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Complications of oncologic therapy in the abdomen and pelvis: a review

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Abstract

Cancer therapy has significantly improved in the past few decades with development of various newer classes of cytotoxic chemotherapy as well as novel, molecularly targeted chemotherapy. Similar to chemotherapy, radiotherapy is another important therapeutic option used in the curative and palliative management of various abdominal malignancies. However, both these treatments affect the tumor as well as the normal tissues, leading to significant toxicity. These side effects range from mild to life threatening, and may involve multiple organs. Imaging plays an important role in the early identification of such complications, which may allow more effective patient management. The aim of this article is to discuss and illustrate the wide spectrum of chemotherapy and radiotherapy induced complications in the abdomen and pelvis.

Key words: Cancer therapy complications—Abdominal imaging—Pelvic imaging—Chemotherapy complications—Radiotherapy complications

Cytotoxic chemotherapy agents are classified according to their mechanism of action and include alkylating agents, nitrosureas, platinum-based drugs, antimetabolites, antineoplastic antibiotics, taxanes, vinca alkaloids, and topoisomerase inhibitors. Each drug acts on a different target—for example, alkylating agent such as cyclophosphamide act by forming DNA cross links, antimetabolites such as methotrexate and mercaptopurine inhibit folic acid synthesis and purine synthesis, respectively, and vinca alkaloids act on tubulin, preventing the formation of microtubulin. The final effect of all these drugs is to inhibit cell division in rapidly diving cells and thereby reduce the cell turnover in cancer tissues. Unfortunately, these drugs can also affect the normal cells, especially those with rapid cell division, leading to significant complications. This is the reason why the GI tract and bone marrow (organs with rapid cell turnover) are more susceptible to injury in patients undergoing cytotoxic chemotherapy. However, it may affect almost any organ in the body. Further, chemotherapy associated toxicity may either be due to narrow therapeutic index of the drugs or arise from idiosyncratic reactions.

Tumor biology of various cancers are now being better understood following significant advances in molecular cytogenetics. This has led to the development of novel, molecular targeted therapies. These were developed as an attempt to selectively target the tumor cells and modify their biological characteristics, act on various targets including growth factor receptors, signaling molecules, cell-cycle proteins, molecules that involve in apoptosis and angiogenesis. Targeted therapies are classified according to their mechanism of actions and include those which inhibit membrane receptors (tyrosine kinase inhibitors, monoclonal antibodies, etc.) and those acting on various intracellular signaling pathways (mammalian target of rapamycin inhibitors, mTOR inhibitors). Examples of commonly used tyrosine kinase inhibitors include sunitinib and sorafenib, which act by inhibiting vascular endothelial growth factor (VEGF) receptors. Rituximab (CD 20 antibody used in lymphoma) and bevacizumab (VEGF receptor antibody used in metastatic renal/colonic tumors) are some of the commonly used monoclonal antibodies as targeted therapy. However, many of these new targeted therapies may act on multiple pathways, which are not yet completely understood, and hence may result in unexpected complications. Further, since the mechanisms of action of these drugs are different to that of the classic cytotoxic chemotherapy, their toxicity profile also varies.

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Radiotherapy is a well-established treatment option for various abdominal and pelvic malignancies. In a broad sense, radiotherapy is a regional, whereas chemotherapy is a systemic. Radiotherapy works by using ionizing radiation to induce double stranded breakage in nuclear DNA. This results in inhibition of cell division and finally cell death. Although radiation can cause direct tissue damage, it acts predominantly by causing indirect cell damage, via free radicals and reactive oxygen species (ROS). However, similar to chemotherapy, radiotherapy also causes cell damage to both tumor as well as normal tissues. The degree of radiation-induced injury depends on multiple factors such as the total radiation dose, the dose per fraction, the volume of tissue irradiated, previous surgery, and chemotherapy combined to radiation therapy [1]. Further, the method of delivery of radiotherapy may also influence the extent and severity of side effects [1].

Radiotherapy-induced complications may be acute (occurs within 2 months) or chronic (occurs months to years after therapy) [2]. It is imperative for the radiologists to be aware of the clinical manifestations and salient imaging features of these complications in order to make the correct diagnosis and help the physicians initiate timely management. Further, combined chemotherapy and radiotherapy are commonly used in the treatment of many malignancies, which further increases the extent of injury [3].

The aim of this article is to familiarize the radiologist with the imaging spectrum of oncologic therapy (both chemotherapy and radiotherapy) related complications in the abdomen and pelvis, using a systematic organ based review.

Gastrointestinal tract

Chemotherapy induced complications may be seen in the stomach, small bowel, and large bowel.

Stomach

Hepatic arterial infusion of fluorodeoxyuridine has been reported to cause inflammation and ulceration in the stomach and duodenum. This is thought to be arising from misdirected perfusion of the chemotherapy to the stomach and proximal duodenum either due to malpositioning of the infusion catheter tip into the gastroduodenal artery or due to the presence of aberrant collateral circulation between the hepatic arterial system and the proximal gastrointestinal tract [4–7].

Small bowel

Enteritis is common complication of classic cytotoxic and selected targeted chemotherapeutic agents [8]. The classic cytotoxic agents that commonly cause enteritis include 5-fluorouracil (5FU), oral capecitabine (Xeloda), paclitaxel, irinotecan, and oxaliplatin. Enteritis induced by these drugs is due to the toxic effect on the rapidly divided cells of the gastrointestinal mucosa [7–11]. The mechanism of diarrhea induced by these drugs often differs, for example, 5 FU causes secretory diarrhea, whereas irinotecan causes diarrhea by cholinergic stimulation. Importantly, most of the cancers are currently treated by combination therapy and the toxicities of these drugs increases due to additive effects [8, 12–16]. 5 FU, leucovorin and oxaliplatin (FOLFOX) and 5 FU, leucovorin and irinotecan (FOLFIRI) are examples of such combination chemotherapy regimen.

Molecular targeted therapy such as epidermal growth factor receptor (EGFR) inhibitors (cetuximab, gefitinib, and erlotinib) as well as VEGF inhibitors (sunitinib and sorafenib) can also cause enteritis (Fig. 1) [17, 18]. While the mechanism of diarrhea associated with VEGF inhibitors is unknown, diarrhea arising from the use of EGFR inhibitors is thought to be related to excessive chloride secretion [7, 18]. Patients usually present with nausea, vomiting and diarrhea [19]. Acneiform skin rash may be seen in patients receiving EGFR inhibitors, and can be a helpful in making the diagnosis [18]. Plain radiography is commonly performed as the initial diagnostic test and may show dilated small bowel loops with air fluid levels as well as mural thickening. Computed tomography (CT) scan is more sensitive for detecting bowel wall thickening. The bowel wall may also exhibit the target sign in which there is enhancement of the mucosa and serosa with hypo attenuation of the submucosa in between due to edema [7].

Besides enteritis, chemotherapeutic agents may also cause other side effects in small bowel. For example, 5FU can cause ileal strictures with proximal bowel dilatation [6, 19]. Further, neurotoxic chemotherapeutic agents such as vincristine and vinblastine have been reported to cause small bowel ileus, due to their effect on the autonomic nervous system of the gastrointestinal tract [7, 14, 20].

Large bowel

Pneumatosis. Transient pneumatosis (air in the bowel wall) can occur in the large bowel and/or small bowel in patients receiving chemotherapy for hematological malignancies. This is thought to be related to increased mucosal permeability (without breach in mucosal integrity) from immunosuppression associated with chemotherapy. This condition is usually benign, asymptomatic and tends to resolve after the therapy is stopped [21].

However, pneumatosis can also result from serious conditions such as bowel necrosis or ischemia arising from the use of chemotherapy such as bevacizumab, sorafenib, and sunitinib (Fig. 2). If conservative

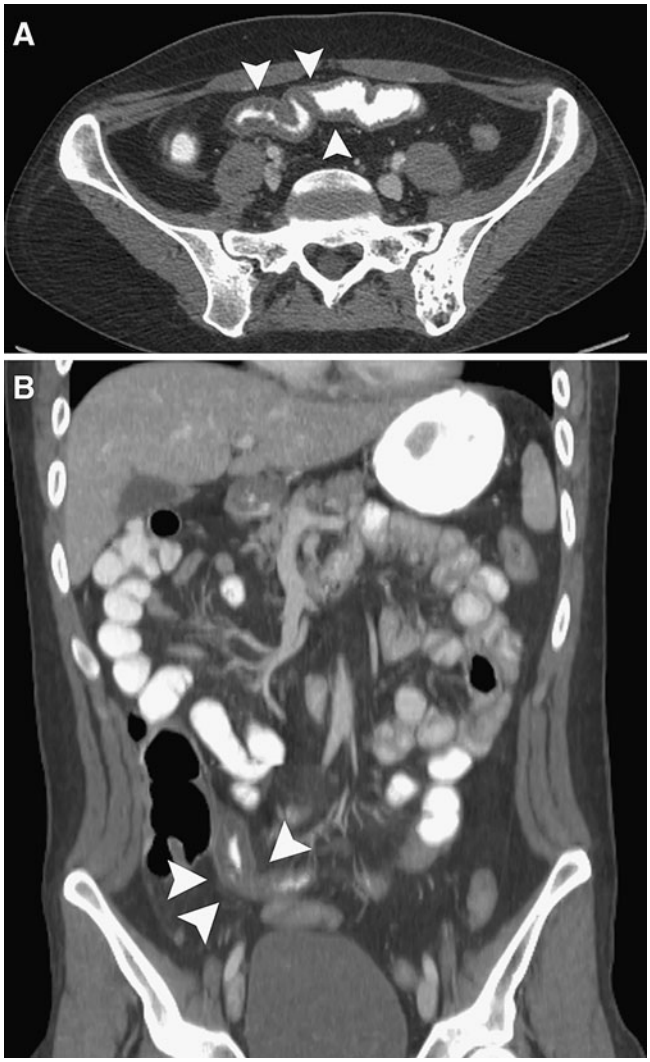

Fig. 1. A 25-year-old male with Ewing sarcoma treated with sorafenib presented with nausea, vomiting, abdominal pain, and diarrhea. Post contrast CT in axial (**A**) and coronal (**B**) plane shows circumferential thickening of the terminal ileum (*arrowheads*), consistent with chemotherapy-induced enteritis.

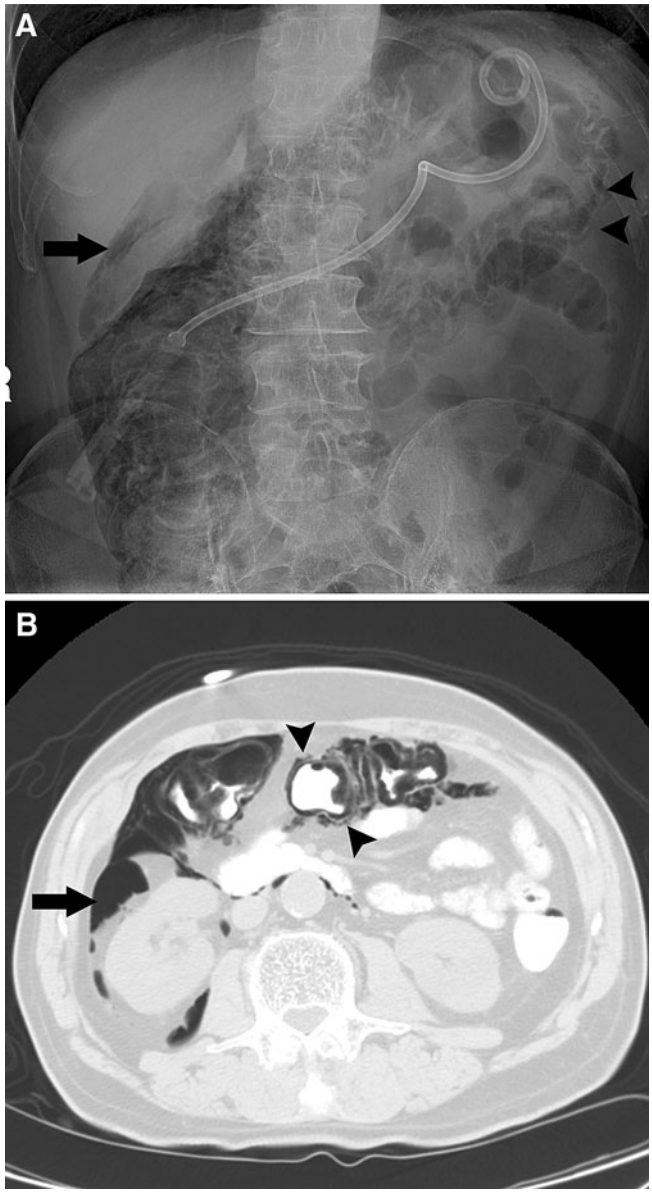

Fig. 2. A 63-year-old male patient with supraglottic squamous cell carcinoma treated with cisplatinum presented with abdominal pain. **A** Plain radiograph of the abdomen shows pneumatosis of the colon as well as free air in the right upper quadrant (*arrow*). **B** Post-contrast axial CT confirms these findings and shows presence of air within the wall of the transverse the colon and free air in the right perinephric space (*arrow*) denoting perforation.

treatment fails, emergency surgery may be required in such conditions. Obviously, differentiating benign transient pneumatosis from ischemic colitis/bowel necrosis is important due to the marked difference in the management of these conditions but this can often be difficult. Radiological findings such as presence of bowel wall thickening, portomesenteric venous gas, free intraperitoneal air, absent or intense mucosal enhancement are usually suggestive of bowel ischemia/necrosis [22, 23]. Further, clinical correlation is very useful in these situations as patients with necrotic bowel/ischemic colitis may be symptomatic.

Neutropenic enterocolitis. Neutropenic enterocolitis or typhlitis is an infectious process that occurs in neutropenic patients and is considered an oncologic emergency [19]. In a systematic review of 145 published articles, the pooled incidence rate of neutropenic enterocolitis was reported to be 5.3% in adult patients undergoing treatment of hematologic malignancies or receiving high dose chemotherapy for the treatment of solid tumors [24]. Although this condition may affect any segment of the bowel, the cecum and ascending colon are most frequently involved (Fig. 3) [19]. This is seen in patients

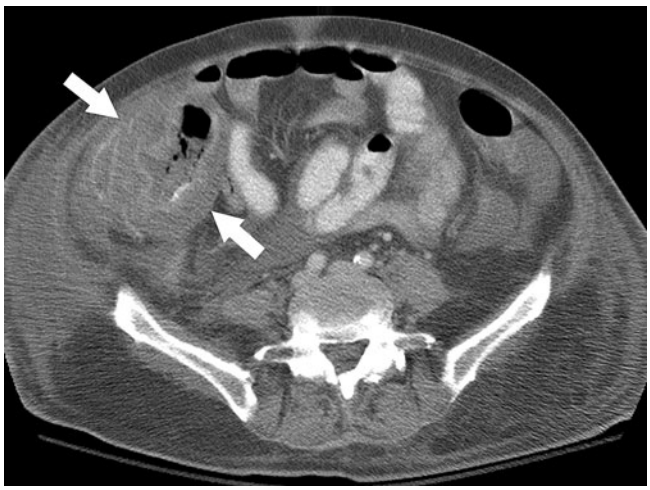

Fig. 3. A 70-year-old man with lymphoma treated with rituxan and CVAD presented with abdominal pain. The patient was also neutropenic. Axial intravenous and oral contrast enhanced CT scan shows bowel wall thickening in the cecum (*arrows*) and ascending colon. Given the clinical history of immunosuppressive chemotherapy and neutropenia, the appearances are consistent with typhlitis.

receiving immunosuppressive chemotherapy such as 5 FU, docetazel, paclitaxel, etc. Further, leukemic patients, or those who have had stem cell transplantation can also be affected. Combination of factors including mucosal injury, ischemia and bacterial invasion secondary to impaired host defenses result ultimately in necrosis of the bowel wall [7, 8, 25].

Classic triad for typhlitis includes fever, abdominal pain, and neutropenia. However, any of these features may be absent and it is important to be alert to the possibility of this condition, especially in patients with risk factors mentioned above. Imaging is very useful to diagnose this condition and to exclude other causes of abdominal pain such as appendicitis or perforated bowel.

Plain radiographic films may show distended cecum, paralytic ileus and pneumatosis intestinalis [8, 26]. Ultrasound often used in in children, particularly those who are too sick to be mobilized for a CT scan, may show bowel thickening and hyperemia. On CT, typhlitis is characterized by the presence of distension and diffuse circumferential thickening of the cecal wall, with associated stranding of the adjacent pericolonic fat. CT is also very useful in detecting complications such as pneumatosis, pneumoperitoneum and abscesses, which may necessitate surgery.

Initially, conservative treatment with bowel rest, parenteral nutrition and antibiotics is attempted but surgery may be required if this fails or patient becomes septic or CT scan shows complications mentioned before. Early diagnosis is an important factor influencing outcome and hence imaging plays an important role [8, 19, 26–28].

Ischemic colitis. Ischemic colitis has been reported as rare complications of docetaxel and paclitaxel [29, 30]. Patients may present with abdominal pain and bloody diarrhea. Colonic wall thickening with surrounding stranding is seen in cross sectional imaging. The exact mechanism of chemotherapy induced ischemic colitis is unclear but it is thought to be due to direct effect of the taxanes on gastrointestinal epithelium, causing necrosis of the gastrointestinal mucosa. Differentiating this entity from neutropenic enterocolitis and pseudomenbranous colitis by imaging alone may be difficult. However, clinical correlation may be useful (neutropenia in typhlitis, positive stool culture for clostridium difficile in pseudomenbranous colitis and blood containing stool in ischemic colitis).

Clostridium difficile-associated colitis. Although pseudomembranous colitis or *Clostridium difficile* colitis is most commonly seen in patients using broad spectrum antibiotics, it may occur in immunocompromised patients receiving chemotherapy, even without prior antibiotic therapy [8, 19, 28]. Methotrexate, fluorouracil, cyclophosphamide and doxorubicin are some of the common cytotoxic agents causing pseudomembranous colitis [8, 31]. Patients may present with symptoms including diarrhea, abdominal pain, or fever. Although most cases are mild, some patients may develop fulminant colitis with toxic megacolon.

Plain radiograph may show thumbprinting sign, which is a nonspecific sign implying colitis due to any etiology (Fig. 4). CT scan shows diffuse bowel wall thickening, stranding of the pericolonic fat, and ascites. Accordion sign has been described in this condition and refers to the presence of oral contrast trapped between the thickened nodular mucosal folds but this is not a specific sign of pseudomembaranous colitis, and has been reported in other conditions causing colitis [32]. Although diagnosis is confirmed by stool culture, empirical treatment can be started on basis of radiological suspicion, in order to decrease mortality [28].

Bowel perforation. In a large meta-analysis involving 12,294 patients, Hapani et al. reported that the incidence of gastrointestinal perforation in patients receiving bevacizumab was 0.9% (Fig. 5) [33, 34]. Although this is an uncommon complication, bevacizumab-induced bowel perforation is associated with a relatively high mortality rate of 21.7%. Risk of this complication appears to be dependent on dose and the type of tumor being treated. Increased risk of perforation is seen in patients with colorectal carcinoma, renal cell cancer and ovarian cancer [33]. Presence of an intact primary tumor, concomitant abdominal radiotherapy or combination therapy with taxanes, recent endoscopy, diverticulitis and use of non steroidal anti-inflammatory drugs are some of the other factors which increase the risk of perforation [8].

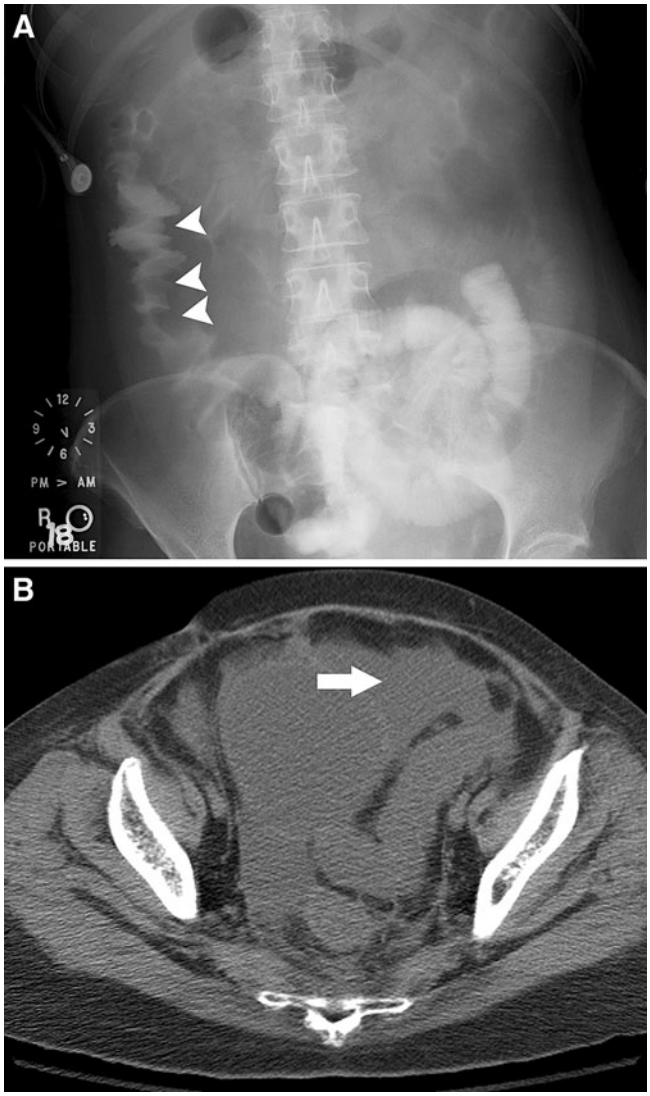

Fig. 4. A 48-year-old female with acute lymphocytic leukemia under chemotherapy presented with fever, worsening abdominal pain and diarrhea. Abdominal radiograph (**A**) shows thumb-printing sign (*arrowheads*). This is a nonspecific sign and can denote any type of colitis including inflammatory bowel disease, ischemic colitis and pseudomembranous colitis. However, this patient had a positive stool culture for *Clostridium difficile*, confirming the diagnosis of pseudomembranous colitis. Patient had renal impairment and hence had an unenhanced CT scan (**B**), which shows ascites (*arrow*). The bowel wall thickening and edema are difficult to appreciate on the unenhanced image.

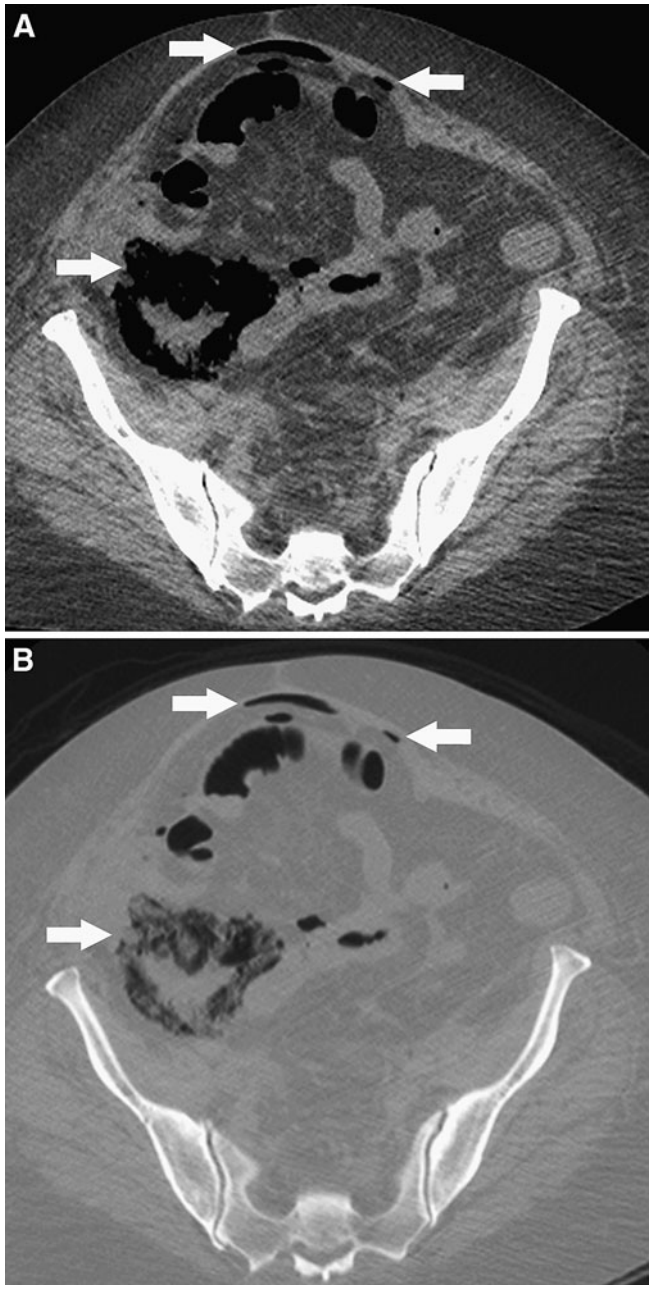

Fig. 5. A 55-year-old female patient with history of advanced endometrial carcinoma treated with bevacizumab presented with abdominal pain. Post-contrast CT in axial plane (**A**, **B**) shows pneumoperitoneum (*arrows*). Bowel perforation is a rare but well-recognized complication of bevacizumab.

Although the exact mechanism is unknown, it is postulated that thrombosis of the mesenteric vessels leading to bowel infarction and necrosis of tumor involving the bowel serosa may be causing the perforation [35]. Apart from perforation, Bevacizumb is reported to cause complications in the anastomotic site, including delayed anastomotic leak [36]. On CT, this may manifest as collection near the anastomotic site (Fig. 6). A barium enema using water-soluble contrast studies can confirm the site of leak.

Paclitaxel used in patient with breast and ovarian cancers has also been reported to cause intestinal perforation. This is thought to be due to direct effect of the drug on the intestinal mucosa causing mitotic arrest with subsequent epithelial necrosis [37]. Bowel perforation has

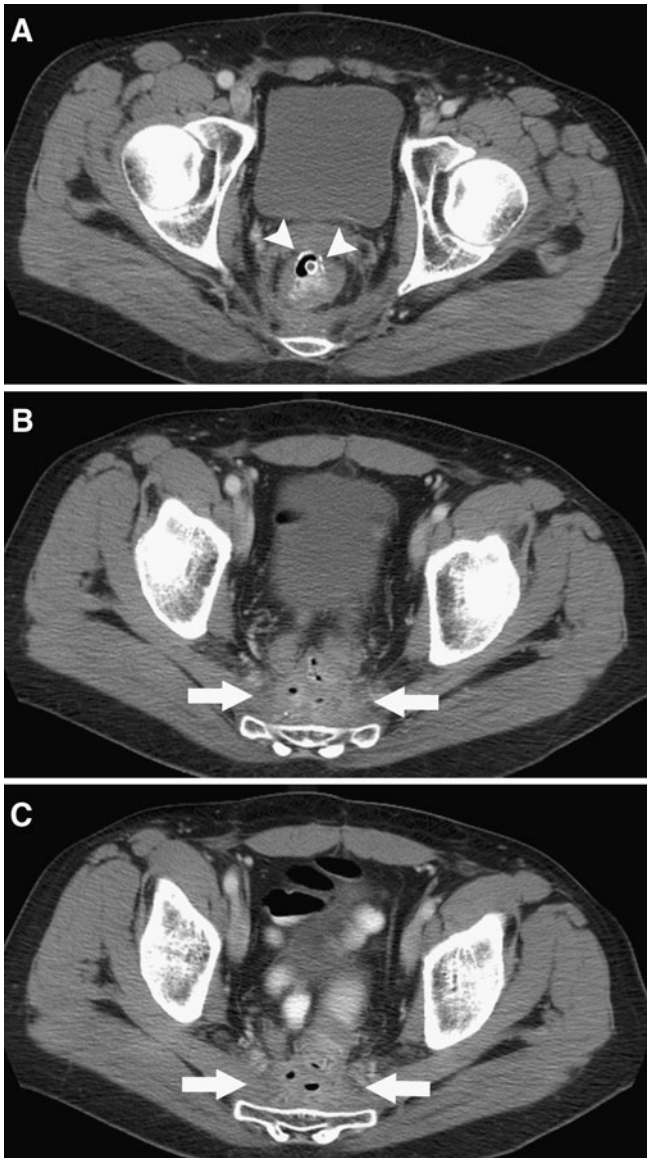

Fig. 6. A 45-year-old male with metastatic rectal cancer underwent low anterior resection and postsurgical chemotherapy with bevacizumab. Post contrast axial CT images (**A**) show the surgical stables at the anastomotic site (*arrowheads*). Axial CT scan images within the pelvis, immediately superior to the anastomotic site (**B**, **C**) show collection in the presacral space surrounding the anastomotic site (*arrows*). Bevacizumab is known to cause complications at the anastomotic site, including delayed anastomotic leak.

also been reported as a very rare complication of IL-2, 5-FU and cisplatin [38, 39]. Besides perforation, infection of the bowel resulting in abscesses is a known complication with these agents (Fig. 7).

Gastrointestinal bleeding. Gastrointestinal bleeding has been reported in 3%–5% of patients with gastrointestinal stromal tumors (GIST), who have been treated with imatininb (Fig. 8) [40]. The risk is increased in GISTs

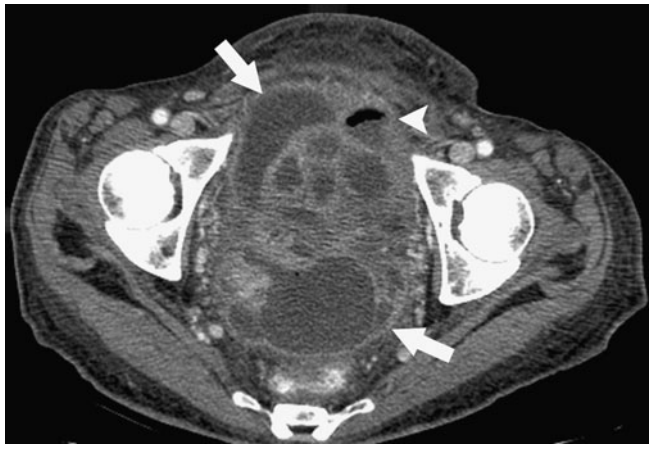

Fig. 7. A 61-year-old female with ovarian cancer treated with Paclitaxel, presented with abdominal pain and distention. Post contrast CT in axial plane shows multiple, loculated pelvic collections (*arrows*). Note gas within the collection (*arrowhead*).

located in the duodenum [40]. Following targeted therapy with imatinib, these tumors undergo necrosis and bleed into the lumen of the gastrointestinal tract. Hemorrhage within the tumor may result in apparent increase in size of the tumor, which may be mistaken for progression of disease. However, careful evaluation usually shows presence of high attenuation hemorrhage, fluid/fluid levels or air within the tumor, leading to correct diagnosis [41]. Gastrointestinal lymphomas have also been reported to cause GI bleeding following chemotherapy [42, 43].

Radiation therapy

Gastritis

Radiation-induced gastritis with or without ulceration can occur following doses of 45–60 Gy given over 5 weeks [44, 45]. In the acute phase, the gastric mucosa becomes edematous and inflamed whereas in the chronic phase, the submucosal layer becomes fibrotic. Radiological features mirror the pathological findings—gastric ulcers may be seen in early stages and better seen in barium studies whereas fixed fibrotic deformity or stenosis may be seen in the gastric antrum. CT scan is usually non specific and may show gastric wall thickening with perigastric stranding.

Radiation enteritis

Radiotherapy can damage the mucosal stem cells in the small bowel, causing mucosal edema, inflammation and atrophy during the acute stages. Patients with acute radiation enteritis usually develop symptoms such as

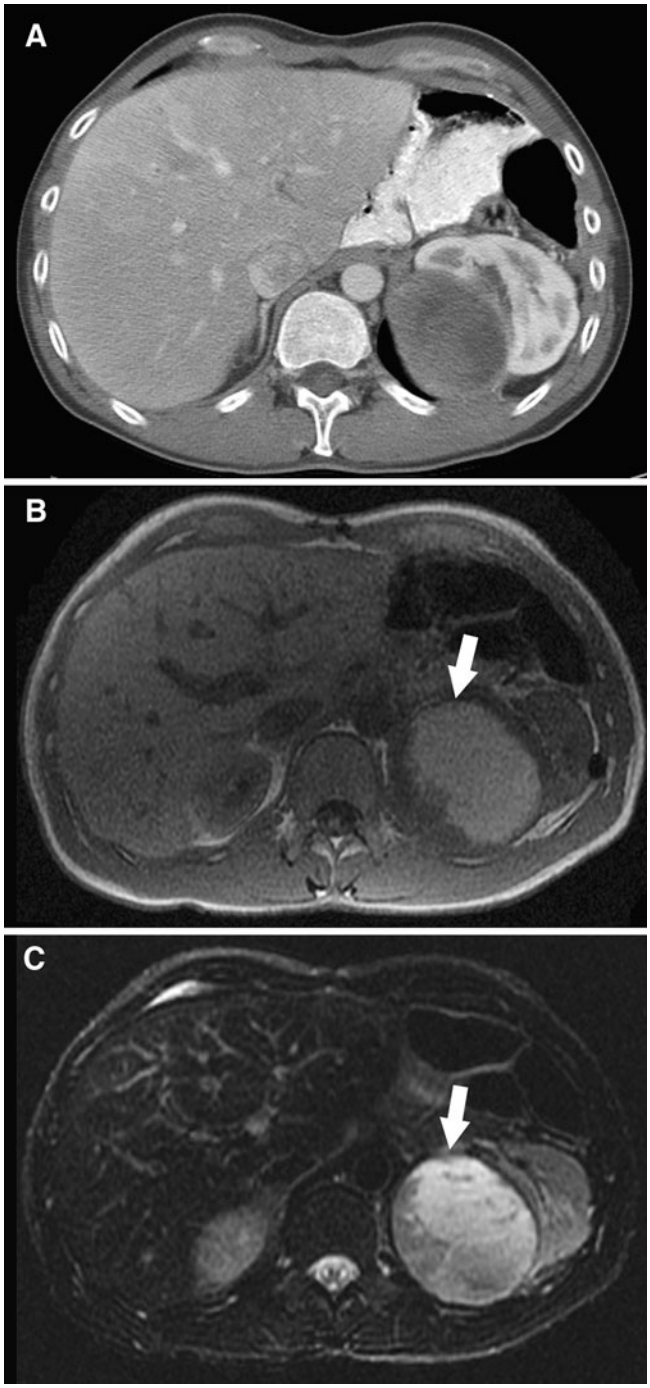

Fig. 8. A 36-year-old man with recurrent GIST in the left suprarenal region. Intravenous contrast enhanced axial CT scan (**A**) shows a predominantly solid, enhancing mass in the left suprarenal region, consistent with recurrent GIST. Patient was started on imatininb. Axial T1 (**B**) and T2 weighted (**C**) MRI show that the lesion has high T1 and T2 signal intensity, consistent with hemorrhage (*arrow*). Hemoglobin had dropped from 14.4 to 12 following therapy. Also, note that the lesion has now increased in size due to the bleeding, but this may be mistaken for tumor progression.

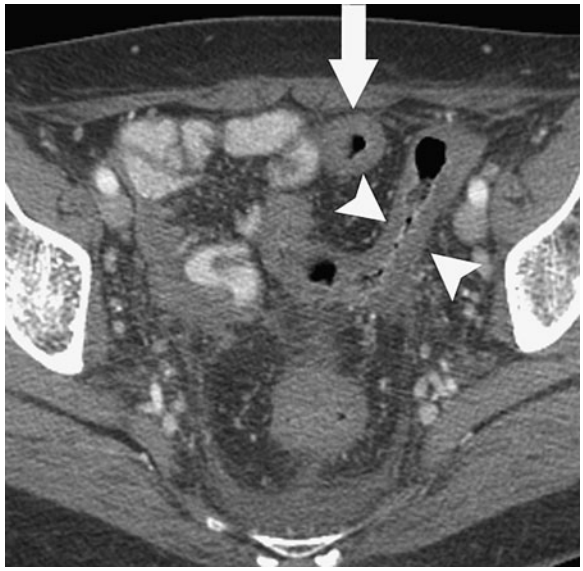

Fig. 9. A 58-year-old female with rectal carcinoma treated with postoperative radiotherapy. Post contrast axial CT shows diffuse thickening of the sigmoid colon (*arrowheads*) and the distal ileal loop (*arrow*). Appearances are consistent with radiation enterocolitis.

diarrhea, abdominal pain, nausea and vomiting, around the third week of therapy. Acute radiation enteritis is usually self-limiting and tends to resolve in 2–6 weeks after treatment with symptomatic treatment. On CT scan, this can present as small bowel thickening and edema (Fig. 9).

On the other hand, chronic radiation enteritis is a difficult clinical condition to treat and may significantly affect the patients' quality of life. Following the increase in the role of combined chemoradiation in many pelvic cancers, the incidence of radiation-induced gastrointestinal toxicity is to also thought to be increasing. Chronic radiation enteritis is dose dependent. Around 5% of patients are affected at dose of 45 Gy but this increases to 50% with doses of 65 Gy [46, 47].

The primary pathophysiology behind chronic radiation enteritis is fibrosis of the bowel and its mesentery. Mesenteric vascular injury leading to bowel ischemia may also be a significant factor. Late onset radiation injury to the bowel usually develops 6–12 months following radiation therapy and causes small bowel wall thickening and edema, ulcerations, stricture formation, fistula, and abscess formation [48, 49]. Small bowel fibrosis, strictures (causing acute or subacute obstruction) and fistulae are late complications. The terminal ileum is more commonly affected, owing to its fixed position. Fluoroscopy is useful for demonstrating these complications and may also show tethering of small bowel loops and altered peristalsis. CT scan, MR

enterography/enteroclysis are also very useful to evaluate the small bowel and may be particularly useful to assess for abscess.

Radiation colitis

The pathophysiology of radiation colitis is similar to that of radiation enteritis. In acute radiation colitis, bowel wall edema and thickening are seen, along with perirectal fat stranding (Fig. 9). Patients may present with hematochezia and rectal pain. Most of the cases may settle with symptomatic relief [50]. Chronic radiation colitis develops following vascular damage, resulting in ischemia and fibrosis. Strictures of variable length may develop and can lead to obstruction, fistula formation and abscesses. These complications can be demonstrated by fluoroscopy or by cross sectional imaging. [51]. Extent and the colonic segment injured depends upon the site and dose of radiotherapy. For example, the rectum and sigmoid colon are at particular risk in pelvic radiotherapy, due to their proximity to radiation site. Chronic radiation colitis and proctitis is reported to occur in 1%–5% of patients treated with 45–55 Gy of external beam radiation [52].

Liver

Chemotherapy related hepatic complications are relatively common. The spectrum of pathology ranges from reversible heaptic steatosis to advanced cirrhosis and vascular injury.

Fatty liver

Steatosis and steatohepatitis are side effects of chemotherapy and have been seen in patients receiving treatment for breast cancer and colorectal carcinoma. Several chemotherapeutic agents such as tamoxifen, irinotecan, and 5-fluorouracil and leucovorin can cause steatosis [7, 53]. It is thought to be mediated by production of ROS, resulting in oxidative stress in hepatocytes [53–55]. Findings of steatosis are reversible if chemotherapy is discontinued. Steatosis greater than 30% has been associated with higher morbidity after surgery [53, 56–58].

Steatohepatitis is a more severe form of fatty liver disease and is pathologically distinct from steatosis. This is characterized by the presence of hepatocyte ballooning and lobular inflammation, besides fat accumulation in the hepatocytes [7, 53]. Irinotecan, a cytotoxic chemotherapy used in patients with metastatic colorectal cancer, is associated with development of steatohepatitis which affects the hepatic reserve for regeneration leading to increase risk of 90-day post operative mortality especially if the BMI is more than 25 kg/m^2 [54, 59, 60]. Hence, the presence of fatty liver should be reported in patients undergoing chemotherapy, as it has the potential to change management. Close follow up may be essential when used for patients who are candidate of major hepatic resection [60, 61].

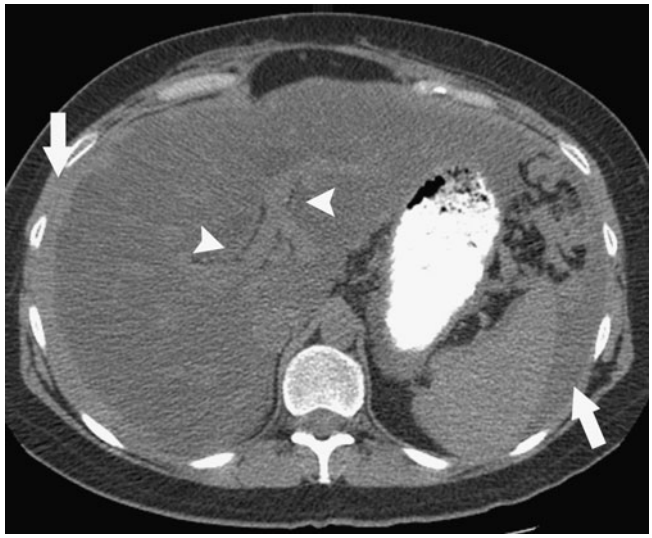

Fig. 10. A 36-year-old female with metastatic ovarian cancer treated with carboplatin and paclitaxel. Unenhanced CT in axial plane reveals diffuse low attenuation in the liver. The intrahepatic vessels (*arrowheads*) appear hyperattenuating against the liver parenchyma, which is characteristic of diffuse fatty liver. Extensive perihepatic peritoneal implants and ascites are also seen.

On CT and MRI, fatty infiltration typically has a well-defined, geometric pattern. On unenhanced CT scan, the attenuation of the liver will be lower than the spleen due to the deposition of fat within the hepatocytes, and the Hounsfield unit measurement may be less than 40. Further, the intrahepatic vasculature appears hyperattenuating against the liver parenchyma on unenhanced CT scan in the presence of severe steatosis (Fig. 10) [62, 63].

MRI with fat-suppressive and in-and-out of phase techniques can be used if findings are equivocal on CT, especially to differentiate a focal fatty infiltration from metastasis; the area of fatty deposition will drop out of signal in the out of phase images.

Pseudocirrhosis

Although pseudocirrhosis may be seen as a complication after any chemotherapy, it is most commonly encountered in patients with metastatic breast cancer who have undergone chemotherapy [7, 64, 65]. Although capsular retraction was initially reported to occur adjacent to metastases which shrink following therapy, further studies have shown that these may also be seen when metastases increase in size [7, 65]. These changes can be diffuse in case of extensive metastatic disease mimicking cirrhosis hence called pseudocirrhosis [7, 66]. However,

pathologically, pseudocirrhosis differs from cirrhosis, in that the liver parenchyma in between the dense fibrotic bands has normal architexture. Also, it may develop rapidly over 1–3 months suggesting the treatment related toxicity rather than true cirrhosis (Fig. 11) [66]. Pseudocirrhosis is thought to arise from nodular regenerative hyperplasia [65–67].

In early cases, cross sectional imaging shows focal flattening or concavity of the normally convex hepatic contour in the vicinity of previously identified metastases [64, 65]. In advanced stages, the liver may shrink in size and have a nodular contour with irregular borders. Features of portal hypertension such as splenomegaly, ascites and porto-systemic collaterals may be noted [67, 68].

It is important to be able to recognize pseudocirrhosis as a post-treatment complication rather than true cirrhosis as the chemotherapy can be stopped or changed so as to prevent further liver damage and progression to portal hypertension [67].

Hepatic veno-occlusive disease (HVOD)

Hepatic veno-occlusive disease (HVOD) or sinusoidal obstruction syndrome is a serious but rare complication seen in patients treated with oxaliplatin for metastatic colorectal carcinoma [60]. It is more commonly seen as a complication of cytoreductive therapy in stem cell transplantation (10%–60%) or following intensive chemotherapy in patient with hematological malignancies [69, 70].

The histological findings seen in HVOD include necrosis of the hepatocytes, sinusoidal fibrosis and occlusion of hepatic venules with subsequent hepatic congestion [71, 72].

Clinically the patient presents with jaundice, tender hepatomegaly, unexplained weight gain with or without ascites. Liver enzymes may be abnormal and thrombocytopenia may develop, which is refractory to transfusion [69, 73].

In patients undergoing hemopoietic stem cell transplant, it is important to differentiate development of graft versus host disease (GVHD) from HVOD especially if the clinical presentation is vague because the treatment differs—GVHD is treated with steroids whereas HVOD requires antithrombotic therapy [74]. Ultrasound findings such as hepatosplenomegaly, thickened gallbladder wall thickening and ascites are frequently present but nonspecific as they are seen in both conditions. Ertek et al. reported that the measurement of the right hepatic vein may be a useful discriminator as usually HVOD is associated with a decreased caliber of hepatic veins below 0.45 mm. Findings on Doppler ultrasound such as hepatic arterial RI of 0.75 or

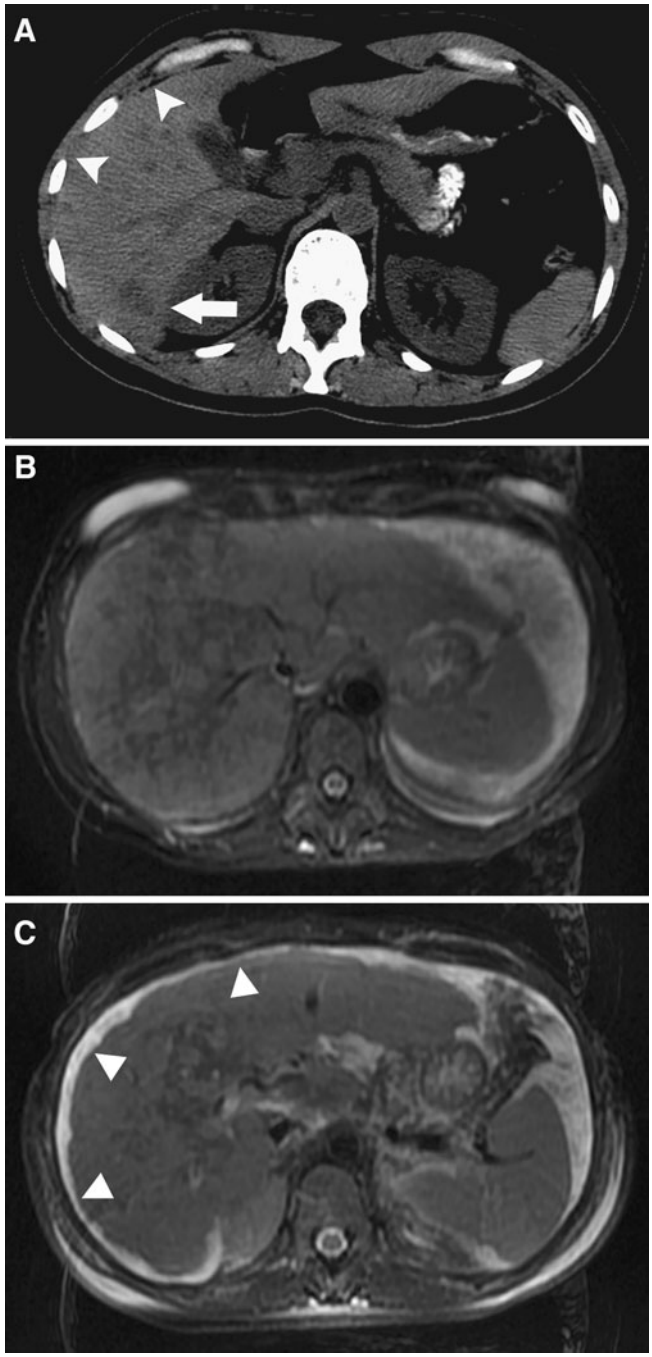

Fig. 11. A 37-year-old female with metastatic breast cancer treated with Avastin, gemcitabine and Taxol. Unenhanced axial (**A**) CT scan shows liver metastasis in the right lobe of the liver (*arrow*). Note that the liver has a normal contour (*arrowhead*). Axial T2 weighted MRI (**B**, **C**) performed 6 weeks after chemotherapy shows extensive, heterogenous architecture within the liver. Note the development of nodular contour in the liver (*arrowhead*) and presence of ascites. Given that these changes have developed within 6 weeks, appearances are consistent with pseudocirrhosis.

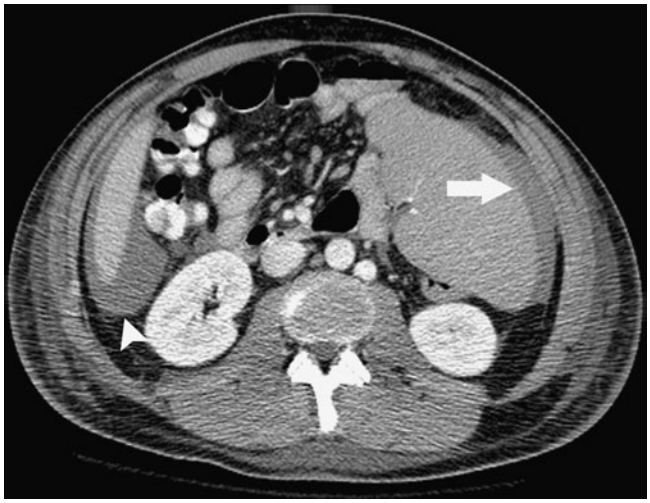

Fig. 12. A 28-year-old male with AML treated with cytarabine presented with severe abdominal pain. Post-contrast axial CT shows layering of high density fluid around the spleen (*arrow*) and in the right paracolic gutter (*arrowhead*), denoting intraperitoneal hemorrhage from the spleen.

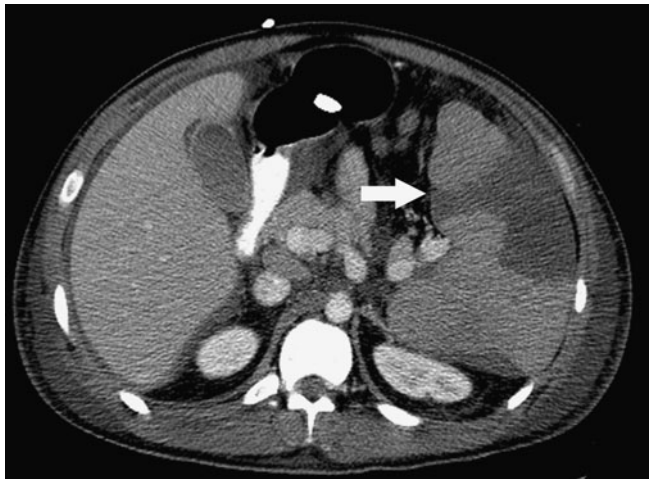

Fig. 13. A 28-year-old male with AML treated with idarubicin presented with abdominal pain. Post-contrast axial CT shows splenic rupture (*arrow*). Spontaneous splenic rupture is a rare complication of certain chemotherapeutic drugs.

more, decreased velocity or even flow reversal in the portal vein, visualization of para umbilical vein are also suggestive of HVOD [70, 75]. On CT scan, findings of HVOD include periportal edema, ascites and narrowed right hepatic vein [74, 75]. Small bowel wall thickening is not usually seen and hence the presence of this finding may suggest GVHD rather than HVOD. Although imaging can be helpful, liver biopsy may be required for definitive diagnosis in some cases.

Oxaliplatin has been reported to cause sinusoidal injury. Nakano et al. [76] reported that 51% of their patients developed hepatic sinusoidal injury following oxaliplatin. It is unclear as to how many patients with oxliplatin-induced sinusoidal injury go on to develop portal hypertension but this has certainly been documented [77]. Progressive increase in spleen size may indicate development of portal hypertension following oxaliplatin therapy. Other features such as ascites, gastroesophageal varices, rectal collaterals, etc. may also be detected [77]. Also, it should be remembered that development of ascites in a patient undergoing oxaliplatin may not always represent peritoneal disease but may be a sign of toxicity and this should be included in the differential [7, 78].

HVOD is a relatively serious complication with high morbidity and mortality and there is no specific treatment for HVOD. Hence, the focus is on prevention and early diagnosis is essential to prevent complications.

Radiation change

Radiation change within the liver is typically seen within 2–8 weeks of completing radiotherapy. Radiation-induced liver disease (RILD) 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, usually between 2 weeks and 4 months following radiotherapy [1, 79]. Risk of RILD is increased in patients with pre-existing liver disease, concurrent chemotherapy, portal vein thrombosis, etc. Reactivation of hepatitis B has also been reported after radiotherapy. Most patients with radiation hepatitis recover completely; a few may progress to chronic liver failure or even fulminant hepatic failure. Pathologically, the findings are very similar to veno-occlusive disease, with congestion of the lobules and injury to the endothelial cells. Transforming growth factor levels are elevated in radiation hepatitis and it is thought that they may play a role in the development of veno-occlusive disease, following radiotherapy [3]. On CT, radiation change is hypodense due to inflammation and edema. This finding may be misleading and can be confused with metastases or tumor progression. However, usually, the area of low density secondary to radiation changes is sharply demarcated in a linear fashion, corresponding to the radiation port. Further, these changes in density may be transient and resolve in a few months. However, radiation can cause atrophy of the injured liver. MRI findings are similar to CT and show low T1 signal and a high T2 signal in the area of radiation. In difficult cases where differentiation between metastasis and radiation change is not clear on cross sectional imaging, 18F-FDG PET-CT may be used but this may also show false positive uptake in areas of radiation injury in liver, and hence extreme care should be exercised when interpreting these studies to prevent patients from receiving unnecessary therapy [80, 81]. The

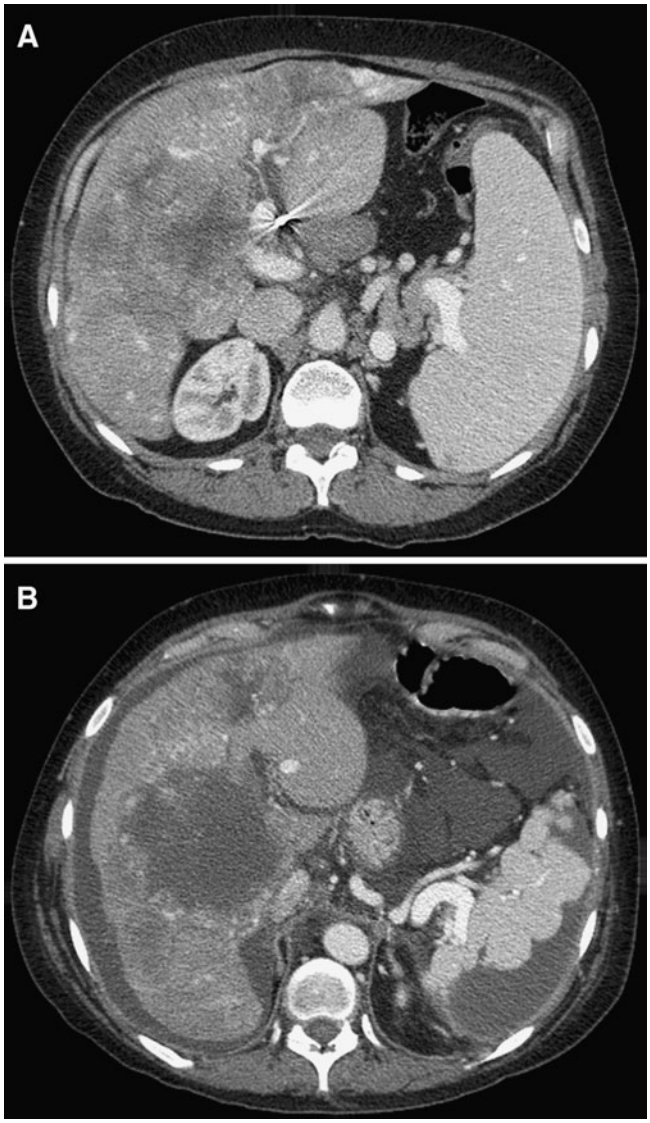

Fig. 14. A 51-year-old female with colorectal cancer and extensive liver metastases and malignant ascites treated with oxaliplatin (FOLFOX regimen). Post contrast CT in axial plane (**A**) shows splenomegaly with collaterals in the portal circulation. Patient had symptomatic hypersplenism and thrombocytopenia, hence underwent partial splenic embolization. Post-embolization CT scan (**B**) shows reduced spleen size.

increased metabolic activity in the area of injury on 18F-FDG PET-CT is felt to be due to leukocyte injury [80].

Gallbladder and biliary system

Gallstones have been reported to develop with high dose of cytarabine and asparaginase in children and may disappear spontaneously [82]. Similarly, acalculous cholecystitis has been reported in children with leukemia, who have been treated with vincristine, cyclophosphamide, and cytosine-arabinoside [83, 84].

Biliary strictures and sclerosing cholangitis have been reported following use of intrahepatic arterial infusion of fluoropyrimidines, especially fluoxouridine, with reported incidences varying from 8%–55% [85, 86]. Microvascular injury to biliary epithelium resulting in ischemia is thought to be the etiology of the cholangitis. Radiologically, chemotherapy-induced sclerosing cholangitis and primary sclerosing cholangitis have similar appearance [7, 87, 88]. Ductal stenosis, mural nodularity, periductal edema, ductal dilatation, wall thickening and mural enhancement have been described [88]. The common hepatic duct and its bifurcation are typically involved.

Pancreas

Pancreatitis can occur following administration of certain cytotoxic and targeted chemotherapeutic agents. Examples include L-asparaginase, ifosfamide, paclitaxel, cisplatin, vinorelbine, cytarabine, tretinoin, sunitinb, and sorafenib [7, 89]. It can also develop in patients with pseudomyxoma peritonei treated with intraperitoneal chemotherapy [90]. Fatal necrotizing pancreatitis has also been reported following combined therapy of erlotinib and sunitinib in a patient with metastatic NSCLC [91].

A patient presents with abdominal pain and elevated lipase and amylase. However, elevation of serum lipase alone without clinical signs or symptoms of pancreatitis may be seen in patients receiving sunitinib [92]. Time of onset is variable and ranges from a few hours to a month after therapy. Pancreatitis can progress rapidly and the use of alternate chemotherapy should be considered [89].

Chemotherapy-induced pancreatitis is usually associated with CT features similar to pancreatitis from other etiologies [93]. Findings include pancreatic edema, peripancreatic fat stranding, and fluid collections [89, 93]. Clinical correlation and awareness of the common chemotherapeutic agents causing pancreatitis usually help to make the correct diagnosis.

Although the pancreas is relatively radioresistant, chronic pancreatitis and eventually pancreatic atrophy can occur following radiation therapy [3, 94].

Spleen

Splenic rupture

Rupture of the spleen is a rare but serious complication that has been reported in patients treated with granulocyte-colony stimulating factor (G-CSF) [95, 96]. G-CSF is used in cancer patients to counter chemotherapy-induced neutropenia allowing higher intensity treatment regimens [96, 97]. It is also used to induce stem cell mobilization prior to autologous and allogeneic bone marrow transplant [98, 99]. Splenic rupture following G-CSF is postulated to be due to massive extramedullary hemopoiesis and

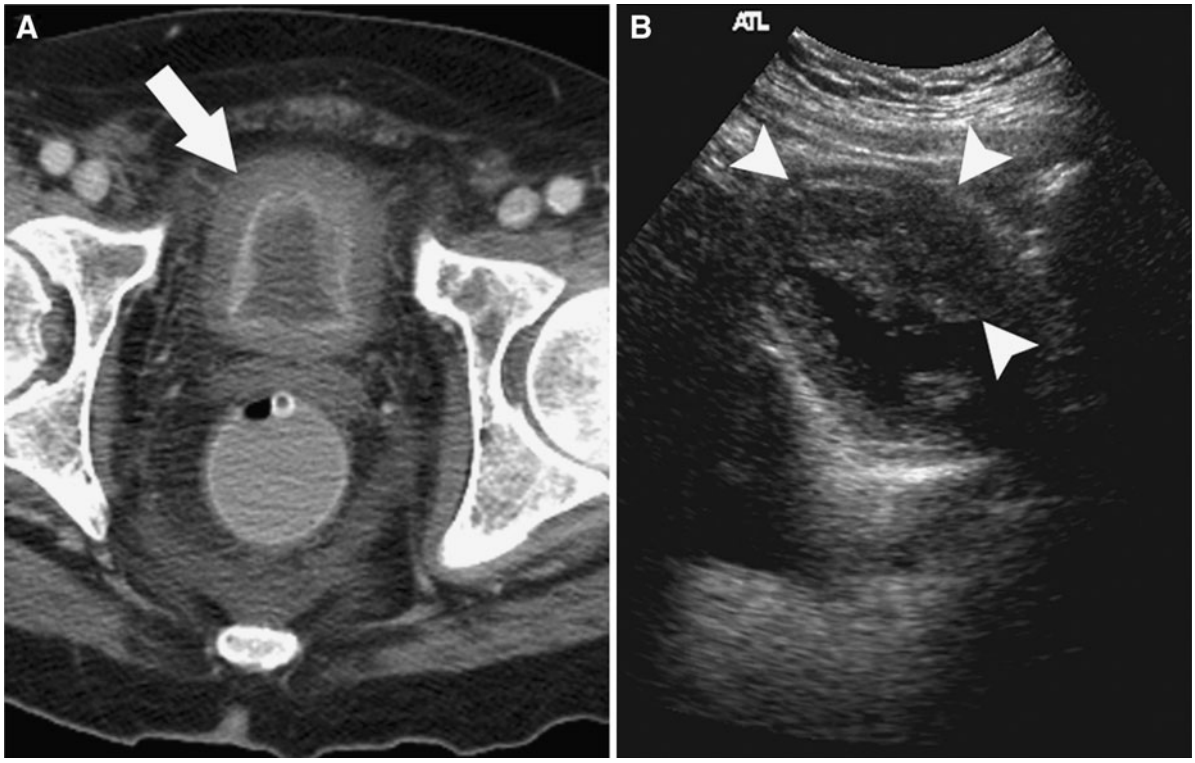

Fig. 15. A 61-year-old male with a history of ALL treated with cyclophosphamide presented with hematuria. Post-contrast CT in axial plane (**A**) shows thickened bladder wall and hyperemic mucosa (*arrow*). Transabdominal ultrasound (**B**) confirms the diffuse bladder wall thickening (*arrowheads*). Although non-specific, given the clinical history, appearances are consistent with cyclophosphamide-induced hemorrhagic cystitis.

intrasplenic sequestration of blood cells with subsequent splenic congestion and ultimately rupture [96, 100].

Splenic rupture has also been described as a side effect of Imatinib in a patient with chronic myeloid leukemia and myelofibrosis [95]. Splenic rupture following treatment with idarubicin has also been reported (Fig. 12) [101].

The patients usually present with sharp left upper quadrant abdominal pain, tenderness and rigidity as well as decrease in hematocrit level due to hemoperitoneum (Fig. 13). The condition may be severe leading to hypovolemic shock. Findings on CT scan include splenomegaly (arising from congestion), splenic disruption with low attenuation changes in the parenchyma, active arterial extravasation, and hemoperitoneum [102].

Splenomegaly

Splenomegaly can be seen in patients with colorectal liver metastases receiving oxaliplatin based chemotherapy (Fig. 14). This is attributed to oxaliplatin induced sinusoidal injury, which leads to portal hypertension [103, 104]. Thrombocytopenia can also be seen as a result of splenic sequestration of platelets and this may require splenic embolization [104]. Rapidly enlarged spleen may lead to abdominal discomfort and spontaneous splenic rupture [105].

Patients may present with ascites, jaundice, or variceal bleeding [104]. CT scan shows splenomegaly and features of portal hypertension. Further, imaging is useful to follow up the spleen size in oxalaplatin-induced splenomegaly as increasing spleen size is an indicator for development of portal hypertension and HVOD [104].

A case report of splenomegaly was also described in a patient with metastatic melanoma receiving Cytotoxic T-lymphocyte antigen 4 (CTLA4) therapy. The mechanism is still not clear but is thought to be due to accumulation of abnormal lymphoid cells in the spleen or over activation of the immune system attacking the spleen.

Radiation changes

The spleen is a very radiosensitive organ, and injury may occur at doses as low as 4–8 Gy [106]. Splenic atrophy may be seen at doses of 35–40 Gy [3]. Although most of these changes are clinically insignificant, fulminant pneumococcal sepsis may occur rarely.

Genito-urinary complications

Nephrotoxicity

Chemotherapy-related nephrotoxicity is a recognized complication seen in many classic chemotherapeutic agents such as cisplatin, ifosfamide, nitrosourea,

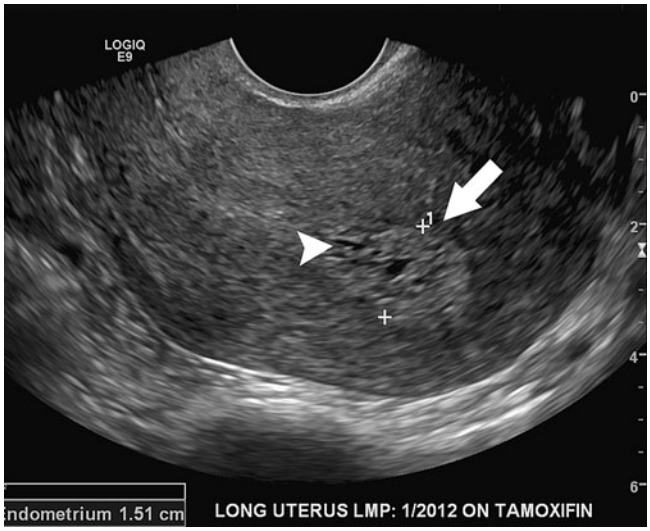

Fig. 16. A 54-year-old female with breast carcinoma treated with tamoxifen presented with postmenopausal vaginal bleeding. Transvaginal ultrasound shows the endometrium is markedly thickened (*arrow*). Also, note cystic changes are seen within the endometrium (*arrowhead*). These changes most likely represent tamoxifen induced hyperplasia, but endometrial carcinoma cannot be excluded. Endometrial biopsy may be necessary in such cases.

mitomycin, and methotrexate. Depending on the drug, renal glomeruli, tubules, or blood vessels may be affected [7, 107].

Targeted therapies with VEGF inhibitors are also associated with significant renal toxicity. VEGF is an important regulator for angiogenesis, and VEGF receptor inhibitors were introduced specifically to inhibit angiogenesis, thereby inhibiting cancer growth. However, VEGF plays key roles in normal cells such as in the kidneys where it is important for maintaining the normal function of the fenestrated endothelial cells. VEGF receptor inhibitors interfere with this important function of VEGF, leading to abnormal glomerular function and renal failure. The patient may present with proteinuria, nephritic syndrome and renal hypertension [7, 108]. There are no definite findings seen on imaging to suggest acute nephrotoxicity; however, chronic injury from chemotherapy can cause atrophy of the kidneys as seen on CT or MRI. On ultrasound, it may manifest as increased renal cortical echogenicity.

Tumor lysis syndrome

Tumor lysis syndrome is an oncologic emergency seen in patients with tumor of high proliferative rate such as acute leukemia and Burkitt's lymphoma. It usually occurs within 72 h of initiation of therapy but occasionally, it may also occur spontaneously prior to any treatment [109]. Paclitaxel, fludarabine, etoposide, thalidomide, bortezomib, zoledronic acid, and hydroxyurea are some of the anticancer drugs associated with tumor lysis syndrome.

Tumor lysis syndrome occurs due to the sudden and massive cell destruction, with the release of intracellular ions and metabolic products into the circulation. This results in two important complications. First, release of intracellular ions leads to electrolyte disturbances such as hyperkalemia, hyperphosphatemia, and hypocalcemia. Second, hyperuricemia arising from the release of purine components from the cells causes precipitation of uric acid in renal tubules, resulting in urinary tract obstruction and acute renal failure [7, 23, 109–111]. Further, hyperphospatemia also contributes to the renal failure by causing precipitation of calcium phosphate crystals in the renal tubules. On ultrasound, these crystals appear as echogenic tubular structures, while on unenhanced CT they appear as hyperdense foci [23, 112]. Treatment is typically conservative but dialysis may be required if that fails.

Hemorrhagic cystitis

Hemorrhagic cystitis is a well-known adverse effect of cyclophosphamide and ifosfamide therapy [7, 113]. Bladder injury is mediated by urinary excretion of acrolein (a toxic metabolite of cyclophosphamide/ifosfamide), leading to diffuse mucosal irritation and inflammation. Furthermore, chronic mucosal irritation may lead to bladder fibrosis and/or malignancy [107, 113]. The estimated incidence of bladder cancer following cyclophosphamide therapy is reported to be 5% at 10 years and 16% at 15 years [114].

Patients usually present with gross hematuria (78%) or micro hematuria (93%) and dysuria (45%) [113]. Radiological evaluation for these patients should include assessment of the upper urinary tract to exclude other causes of hematuria. US and CT examination can demonstrate bladder wall thickening and determine the degree of involvement which may be focal or diffuse (Fig. 15). This can affect treatment because focal disease can be cauterized while diffuse disease needs intravesicle sclerotherapy. Sometimes, blood clot or sloughed mucosa can be seen within the bladder lumen. Color Doppler ultrasound can show hypervascularity of the bladder wall. MRI usually shows bladder wall edema [115–117].

The risk for developing hemorrhagic cystitis can be largely decreased through adequate hydration and coadministration of the drug mensa, which can neutralize acrolein [107, 118].

Neurogenic bladder

Neurogenic bladder has been described in patients receiving vincristine as well as bortezomib, a recently approved topoisomerase inhibitor. This complication

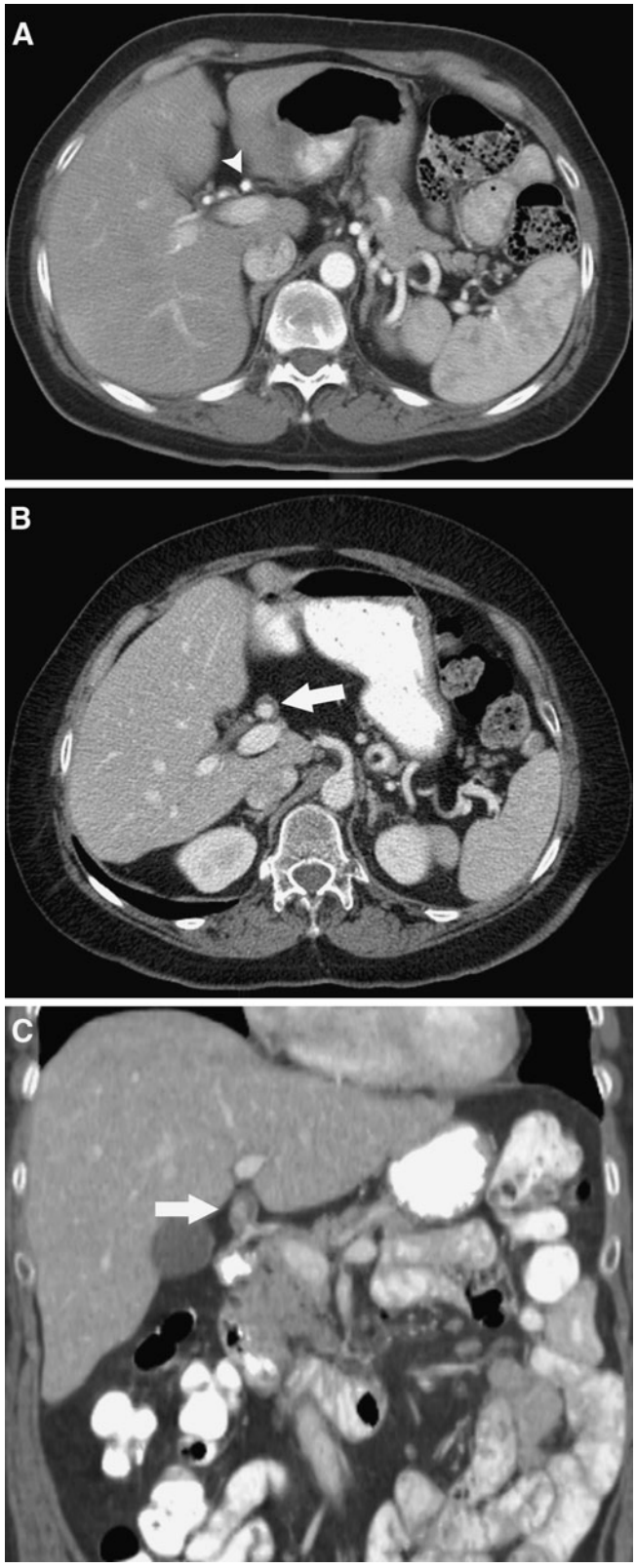

Fig. 17. A 56-year-old female with metastatic colorectal cancer. Baseline contrast enhanced CT scan (**A**) performed prior to therapy shows normal common hepatic artery (*arrowhead*). Axial (**B**) and coronal CT images (**C**) performed after therapy with FOLFOX and Bevacizumab show mild aneurysmal dilatation with thrombosis in the common hepatic artery (*arrow*). Arterial thrombosis and vasculitis are known complications of Bevacizumab. ►

arises as a result of peripheral neurotoxicity induced by these drugs [7, 119–121]. Patients present with urine retention and imaging reveals bladder distension. Radiological evaluation of the spine should be done to exclude central causes of bladder dysfunction [7].

Radiation changes

The kidney is a radiosensitive organ. Doses of 28 Gy to both kidneys given for 5 weeks may cause renal failure [122]. Imaging is not of much use in acute radiation nephritis, other than excluding other causes of renal failure. Renal atrophy may be seen at later stages and malignant hypertension has also been reported as a complication of renal irradiation [122].

Radiation injury to the bladder may be seen during radiotherapy given for bladder, prostate, rectal and cervical cancers. Radiation injury to the bladder is thought to be dose dependent [123]. Whole bladder dose of 50 Gy is associated with 5%–10% complication rate and this may increase with dose. [123]. Complications following radiation may be acute (within 3 months), subacute (3–6 months) or late (more than 6 months). Acute complications are usually related to cystitis and are self-limiting. Late complications include bladder contracture, vesicovaginal fistula, and incontinence. Perforation of the bladder may occur very rarely [124]. Although the ureter is a relatively radioresistant structure, it must be remembered that ureteral stenosis may develop after a long latency period (1% at 5 years and 3% at 20 years) [125]. Hence, renal function should be continuously monitored, especially in patients with cervical cancer. Further, it is necessary to differentiate hydronephrosis caused by radiation induced ureteral stricture from recurrent cervical cancer and MRI can be helpful in this situation— the former is usually a smoothly tapering stricture whereas recurrent cervical disease causing hydronephrosis manifests changes in the parametrium and often is associated with a mass which has a high signal on the T2 weighted images.

Female genital tract

Endometrial changes

Tamoxifen is a selective estrogen receptor modulator used as an adjuvant systemic therapy for breast cancer. It is associated with increased risk of developing benign and malignant uterine lesions [126, 127]. Endometrial hyperplasia, polyps, cystic changes within the endometrium and cervix, adenomyosis, endometrial carcinoma, and sarcoma have all been reported with use of

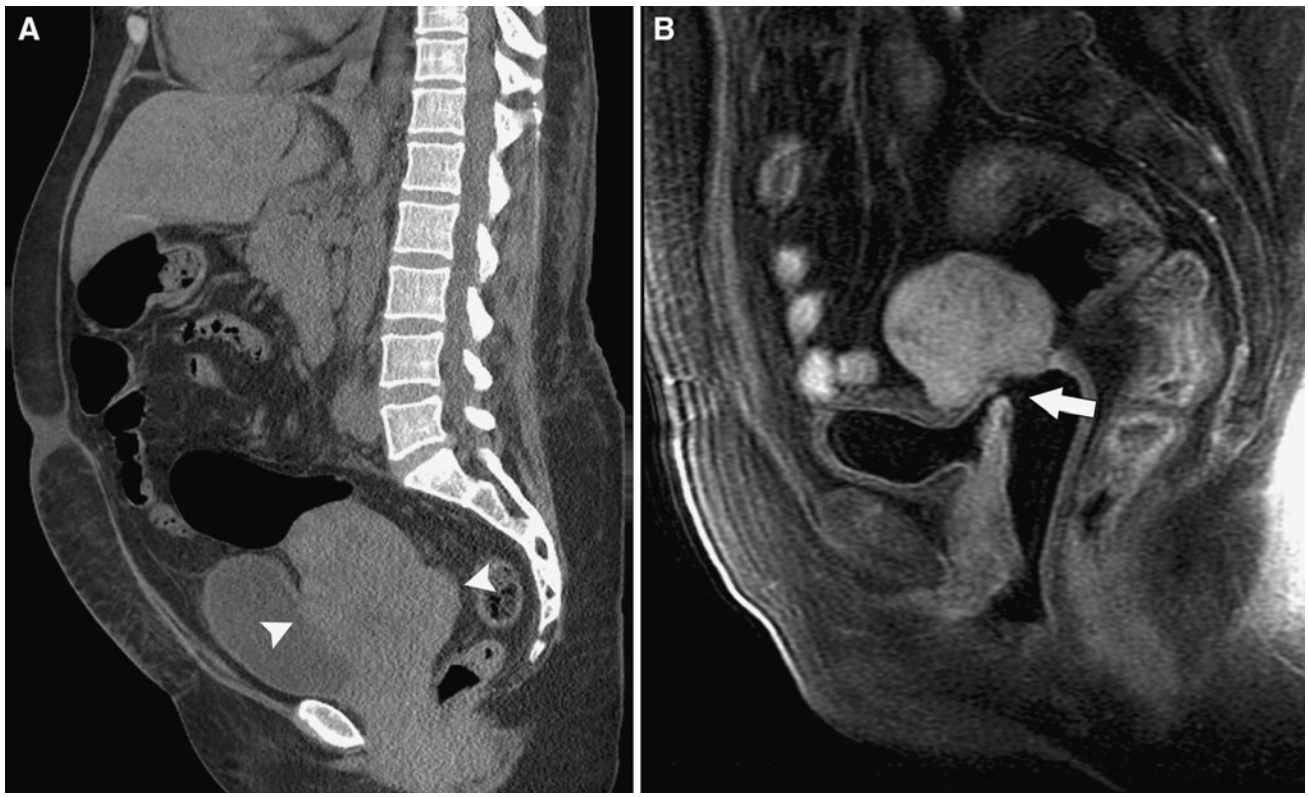

Fig. 18. A 49-year-old female with advanced cervical carcinoma. Unenhanced CT scan in sagittal plane (**A**) shows a large cervical tumor extending into the uterus and involving the bladder (*arrowheads*). Patient underwent external beam radiotherapy with 45 Gy. Post-radiotherapy intravenous contrast enhanced MRI in sagittal plane (**B**) shows vesicovaginal fistula (*arrow*). Note that the cervical tumor has relatively shrunken and residual tumor is seen in uterus. Post contrast dynamic MRI in sagittal plane is very useful for detecting vesicovaginal fistula.

long-standing tamoxifen therapy (Fig. 16) [23, 127]. Tamoxifen doubles the risk of developing endometrial cancers compared to the normal population [128]. Tamoxifen-induced endometrial carcinomas are typically low-grade clear cell or serous tumors.

Clinically, patients may be asymptomatic or present with abnormal uterine bleeding [129, 130].

Patients receiving tamoxifen are routinely screened by ultrasound for early detection of endometrial pathology. Ultrasound has high sensitivity in detecting endometrial pathology but the specificity is low. In cases where the ultrasound is abnormal, further work up by hysterosonography may provide additional information [126, 127, 131]. MRI is useful for staging and treatment planning in cases of endometrial malignancy [130].

Radiation changes

The uterus and ovaries may become atrophic following radiotherapy. In order to preserve fertility in premenopausal women who may undero pelvic irradiation, the ovaries may be transposed to unusual positions such as in the paracolic gutters or anterior to the psoas muscle. This may be mistaken for pathological lesion but careful evaluation may reveal that the mass contains ovarian follicles, which is drained by the gonadal vessels, thereby leading to correct diagnosis [132]. Vesicovaginal fistula and cervical stenosis are well known complications seen after pelvic radiotherapy (Fig. 17).

Vascular complications

The introduction of recent chemotherapeutic agents has been associated with variety of vascular complications [133]. Venous thromboembolism has been reported with use of gemictabine, thalidomide, lenalidomide, semaxibin and prinomastat while arterial thromboembolic complications are seen with bevacizumab, sunitinib, and sorafenib (Fig. 18) [133]. Although the exact underlying mechanism is unclear, it is postulated that chemotherapy may induce apoptosis of the vascular endothelium cells, with subsequent exposure of the basement membrane and activation of clotting cascade. Paradoxical bleeding may also occur from weakening of the basement membrane [133]. In particular, bevacizumab can cause both thrombosis and bleeding and this may be due to its effect

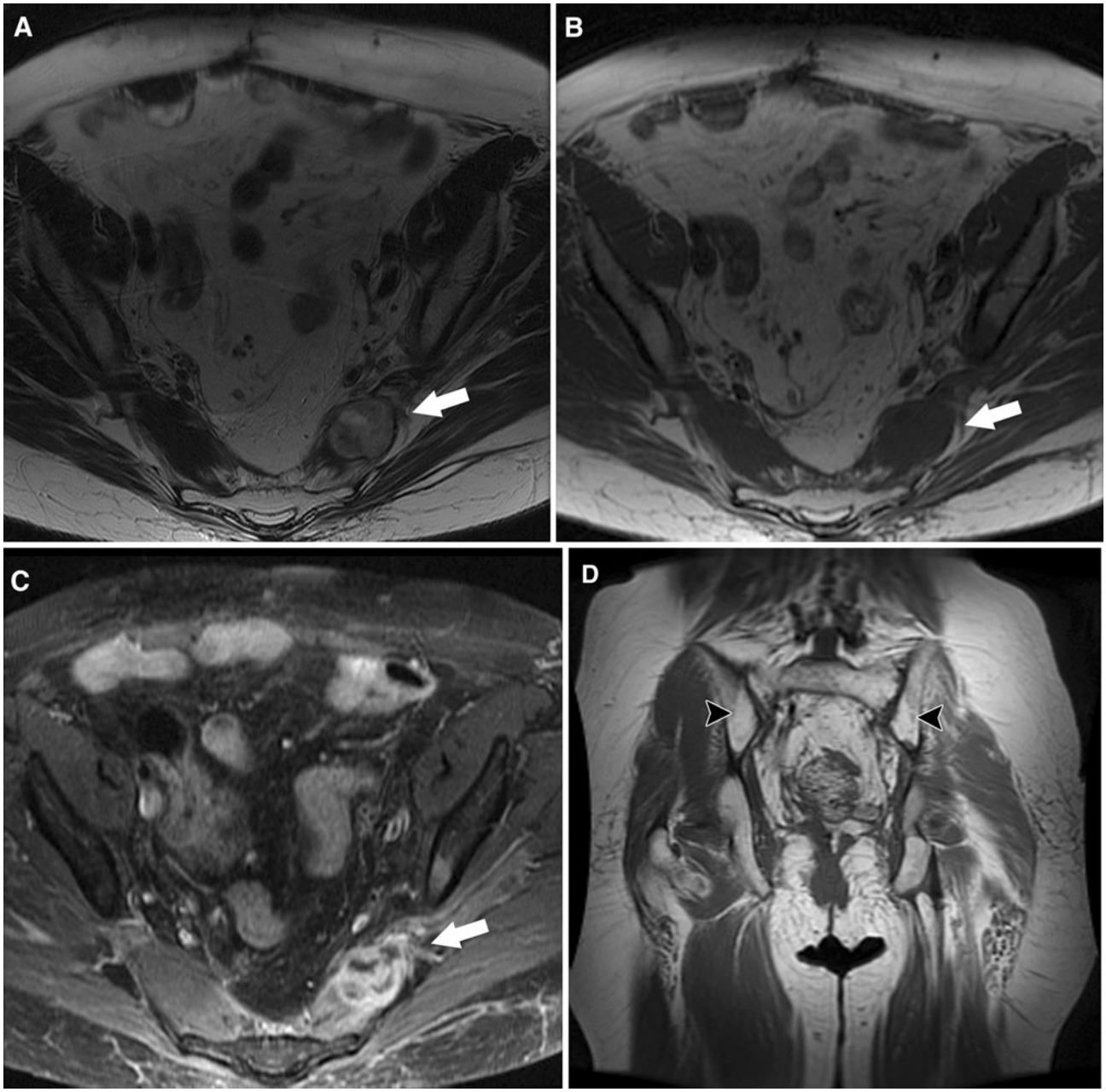

Fig. 19. A 70-year-old female with recurrent rectal cancer treated with pelvic radiotherapy. Axial T2 weighted MRI (**A**) shows heterogenous, high signal mass (*arrow*) in the left piriformis muscle. Pre contrast (**B**) and post contrast (**C**) axial T1 weighted MRI shows avid, hetergenous enhancement within the mass (*arrow*). Biopsy confirmed radiation induced sarcoma. Coronal T1 MRI (**D**) shows abrupt linear change in the marrow signal in iliac bones bilaterally, with fatty marrow seen medially (*arrowheads*) in the radiation treatment port.

on delaying the healing of the endothelial cells [59]. Some drugs may have a spectrum of vascular complications such as gemcitabine, which can cause venous thromboembolism as well as vasculitis and arterial thrombosis [7]. Intravesical Bacille Calmette-Guérin (BCG), used in treatment of superficial bladder cancer, is reported to rarely cause hepatitis and mycotic vascular aneurysms [134].

Radiotherapy may damage both small and large vessels. Endothelial lining in small vessels may develop intracellular edema, ultimately resulting in vascular occlusion. Telangiectasia and arteriolar damage may also occur. Medium-sized vessels develop lymphocytic vasculitis. Rupture of the aorta and femoral vessels has been reported following radiotherapy, although these are very rare [135].

Miscellaneous complications

Radiation-induced cancers

The risk of radiation-induced cancer is reported to be between 0.1% and 1% [136, 137]. Radiation-induced tumors include bone and soft-tissue sarcoma, lymphoma, mesothelioma and carcinomas. The mean latency period for postradiation sarcomas ranges from 4 to 17 years [138]. The most common imaging findings are soft-tissue mass and bone destruction. Although imaging findings are not specific, appreciation of the long latency period after radiation therapy may help suggest the diagnosis [138].

Transplant complications

Graft versus host disease (GVHD). GVHD is a serious complication in patients, who receive hematopoietic stem cell transplant [139]. Classically, acute GVHD is described to occur within 100 days of transplant and chronic GVHD occurs after 3 months. Acute GVHD occurs in 15%–50% of patients undergoing hematopoietic stem cell transplant and classically involves skin, liver and gastrointestinal system [140]. However, clinical features may be nonspecific and imaging plays an important role in the diagnosis of acute GVHD. Presence of abnormal bowel wall thickening involving small and large bowel, abnormal wall enhancement and fluid-filled, dilated bowel loops, are highly characteristic findings of acute GVHD in patients who have received hematopoietic stem cell transplant [115, 141–143]. Acute GVHD is associated with a variable prognosis (as low as 5% to as high as 80% mortality) and this depends upon the severity of the disease [144].

Chronic GVHD presents in 40%–45% patients after hematopoietic stem cell transplant. The risk increases in those patients who develop acute GVHD. Radiological findings are similar to acute GVHD but are less frequent. Late complications such as strictures may be seen in the gastrointestinal tract (Figs. 19, 20, 21).

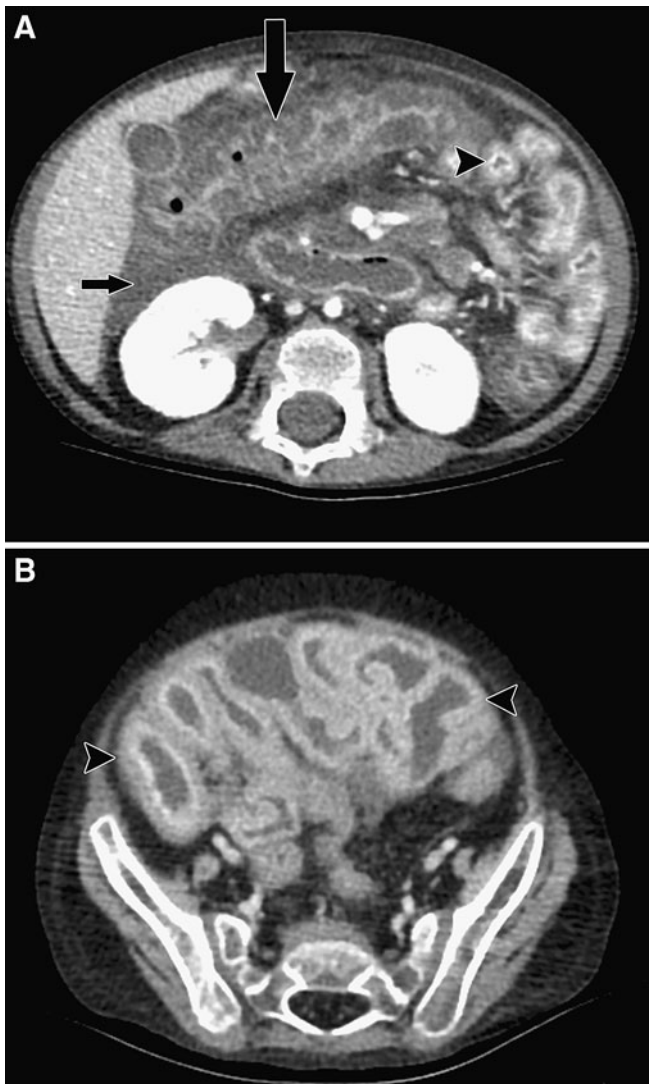

Fig. 20. A 3-year-old boy with acute lymphocytic leukemia treated with hematopoietic stem cell transplant. Post-contrast axial (**A**, **B**) CT scan shows diffuse, abnormal bowel wall thickening and bowel wall enhancement involving both small bowel (*arrowheads*) and large bowel (*long arrow*). Ascites (*short arrow*) is also present. Appearances are highly consistent with Graft Versus Host Disease.

Post-transplant lymphoproliferative disorder. Post-transplant lymphoproliferative disorder (PTLD) is a well known complication after transplantation and is seen in 10% patients following solid organ transplant. This can occur as early as after the first year or as late as after 20 years but typically, it presents at 3–4 years following transplant. This encompasses a spectrum of disorders ranging from benign lymphoid hyperplasia to aggressive and invasive lymphoma, with a mortality exceeding 50%. Most of these lymphomas are B cell (85%). Epstein Barr virus is thought to be the causative agent and is seen in majority of the cases. Clinical features are often non-specific and include fever and lymphadenopathy. Imaging is highly useful to differentiate this entity from conventional non-Hodgkin's lymphoma developing in immunocompetent patients. PTLD is associated with a higher incidence of extranodal involvement and more focal liver involvement [144]. Further, involvement of small bowel is typical in PTLD, whereas this is uncommon in lymphoma developing in immunocompetent patients. Also, unilateral renal involvement is much more common in PTLD [144].

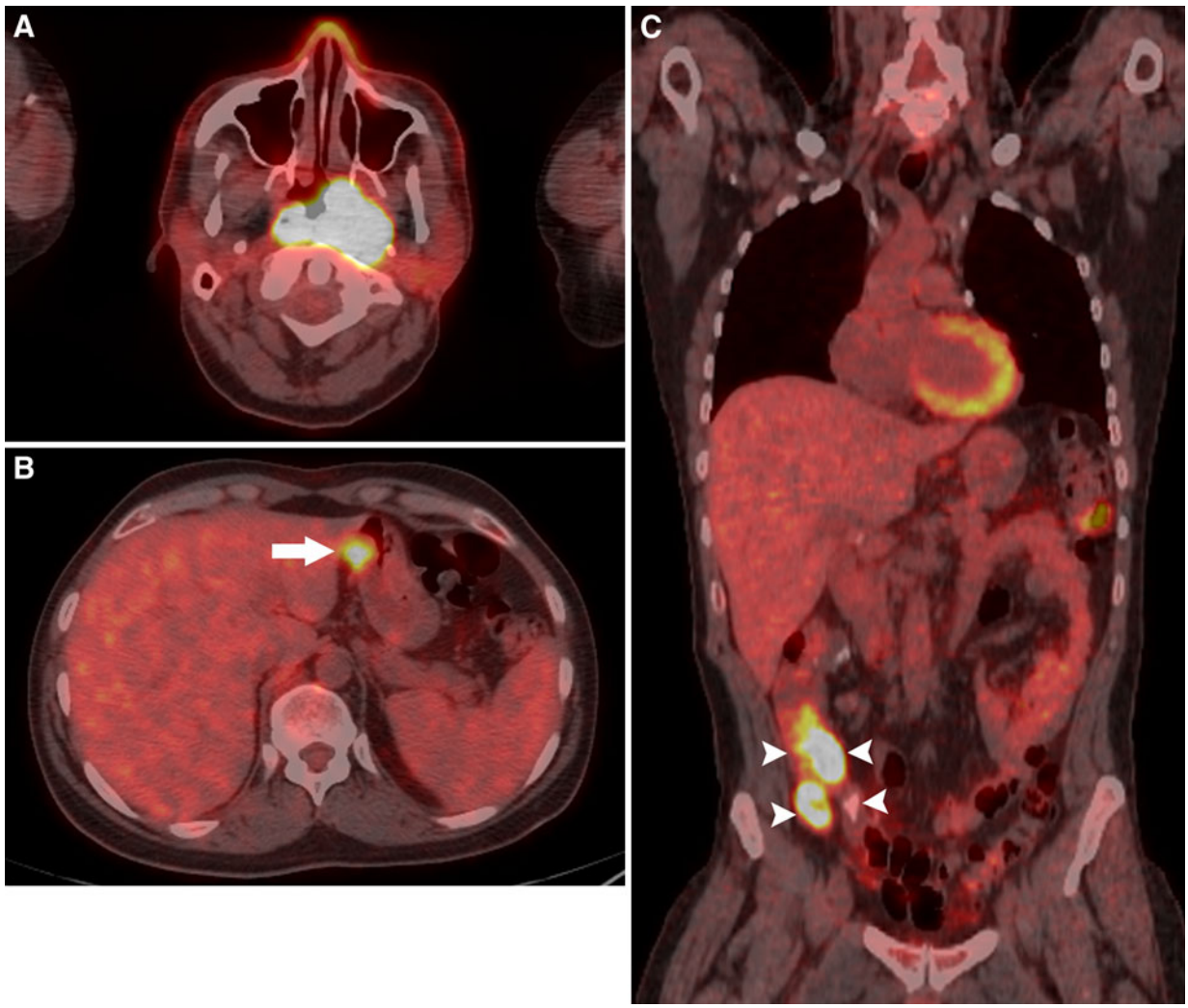

Fig. 21. A 40-year-old male patient with post transplant lymphoproliferative disease, following stem cell transplant. PET-CT examination in axial and coronal planes show avid FDG uptake within the (**A**) nasopharynx, (**B**) stomach (*arrow*), cecum, and (**C**) terminal ileum (*arrowheads*) representing the sites of post-transplant lymphoproliferative disorder.

Conclusion

Although chemotherapy and radiotherapy play an extremely important role in the management of various malignancies, they are associated with significant complications. Introduction of newer molecular targeted therapy has further increased the spectrum of complications associated with oncological therapy. Awareness of these complications can help the radiologist to detect these at early stages, which helps in the appropriate management and results in better outcome.

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