylak D, Savarese D, Budman D. Colitis and docetaxel-based chemotherapy. *Lancet* 2000; 355: 2164. doi:10.1016/S0140-6736(05)72789-6.
- [30] McDonald LC, Owings M, Jernigan DB. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996–2003. *Emerg Infect Dis* 2006; 12: 409–15. doi:10.3201/eid1203.051064.
- [31] Emoto M, Kawarabayashi T, Hachisuga MD, Eguchi F, Shirakawa K. *Clostridium difficile* colitis associated with cisplatin-based chemotherapy in ovarian cancer patients. *Gynecol Oncol* 1996; 61: 369–72. doi:10.1006/gyno.1996.0158.
- [32] Kamthan AG, Bruckner HW, Hirschman SZ, Agus SG. *Clostridium difficile* diarrhea induced by cancer chemotherapy. *Arch Intern Med* 1992; 152: 1715–17. doi:10.1001/archinte.152.8.1715.
- [33] Anand A, Glatt AE. *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. *Clin Infect Dis* 1993; 17: 109–13. doi:10.1093/clinids/17.1.109.
- [34] Kirkpatrick ID, Greenberg HM. Evaluating the CT diagnosis of *Clostridium difficile* colitis: should CT guide therapy? *AJR* 2001; 176: 635–9.
- [35] Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350: 2335–42. doi:10.1056/NEJMoa032691.
- [36] Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? *Gynecol Oncol* 2007; 105: 3–6. doi:10.1016/j.ygyno.2007.01.038.
- [37] Wright JD, Hagemann A, Rader JS, et al. Bevacizumab combination therapy in recurrent, platinum-refractory, epithelial ovarian carcinoma: a retrospective analysis. *Cancer* 2006; 107: 83–9. doi:10.1002/cncr.21969.
- [38] Hong X, Choi H, Loyer EM, Benjamin RS, Trent JC, Charnsangavej C. Gastrointestinal stromal tumor: role of CT in diagnosis and in response evaluation and surveillance after treatment with imatinib. *Radiographics* 2006; 26: 481–95. doi:10.1148/rg.262055097.
- [39] Talamonti MS, Dawes LG, Joehl RJ, Nahrwold DL. Gastrointestinal lymphoma. A case for primary surgical resection. *Arch Surg* 1990; 125: 972–6. discussion 976–7.
- [40] Meyers PA, Potter VP, Wollner N, Exelby P. Bowel perforation during initial treatment for childhood non-Hodgkin's lymphoma. *Cancer* 1985; 56: 259–61. doi:10.1002/1097-0142(19850715)56:2<259::AID-CNCR2820560209>3.0.CO;2-1.
- [41] Henriksson R, Bergstrom P, Franzen L, Lewin F, Wagenius G. Aspects on reducing gastrointestinal adverse effects associated with radiotherapy. *Acta Oncol (Stockh)* 1999; 38: 159–64.
- [42] Horton KM, Corl FM, Fishman EK. CT of nonneoplastic diseases of the small bowel: spectrum of disease. *J Comput Assist Tomogr* 1999; 23: 417–28. doi:10.1097/00004728-199905000-00017.
- [43] Hauer-Jensen M. Late radiation injury of the small intestine. Clinical, pathophysiologic and radiobiologic aspects. A review.

- Acta Oncol (Stockholm, Sweden) 1990; 29: 401–15. doi:10.3109/02841869009090022.
- [44] Galland RB, Spencer J. Spontaneous postoperative perforation of previously asymptomatic irradiated bowel. *Br J Surg* 1985; 72: 285. doi:10.1002/bjs.1800720412.
- [45] Capps GW, Fulcher AS, Szucs RA, Turner MA. Imaging features of radiation-induced changes in the abdomen. *Radiographics* 1997; 17: 1455–1473.
- [46] Sugimura K, Carrington BM, Quivey JM, Hricak H. Postirradiation changes in the pelvis: assessment with MR imaging. *Radiology* 1990; 175: 805–13.
- [47] McDonald GB, Tirumali N. Intestinal and liver toxicity of anti-neoplastic drugs. *West J Med* 1984; 140: 250–9.
- [48] Amar S, Wu KJ, Tan WW. Sorafenib-induced pancreatitis. *Mayo Clinic Proc* 2007; 82: 521. doi:10.4065/82.4.521.
- [49] Li M, Srinivas S. Acute pancreatitis associated with sorafenib. *South Med J* 2007; 100: 909–11. doi:10.1097/SMJ.0b013e31813c695d.
- [50] Levy P, Menzelxhiu A, Paillot B, Bretagne JF, Flejou JF, Bernades P. Abdominal radiotherapy is a cause for chronic pancreatitis. *Gastroenterology* 1993; 105: 905–9.
- [51] Fennessy FM, Morteale KJ, Kluckert T, et al. Hepatic capsular retraction in metastatic carcinoma of the breast occurring with increase or decrease in size of subjacent metastasis. *AJR* 2004; 182: 651–5.
- [52] Chun YS, Laurent A, Maru D, Vauthey JN. Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. *Lancet Oncol* 2009; 10: 278–86. doi:10.1016/S1470-2045(09)70064-6.
- [53] DeLappe EM, Truong MT, Bruzzi JF, Swisher SG, Rohren EM. Hepatic radiation injury mimicking a metastasis on positron-emission tomography/computed tomography in a patient with esophageal carcinoma. *J Thorac Oncol* 2009; 4: 1442–4. doi:10.1097/JTO.0b013e3181bbf208.
- [54] Robinson S, Manas DM, Pedley I, Mann D, White SA. Systemic chemotherapy and its implications for resection of colorectal liver metastasis. *Surg Oncol* 2011; 20: 57–72. doi:10.1016/j.suronc.2009.10.002.
- [55] Lassau N, Leclere J, Auperin A, et al. Hepatic veno-occlusive disease after myeloablative treatment and bone marrow transplantation: value of gray-scale and Doppler US in 100 patients. *Radiology* 1997; 204: 545–52.
- [56] Mahgerefteh SY, Sosna J, Bogot N, Shapira MY, Pappo O, Bloom AI. Radiologic imaging and intervention for gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *Radiology* 2011; 258: 660–71. doi:10.1148/radiol.10100025.
- [57] Khozouz RF, Huq SZ, Perry MC. Radiation-induced liver disease. *J Clin Oncol* 2008; 26: 4844–5. doi:10.1200/JCO.2008.18.2931.