Abdominal Radiology (2019) 44:2182–2195
https://doi.org/10.1007/s00261-019-01954-z

REVIEW

An imaging-based review of systemic therapies and associated toxicities in metastatic pancreatic cancer as per the 2018 ASCO guidelines: what every radiologist should know

Daniel A. Smith[1] · **Bhanusupriya Somarouthu**[2] · **Nikhil H. Ramaiya**[1]

Published online: 28 February 2019

Abstract

Objective To provide an overview of what radiologists should know about systemic agents utilized in the modern treatment of metastatic pancreatic cancer and their associated toxicities.

Results The clinical landscape of metastatic pancreatic cancer has significantly evolved in recent years, with the advent of new first- and second-line systemic therapies. As these systemic treatment options continue to expand, knowledge of their clinically relevant features is becoming critical for radiologists. While the issues of surgical resectability and tumor response evaluation of advanced stages of pancreatic cancer have been thoroughly discussed in the radiology literature, the diagnostic importance of systemic therapies has tended to be less well appreciated. In this review, we provide a primer for radiologists outlining the radiologically pertinent features of modern systemic therapies used in the treatment of metastatic pancreatic ductal adenocarcinoma. These systemic agents are discussed from the standpoint of the newly updated 2018 (https://doi.org/10.1007/s00261-019-01954-z) guidelines for the treatment of metastatic pancreatic cancer from the American Society of Clinical Oncology (ASCO). Understanding the radiology relevance of these modern therapeutic agents is critical, especially with regard to treatment response and toxicity assessment.

Conclusion Knowledge of the modern systemic therapies utilized in the treatment of metastatic pancreatic cancer and their associated toxicity profiles is critical in diagnostic imaging interpretation.

Keywords Metastatic pancreatic cancer · Pancreatic ductal adenocarcinoma · Systemic therapies · Toxicity profiles · Chemotherapy toxicities · ASCO guidelines

Introduction

As one of the most lethal malignancies, pancreatic cancer continues to present significant diagnostic and therapeutic challenges for the medical field. While its prognosis has historically remained grim, recent advances in systemic treatments and surgical techniques have fundamentally altered modern treatment paradigms of advanced and metastatic pancreatic cancer. For patients with pancreatic cancer, systemic treatments remain a critical pillar of treatment in neoadjuvant, adjuvant, and palliative settings. Recent clinical trial data in the past several years have led to an expansion in the number of available first- and second-line therapies for individuals with metastatic pancreatic cancer (Fig. 1). These recent advances have prompted the American Society of Clinical Oncology (ASCO) to publish updated recommendations in 2018 for first- and second-line systemic treatment options for patients with metastatic pancreatic cancer.

From a radiology perspective, the imaging-based assessment of pancreatic cancer has traditionally focused on staging, evaluating resectability, and monitoring tumor response on follow-up imaging. The issues of staging and borderline resectability of advanced stages of pancreatic cancer have

✉ Daniel A. Smith
Daniel.Smith3@UHhospitals.org

Bhanusupriya Somarouthu
bsomarouthu@mgh.harvard.edu

Nikhil H. Ramaiya
Nikhil.Ramaiya@UHhospitals.org

[1] University Hospitals Cleveland Medical Center, 11100 Euclid Ave, Cleveland, OH 44106, USA

[2] Harvard Medical School - Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

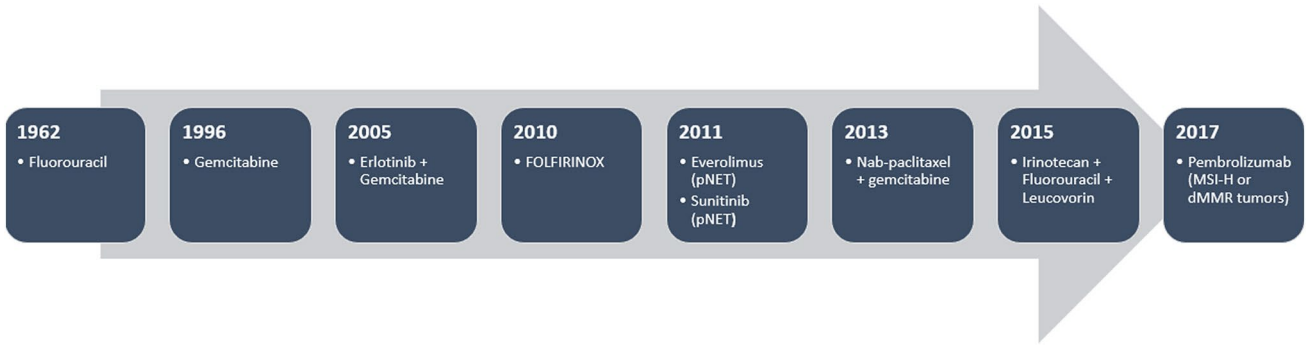

Fig. 1 FDA approval dates of systemic agents and combination therapies for the treatment of advanced/metastatic pancreatic cancer. *pNET* pancreatic neuroendocrine tumor, *MSI-H* microsatellite instability-high, *dMMR* deficient mismatch repair

been thoroughly discussed in the radiology literature. The radiological relevance of systemic therapies has comparatively been less well emphasized, despite the fact that an increasing number of novel regimens are emerging as treatment options for patients with metastatic pancreatic cancer. As more patients are treated with modern systemic therapies, knowledge of these anticancer agents is also becoming critical for image interpretation. In this review article, we present a primer for radiologists focused on the modern systemic therapies used in the treatment of metastatic pancreatic cancer. Specifically, we will provide an overview of the current landscape of systemic treatments for advanced pancreatic cancer from a radiologist's perspective. An overview of the updated 2018 ASCO treatment guidelines for metastatic pancreatic cancer will be summarized from a standpoint of their importance to radiologists. The clinical trials and available evidence supporting the 2018 ASCO guidelines are largely based the treatment of pancreatic ductal adenocarcinoma, as opposed to other less common subtypes of pancreatic cancer. From the standpoint of this review article and the referenced 2018 ASCO guidelines, the terms pancreatic ductal adenocarcinoma and pancreatic cancer will be used interchangeably. Each of the current available systemic therapies for metastatic pancreatic ductal adenocarcinoma will be reviewed with a focus on what every radiologist should know about these commonly used agents and their side effects. The role of radiological assessment of treatment toxicities will be emphasized, as monitoring for these potentially harmful side effects is a critical aspect of imaging interpretation.

Pancreatic cancer: background and staging criteria

In 2018, there were an estimated 55,440 new cases of pancreatic cancer in the United States and a similar estimated number of 44,330 deaths due to this disease [1]. While pancreatic cancer represents approximately 3.2% of all new cases of cancer, it disproportionally causes 7.3% of all cancer mortalities. Survival rates have historically remained quite poor, with an estimated 5-year survival rate between 2008 and 2014 of only 8.5%. Although this survival rate remains low, it has steadily trended up from even worse 5-year survival rates of 2–4% in the 1970–1980s [2].

The vast majority of pancreatic cancer cases are due to pancreatic adenocarcinoma, an exocrine cancer that represents approximately 85% of all pancreatic neoplasms [3]. Other types of exocrine cancers less commonly occur, including squamous cell carcinoma, adenosquamous carcinoma, and undifferentiated carcinomas. Endocrine tumors occur less frequently, with pancreatic neuroendocrine tumors such insulinomas, gastrinomas, and glucagonomas representing only 1–2% of all pancreatic neoplasms [4].

Pancreatic adenocarcinoma is typically divided into one of the several stages at the time of diagnosis based on resectability features and extent of disease. Slightly greater than 50% of all cases of pancreatic cancer present with metastatic disease that is unresectable. In contrast, 15–20% of patients present with disease that is resectable and thus amenable to upfront surgical treatment. The remainder of patients present with categories of disease defined as either borderline resectable (BR) or locally advanced (LA). The precise benchmarks for defining borderline resectable pancreatic cancer are frequently discussed in the radiology and surgical literature, with proposed criteria largely based on the degree of tumor involvement of adjacent arterial and venous vasculature [5, 6]. While surgery may be an option for individuals with borderline resectable disease, those with locally advanced unresectable pancreatic cancer have more extensive malignant invasion into adjacent vasculature that often precludes surgery [7].

Treatment decisions for pancreatic cancer are affected by several factors, such as histological subtype, tumor grade, and disease staging. Surgical resectability factors also guide treatment based on imaging features to distinguish

resectable disease from disease that is non-resectable, borderline resectable, or locally advanced. Treatment is also guided by performance status and patient preferences with regards to decisions such as pursuing upfront surgery versus neoadjuvant therapy. The majority of pancreatic adenocarcinoma presents as unresectable disease due to the presence of metastatic disease or extensive local malignant invasion of adjacent vasculature. For these patients, treatment is often pursued with a systemic chemotherapy or radiation therapy.

Due to the high prevalence of metastatic pancreatic cancer, imaging patterns of metastatic presentations have been thoroughly described in the radiology literature. According to a recent retrospective analysis of over 200 patients with locally advanced pancreatic cancer, the most common sites of metastatic disease include the peritoneum/omentum (43%) and the liver (41%) [8]. A smaller proportion of patients develop metastases to the lung (14%) and distant lymph nodes (9%). Osseous metastatic disease occurs less commonly. CNS involvement of disease is extremely rare and is estimated to occur in only 0.3% of patients [9].

Updated ASCO guidelines for metastatic pancreatic cancer

In 2016, the American Society of Clinical Oncology (ASCO) developed a clinical practice guideline that proposed evidence-based recommendations for first- and second-line treatment options for patients with metastatic pancreatic cancer [10]. These guidelines also presented recommendations for initial assessment, including pre-treatment imaging evaluation with multiphase CT of the chest, abdomen, and pelvis to assess disease burden. Prior to treatment, patients should also have a baseline performance status calculated, usually graded via the Eastern Cooperative Oncology Group performance status (ECOG PS) system. Other components of a patient's initial evaluation include assessment of symptom burden, comorbidity profile, goals of care, and clinical trial eligibility [11].

Since ASCO's initial 2016 guideline publication, new evidence has emerged regarding promising second-line therapy options in patients with advanced pancreatic cancer who have failed first-line therapy regimens. In response to a number of recent clinical trials, an updated 2018 guideline was recently published by ASCO which proposed new recommendations for second-line therapy regimens [11]. These novel second-line therapy options have been recommended for treatment of metastatic pancreatic cancer in patients who develop progressive disease or intolerable side effects while on first-line regimens.

For first- and second-line treatment of metastatic pancreatic cancer, several treatment regimens are recommended by the recently updated ASCO guidelines (Table 1) [11]. One of the most common current first-line treatments is FOLFIRINOX, which consists of a combination of folinic acid, fluorouracil, irinotecan, and oxaliplatin. While this regimen is among the most effective available for first-line treatment, it is often not selected if patients have unfavorable comorbidity profiles. Another commonly used regimen is combination therapy with gemcitabine plus nab-paclitaxel. For individuals with multiple poorly controlled comorbidities, gemcitabine monotherapy can be used as first-line therapy with the optional addition of either capecitabine or erlotinib.

Patients who fail initial therapy with first-line treatment often are now able to start treatment with one of the several second-line therapy options. Many of these second-line therapies have recently been approved based on promising clinical trial data demonstrating survival benefits. These second-line systemic treatments recommended by the ASCO guidelines include gemcitabine plus nab-paclitaxel, gemcitabine monotherapy, fluorouracil plus nanoliposomal irinotecan or irinotecan, fluorouracil plus oxaliplatin, and fluorouracil monotherapy. For patients testing positive for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) biomarkers, the PD-1 immune checkpoint inhibitor pembrolizumab is also now recommended as a second-line therapy option. MSI-H and dMMR biomarkers are both indicative of deficiencies in mismatch repair. Deficiencies in MMR proteins (e.g., MLH1, MSH2, MSH6, PMS2) lead to DNA replication errors and resulting accumulation of microsatellites, somatic mutations, and high neoantigen loads [12]. The resulting high neoantigen load promotes activation of T cells and other inflammatory responses, which makes these tumors potentially responsive to immunotherapeutic agents. Pembrolizumab can be initiated in patients who undergo genetic testing following progression of disease on first-line therapies such as FOLFIRINOX (Fig. 2). While the tyrosine kinase inhibitor erlotinib had previously shown some initial promise for treatment of pancreatic cancer, recent studies have demonstrated that this drug offers no survival benefit in combination with gemcitabine compared to gemcitabine monotherapy [13, 14]. This agent is therefore not commonly used in modern treatment regimens and is not recommended by the updated ASCO guidelines.

Imaging-based toxicity assessment

With the advent of new first- and second-line therapy options for metastatic pancreatic cancer, unique patterns of toxicities with specific radiological findings have slowly come to light. Imaging plays a key role in monitoring for toxicities, as many of the modern pancreatic cancer therapeutics cause side effects with detectable imaging findings. In the field of oncologic imaging, interpreting radiologists must be acutely aware of side-effect profiles when interpreting imaging from

Table 1 2018 ASCO guidelines of first- and second-line systemic therapies for metastatic pancreatic cancer

Therapy	Recommendation	Qualifying criteria	Recommendation basis	Evidence quality	Strength of recommendation
FOLFIRINOX	First line	ECOG PS 0 to 1, favorable comorbidity profile, preference/support for aggressive therapy, chemotherapy port/infusion pump services access	Evidence based, benefits outweigh harms	Intermediate	Strong
Gemcitabine + nab-paclitaxel	First line	ECOG PS 0 to 1, relatively favorable comorbidity profile, preference/support for aggressive therapy	Evidence based, benefits outweigh harms	Intermediate	Strong
Gemcitabine alone (± capecitabine or erlotinib)	First line	ECOG PS of 2 or unfavorable comorbidity profile	Evidence based, benefits outweigh harms	Intermediate	Moderate
Pembrolizumab (PD-1 immune checkpoint inhibitor)	Second line	Positive testing for dMMR or MSI-H	Evidence based, benefits outweigh harms	Intermediate	Moderate
Gemcitabine + nab-paclitaxel	Second line	First-line treatment with FOLFIRINOX, ECOG PS 0 to 1, relatively favorable comorbidity profile, preference/support for aggressive therapy	Informal consensus, benefits outweigh harms	Low	Moderate
Fluorouracil + nanoliposomal irinotecan, or fluorouracil + irinotecan	Second line	First-line treatment with gemcitabine + nab-paclitaxel, ECOG PS 0 to 1, relatively favorable comorbidity profile, preference/support for aggressive therapy, chemotherapy port/infusion pump services access	Informal consensus, benefits outweigh harms	Low	Moderate
Fluorouracil + oxaliplatin	Second line	First-line treatment with gemcitabine + nab-paclitaxel, ECOG PS 0 to 1, relatively favorable comorbidity profile, preference/support for aggressive therapy, chemotherapy port/infusion pump services access	Informal consensus, benefits outweigh harms	Low	Moderate
Gemcitabine or fluorouracil	Second line	ECOG PS of 2, unfavorable comorbidity profile	Informal consensus, benefits outweigh harms	Low	Moderate

Information and recommendations compiled from [11]

FOLFIRINOX folinic acid, fluorouracil, irinotecan, and oxaliplatin, *ECOG PS* Eastern Cooperative Oncology Group performance status, *MSI-H* microsatellite instability-high, *dMMR* deficient mismatch repair

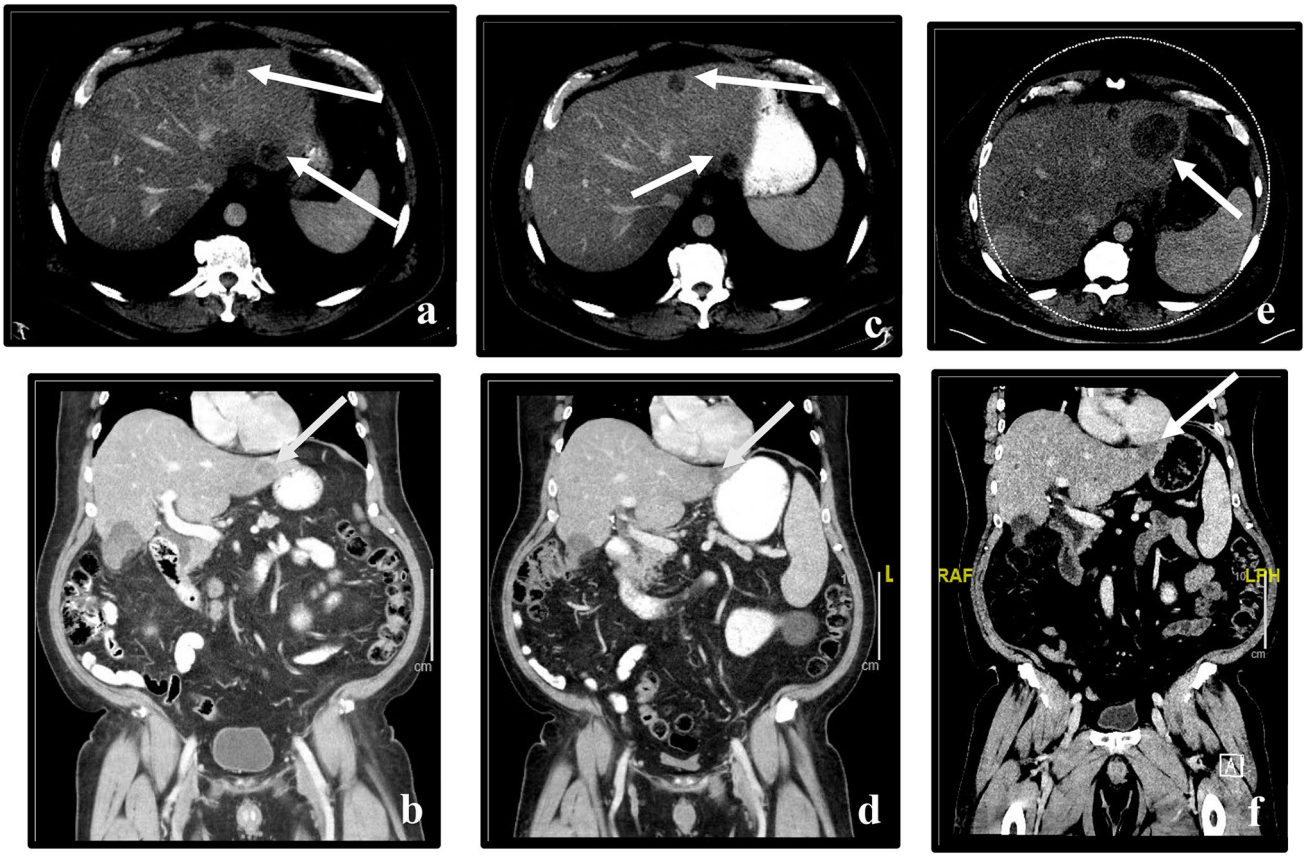

Fig. 2 A 64-year-old-male with metastatic pancreatic adenocarcinoma who developed liver metastases while being treated with first-line FOLFIRINOX. Contrast-enhanced axial and coronal CT images after 2 years of FOLFIRINOX treatment show development of several hypodense metastatic lesions in the right and left hepatic lobes, compatible with metastatic lesions (arrows in **a**, **b**). The patient was subsequently started on pembrolizumab. Follow-up CT images 2 months later demonstrate stable-to-improved metastatic disease (arrows in **c**, **d**). Repeat imaging after 3 months show progression of disease with significantly increased size of a hypodense metastatic lesion in the left hepatic lobe (arrows in **e**, **f**)

patients undergoing specific therapeutic regimens. Knowledge of specific toxicity findings on imaging will enable the astute radiologist to recognize imaging evidence of potentially harmful side effects with consistency. Gaining a familiarity with the common presentations of chemotherapy-related toxicities will also enable radiologists to distinguish imaging-detectable drug toxicities from disease progression.

In the following sections, we present an overview of the imaging presentations of toxicities associated with first- and second-line treatments for metastatic pancreatic cancer (Table 2). These treatment-related toxicities are not just limited to patients with metastatic pancreatic cancer, as patients with borderline resectable or resectable disease will often receive neoadjuvant treatment with similar regimens. Therapy-associated toxicities can thus present in patients of any stage treated with these agents. Early diagnosis of toxicity via imaging is critical, as side effects can be more effectively managed early with cessation of medications or specific treatments such as steroid therapy. It is therefore useful for interpreting radiologists to have knowledge of specific side-effect profiles of modern therapies for metastatic pancreatic cancer when interpreting follow-up imaging for patients undergoing treatment.

Pulmonary toxicity

Pulmonary side effects are among the most common forms of imaging-detectable toxicities for many of the modern systemic agents used in the treatment of metastatic pancreatic cancer. Up to 23% of gemcitabine-treated patients will develop some degree of dyspnea during treatment, although not all will necessarily present with radiographic findings [15]. If detected in its early phases, gemcitabine pulmonary toxicity can often be successfully treated with steroid therapy with complete resolution of lung findings. While mild symptoms of dyspnea and bronchospasm are most common, severe toxicities such as interstitial pneumonitis or pulmonary fibrosis have also been reported. CT

Table 2 Mechanisms of action and common imaging-detectable toxicities of systemic therapies for advanced pancreatic cancer

Drug	Mechanism of action	Common imaging-detectable toxicities
Gemcitabine	Interferences with DNA synthesis by halting chain elongation [65]	Pneumonitis/pulmonary fibrosis, venous thrombosis, capillary leak syndrome, vasculitis
Nab-paclitaxel	Taxane agent; inhibits mitosis by interfering with microtubule depolymerization [66]	Pneumonitis/pulmonary fibrosis, colitis
Fluorouracil	Pyrimidine analog; exerts a cytotoxic effect by incorporating fluoronucleotides into DNA/RNA and inhibiting thymidylate synthase [67]	Enteritis, colitis, pneumatosis, neurotoxicity (cerebellar vs diffuse)
Nanoliposomal Irinotecan	Topoisomerase 1 inhibitor; inhibits DNA replication and promotes apoptosis [68]	Steatosis, acute hepatitis, enteritis, colitis
Oxaliplatin	Third-generation platinum-based compound; damages cells by directly inducing DNA lesions, inhibiting DNA/mRNA synthesis [69]	Pneumonitis/pulmonary fibrosis, sinusoidal obstruction syndrome (SOS), splenomegaly, pneumatosis
Pembrolizumab	Anti-PD-1 antibody, immune checkpoint inhibitor [70, 71]	Immune-related adverse events (irAEs): colitis, hepatitis, pancreatitis, pneumonitis/pulmonary fibrosis

findings of gemcitabine pulmonary toxicity can include diffuse ground-glass or solid opacities with thickened septal lines [16]. Diffuse ground-glass opacities in a basilar and perihilar predominant distribution are commonly seen in acute forms of gemcitabine-associated pneumonitis (Fig. 3). The distribution of these findings tends to be bilateral and diffuse with either a symmetric or asymmetric pattern. Interstitial infiltrates can be seen, as well

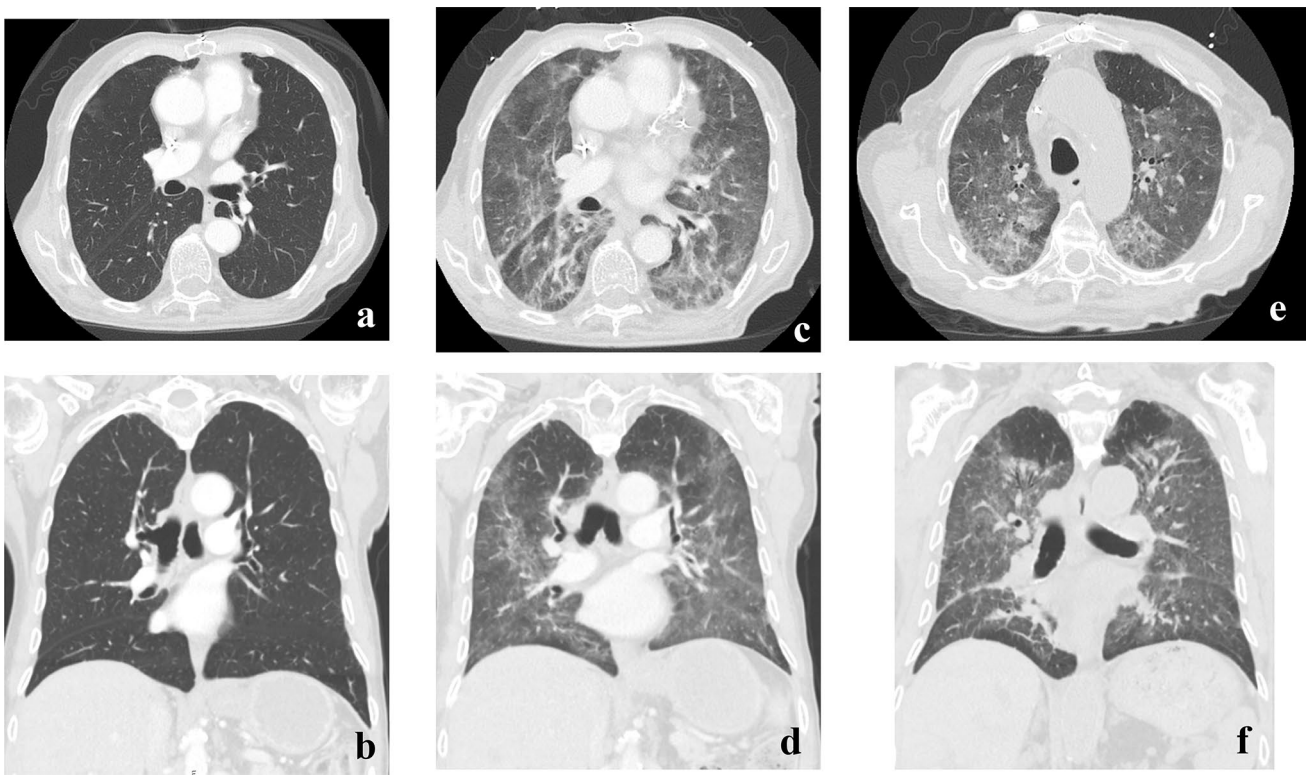

Fig. 3 A 78-year-old male with metastatic pancreatic adenocarcinoma who was hospitalized for worsening hypoxia and respiratory distress after his second cycle of gemcitabine/nab-paclitaxel therapy. Initial axial and coronal CT images while on FOLFIRINOX demonstrate an unremarkable appearance of the lung parenchyma (**a**, **b**). A repeat CT study was obtained 2 months after initiation of gemcitabine/nab-paclitaxel when the patient presented with new-onset respiratory symptoms. These images demonstrate development of diffuse bilateral ground-glass opacities and consolidations (**c**, **d**), concerning for gemcitabine-associated pneumonitis. Follow-up CT obtained after 4 days redemonstrates basilar and perihilar predominant ground-glass opacities with interval worsening in the bilateral upper lobes (**e**, **f**)

as alveolar opacities that can present diffusely throughout the lungs [17].

Paclitaxel-associated pulmonary toxicity has also been reported with an estimated frequency of 1–12% [18]. Taxane-associated pneumonitis typically develops in the first 3 months of treatment with a range of potential presentations on chest imaging. Case reports of paclitaxel-associated pneumonitis have described imaging findings of bilateral ground-glass infiltrates, focal consolidations, extensive or focal fibrosis, and bilateral reticular or reticulonodular infiltrates [19, 20]. Thickened septal lines and focal areas of fibrosis are common radiological findings of paclitaxel-associated pneumonitis (Fig. 4). Rarer cases of fatal paclitaxel-induced pulmonary toxicity have also been reported with imaging findings of severe interstitial pneumonia with extensive ground-glass opacities and traction bronchiectasis [21].

Oxaliplatin treatment is also linked to the development of interstitial pneumonitis that can present rapidly and lead

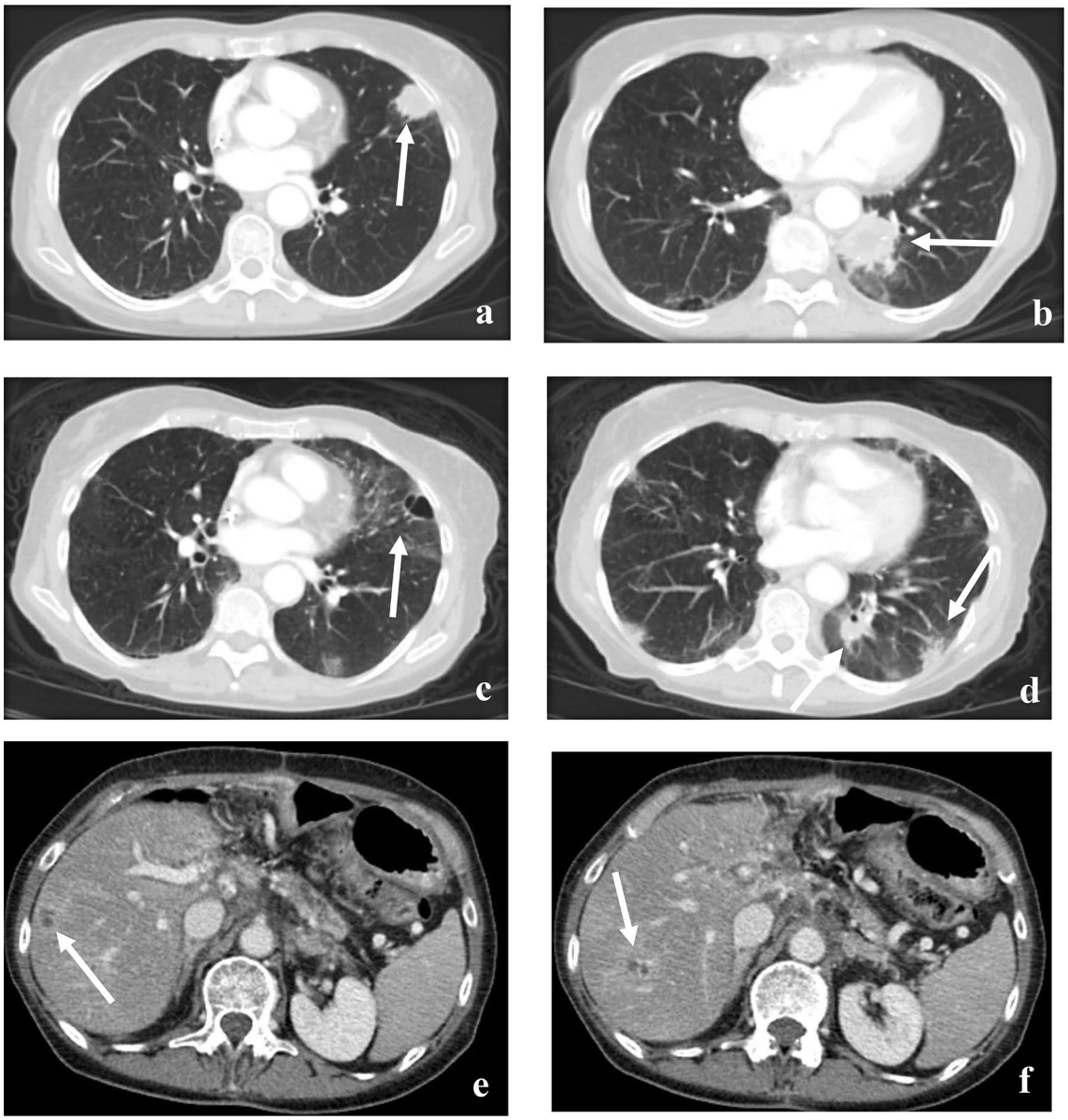

Fig. 4 A 66-year-old female with pancreatic cancer status post Whipple procedure and chemoradiation. The patient subsequently developed lung metastases while on paclitaxel/gemcitabine. Contrast-enhanced axial CT images show lung metastases in upper lobe (arrow in **a**) and lower lobes (arrow in **b**) of left lung. Follow-up images show interval improvement in tumor burden of left lung along with associated pneumonitis changes of focal fibrosis and increasing septal thickening (arrows in **c**, **d**). Follow-up images also note new sharply defined liver lesions showing a rim of enhancement and central areas of low density, compatible with treatment-induced liver abscesses (arrows in **e**, **d**)

to severe pulmonary fibrosis and fatal respiratory insufficiency [22]. Reported CT findings in oxaliplatin-induced interstitial pneumonitis include bilateral peripherally based interstitial infiltrates with ground-glass opacities, areas of emphysema, and interlobular septal thickening. Lung biopsies in these cases have revealed findings suggestive of idiopathic drug-related toxicity, including diffuse alveolar damage, inflammatory infiltrates, and diffuse alveolar septal thickening [22]. In patients who have pre-existing interstitial lung disease, oxaliplatin can also cause worsening of baseline lung disease [23]. CT findings in these patients can include worsening ground-glass opacities and extensive fibrotic infiltrates. Patients may also develop a pattern of usual interstitial pneumonia with sub-pleural honeycombing and traction bronchiectasis [23].

Cases of pembrolizumab-induced pneumonitis have also been reported. Time to onset of anti-PDL-1-related pneumonitis ranges widely from shortly after initiation of therapy to over a year after therapy is started [24]. CT findings include bilateral areas of focal consolidation with ground-glass opacities, a non-specific interstitial pneumonia (NSIP) pattern with ground-glass infiltrates and sub-pleural reticulations, and numerous confluent consolidations with pleural effusions [25]. Biopsy-proven cases of organizing pneumonia have also been reported with CT imaging showing focal upper lobe alveolar infiltrates with air bronchograms [26]. One study of PD-1 inhibitor-related pneumonitis demonstrated that cryptogenic organizing pneumonia (COP) is consistently the most common radiologic pattern across a number of different types of cancers and therapeutic regimens [27]. Less common patterns include NSIP, hypersensitivity pneumonitis, and acute interstitial pneumonia/acute respiratory distress syndrome.

Gastrointestinal toxicity

Treatment with paclitaxel has also been linked to the development of neutropenic colitis. Abdominal plain film and ultrasound findings in these cases include diffuse ileal and colonic dilatation, bowel wall thickening, and air-fluid levels [28]. Findings of ileus, bowel wall obstruction, pneumoperitoneum, and pneumatosis can also occur less frequently. On CT imaging, taxane-induced colitis typically presents as diffuse or focal colonic wall thickening with pericolic edema [29]. In more severe cases, patients can present with imaging evidence of severe typhlitis, bowel perforation, and bowel necrosis secondary to ischemic colitis.

Chemotherapy-induced pneumatosis intestinalis (PI) can also occur in isolation with the absence of any other significant abdominal findings. Patients treated with 5-fluorouracil and oxaliplatin, as well as other agents, have been reported to develop a benign form of PI that can be managed conservatively (Fig. 5) [30]. These patients demonstrate benign clinical abdominal exams with no evidence of bowel ischemia, obstruction, or other concerning findings on CT [31]. It is thus critical for radiologists to be able to distinguish between benign uncomplicated PI, which can be managed conservatively, and PI associated with more worrisome underlying causes.

The toxic effects of fluorouracil can involve both the small and large bowel, including development of enteritis and neutropenic colitis [32]. Abdominal plain films tend to be of limited utility in the diagnosis of neutropenic enteritis, although free air on plain films can be an indicator of bowel perforation. Other plain film findings tend to be non-specific, including the absence of bowel gas in the right lower quadrant, small bowel obstruction, or dilatation of the cecum or ascending colon [33]. Additional findings include focal or diffuse thumb printing indicative of mucosal edema or pneumatosis intestinalis of the cecum or ascending colon [34].

Irinotecan-induced diarrhea can occur in an acute form immediately after administration or can present in a delayed fashion [32]. Imaging findings are similar to those previously discussed in other variants of neutropenic enterocolitis. For instance, radiologic findings of irinotecan-induced enteritis on CT include submucosal edema with mucosal and serosal hyperemia, yielding a classic "target sign" [17]. Findings of small bowel dilatation, thickening of the bowel wall, and air-fluid levels can also be seen. Upper GI series typically demonstrate loss of the normal small bowel fold pattern in cases of severe enteritis [17].

Pembrolizumab can cause a number of immune-related adverse events (irAEs), with gastrointestinal toxicities being among the most common [35]. Immune-related colitis can present on CT in one of the several patterns, including a diffuse pattern, segmental pattern with diverticulosis, or isolated recto-sigmoid involvement without diverticulosis [36]. Common features among these patterns include diffuse thickening of the colonic wall, hyperenhancement of the colonic mucosa, and engorgement of mesenteric vessels.

Hepatic, splenic, and pancreatic toxicity

Hepatic toxicity is among the most common side effects of irinotecan, taking the form of irinotecan-associated steatosis and steatohepatitis (Fig. 6) [37]. The primary finding of hepatic steatosis on CT is decreased attenuation of the liver compared to the spleen. Diffuse fatty infiltration and focal steatosis can both be seen in patients undergoing irinotecan treatment [38]. Focal sparing around the gallbladder or hepatic segment 4 can commonly be seen. Steatosis can also be detected on ultrasound with findings of increased liver echogenicity, with the liver becoming more echogenic than the renal cortex [39]. Steatosis may also be detected using chemical shift gradient-echo (GRE) imaging to demonstrate increased T1 in-phase GRE signal and loss of T1

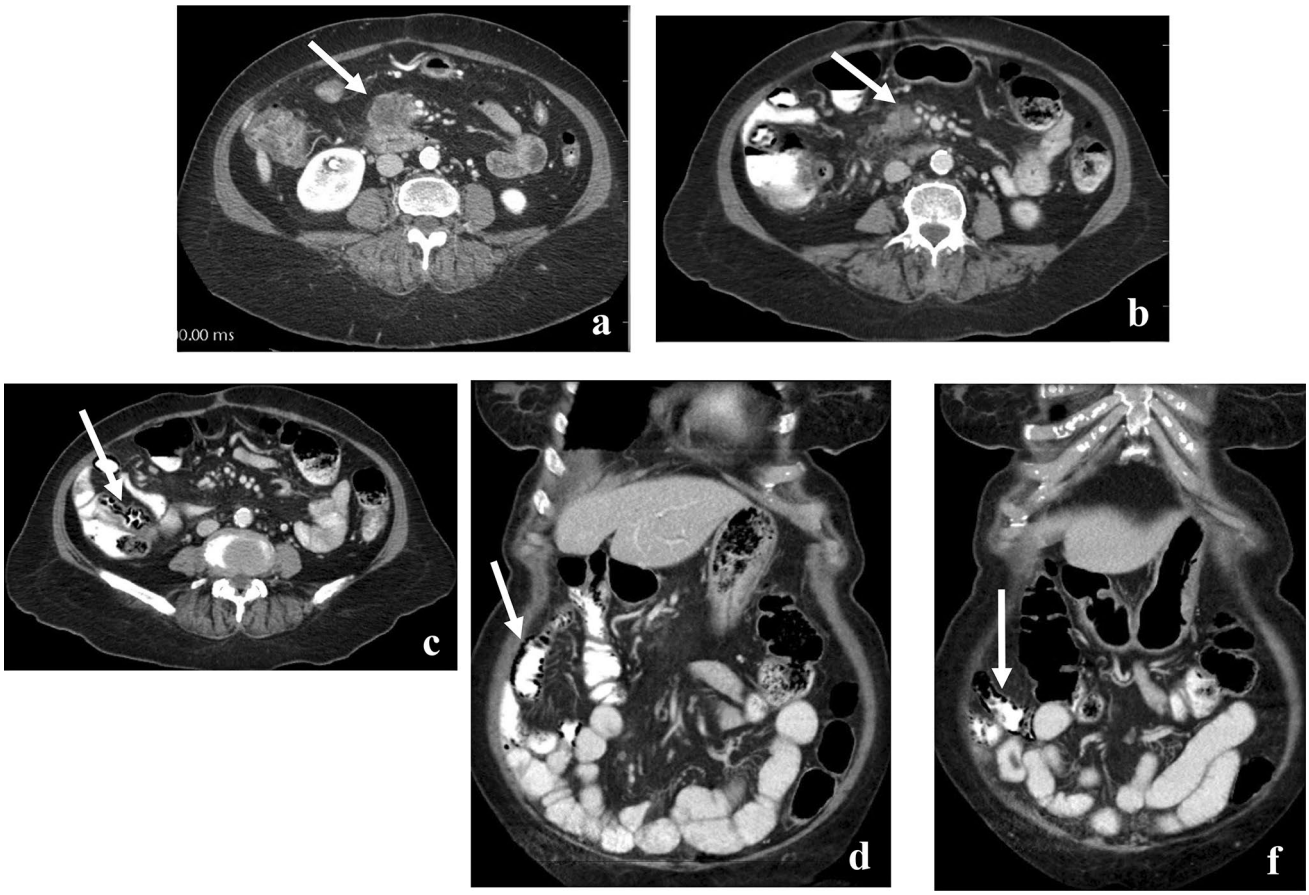

Fig. 5 A 73-year-old male with malignant neoplasm of the pancreas. Baseline contrast-enhanced axial CT image shows a heterogeneous mass in the uncinate process of the pancreas (arrow in **a**). Follow-up contrast-enhanced axial CT image after initiation of fluorouracil/oxaliplatin shows interval decrease in size of the pancreatic mass (arrow in **b**). CT images also demonstrate incidental findings of new pneumatosis involving the terminal ileum extending up to the cecum (arrows in **c**, **d**, **e**), without evidence of mesentery venous gas, free fluid in the pelvis, or bowel obstruction. The patient was managed conservatively with eventual resolution of his uncomplicated pneumatosis intestinalis

out of phase GRE signal. In cases of irinotecan-related acute hepatitis, CT findings tend to be rather non-specific but can include hepatosplenomegaly, decreased liver enhancement, gallbladder wall thickening, periportal edema with widening of the periportal space, and ascites [38].

Hepatic infections can also develop as a result of treatment with most chemotherapy agents. While pancreatic cancer itself can predispose patients to liver abscess formation via causing biliary duct obstruction, treatment with anticancer agents exacerbates this risk by causing immunosuppression [40]. While focal liver abscesses can often mimic metastatic disease, hepatic abscesses typically present as well-defined and spherical hypodense masses with rim enhancement (Fig. 4). Differentiating liver abscesses from new hepatic metastatic disease is an important task for radiologists, as these entities require very different clinical management [41].

Sinusoidal obstruction syndrome (SOS), also known as hepatic veno-occlusive disease (VOD), is a unique form of hepatic toxicity that has been linked to oxaliplatin therapy. In this syndrome, patients treated with oxaliplatin develop hepatic perisinusoidal microvascular lesions leading to fibrosis, congestion, and venous occlusion [42]. On contrast-enhanced CT studies, chemotherapy-induced SOS can present as new diffuse parenchymal heterogeneity of the liver, along with new-onset ascites, periportal edema, and hepatosplenomegaly (Fig. 7) [43]. Several additional CT findings have statistically significant associations with SOS, including micronodular or "puddle-like" appearance of the liver and the so-called "clover-like" sign (preservation of normal liver enhancement near hepatic veins in a heterogenous liver) [44]. Of note, there have also been case reports of SOS mimicking metastatic disease by presenting as focal liver lesions [45]. This is an important mimic that

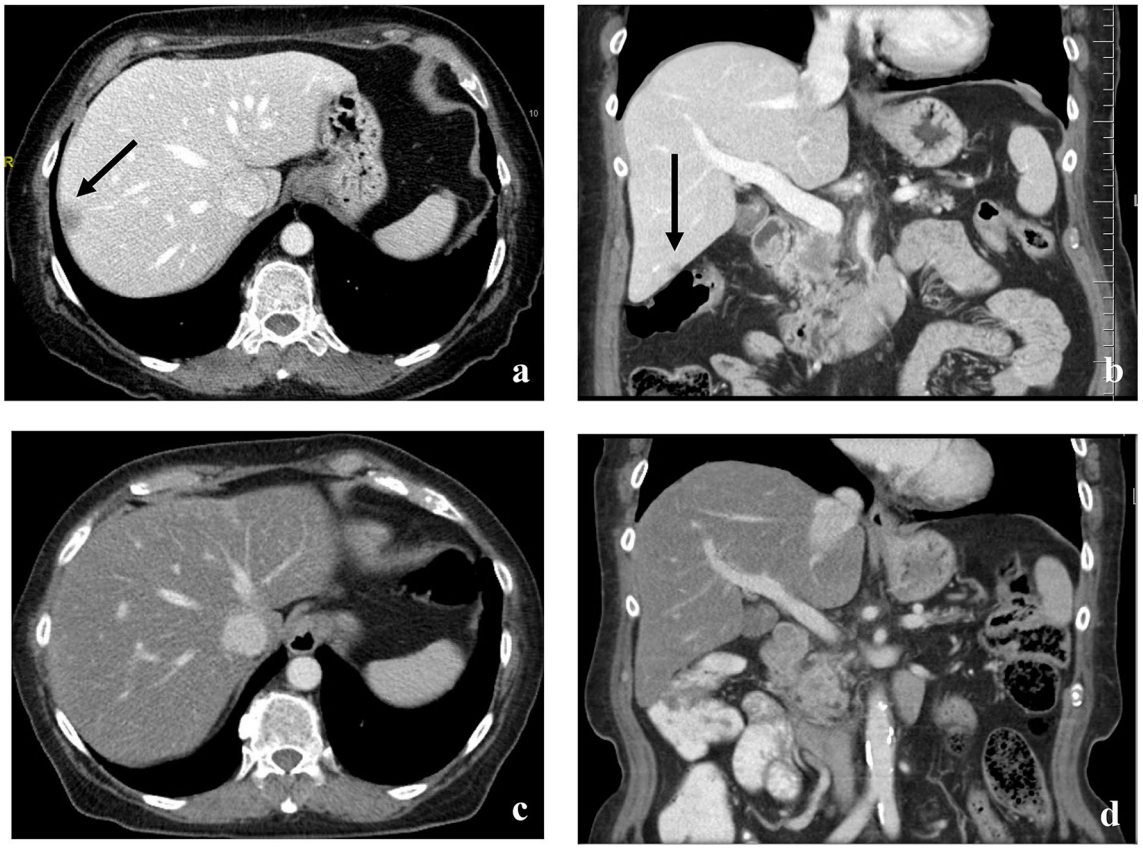

Fig. 6 A 68-year-old female with stage IV pancreatic cancer treated with FOLFIRINOX. Pre-treatment contrast-enhanced CT images (**a**, **b**) show normal liver parenchyma with a focal hypodense lesion (arrows) compatible with hepatic metastatic disease. Post-treatment images (**c**, **d**) demonstrate interval development of diffuse hepatic steatosis, a common side effect seen with irinotecan therapy. These images also demonstrate response to therapy with interval improvement in the patient's metastatic liver lesions, although detection of focal hepatic lesions is limited secondary to the patient's diffuse hepatic steatosis

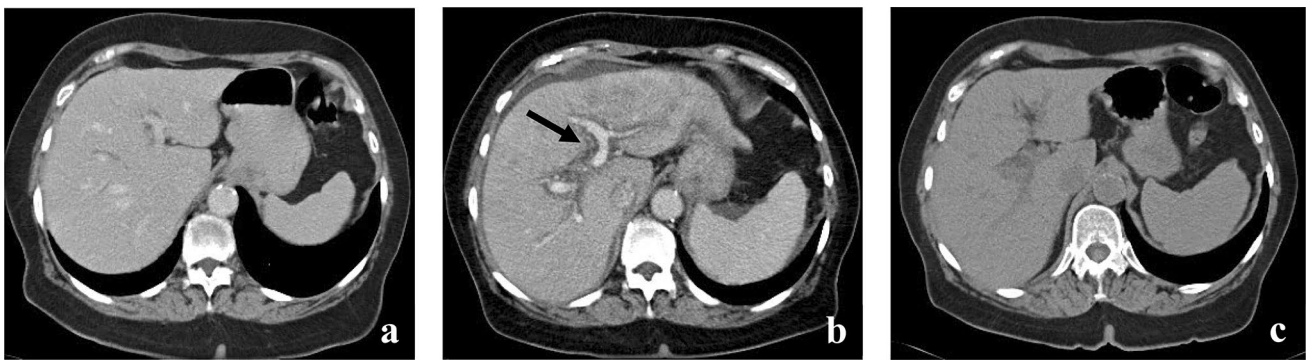

Fig. 7 A 76-year-old female with pancreatic adenocarcinoma who developed liver toxicity during oxaliplatin therapy. Pre-treatment contrast-enhanced axial CT image shows normal liver parenchyma (**a**). Following initiation of oxaliplatin, there is interval development of ascites, hepatosplenomegaly, heterogeneous attenuation of the liver, and prominent periportal low attenuation (arrow) suggestive of periportal edema and diffuse parenchymal abnormality. The patient was subsequently diagnosed with veno-occlusive disease and hepatitis related to oxaliplatin therapy (**b**). Follow-up non-contrast axial CT image after cessation of oxaliplatin shows interval resolution of these findings with appearance of almost normal liver parenchyma (**c**)

radiologists should consider in patients undergoing treatment with oxaliplatin.

Splenomegaly is another common imaging-detectable sequela of toxicity from first- and second-line systemic therapies for metastatic pancreatic cancer. Oxaliplatin in particular commonly causes increased splenic size, which has been shown to predict hepatic sinusoidal damage induced by oxaliplatin (Fig. 8) [46]. Splenomegaly also appears to be a predictive marker for the development of other oxaliplatin-associated toxicities, including peripheral neuropathy [47]. Recognizing increasing splenic size on imaging in these patients is thus a clinically important factor that aids in the diagnosis of various toxicities.

Immune checkpoint inhibitors, including anti-PD-1 inhibitors such as pembrolizumab, have also been shown to cause immune-related hepatitis and pancreatitis. Immune-related hepatitis can present with CT findings of hepatomegaly, periportal edema and lymphadenopathy, and diffuse parenchymal hypoattenuation [48]. Reported ultrasound findings include periportal edema presenting as increased echogenicity of the portal vein wall/periportal space and gallbladder wall edema [48]. Although quite rare, pancreatitis can also occur in patients undergoing treatment with PD-1 inhibitors. Radiologic evidence of pancreatitis on CT and MR includes classic findings of pancreatic enlargement, peripancreatic fat stranding, and decreased enhancement [36].

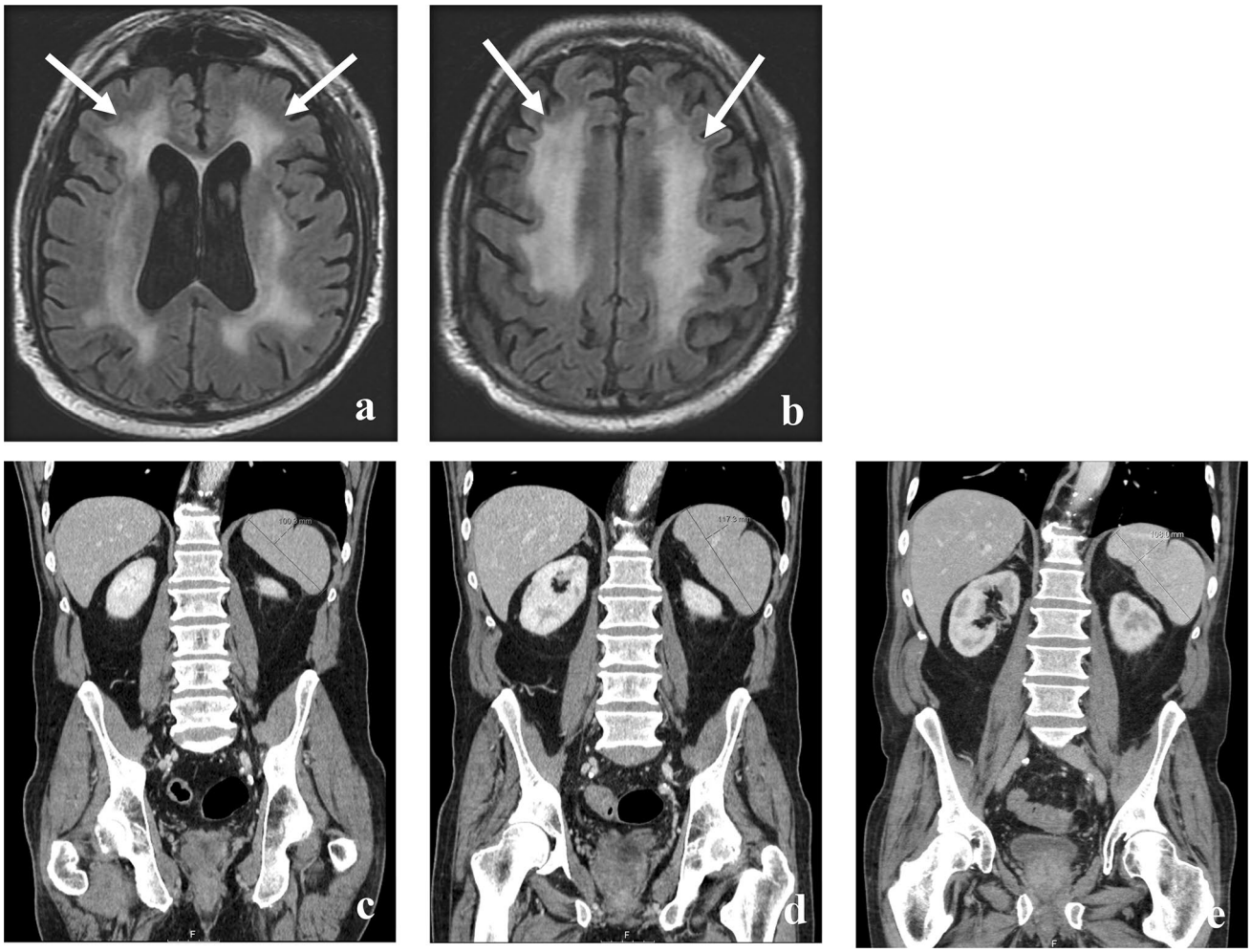

Fig. 8 A 64-year-old male with a history of metastatic pancreatic cancer who developed fluorouracil-associated acute neurotoxicity and oxaliplatin-associated splenomegaly. Axial FLAIR MR images obtained several days after initiation of fluorouracil/oxaliplatin demonstrate new white matter changes with symmetrical high signal intensity in the periventricular region and deep white matter (arrows in **a**, **b**). Given the sudden onset of these findings following therapy initiation, the patient was diagnosed with fluorouracil-associated acute neurotoxicity. Contrast-enhanced coronal CT image of the abdomen in the same patient demonstrates an initial splenic length of approximately 10 cm (**c**). Follow-up CT image obtained 3 months after initiation of fluorouracil/oxaliplatin demonstrates increased spleen size to approximately 12 cm (**d**). Repeat CT 1 month after discontinuation of oxaliplatin demonstrates return of splenic size to the baseline length of 10 cm (**e**)

Neurotoxicity

Acute fluorouracil-induced neurologic toxicity is a well-documented entity that can take the form of either cerebellar toxicity or diffuse encephalopathy [49]. Fluorouracil-induced acute cerebellar syndrome has been described in patients presenting with classic cerebellar symptoms of ataxia, nystagmus, and dysarthria [50, 51]. In most instances, these symptoms present weeks to months after therapy initiation and will completely resolve with discontinuation of fluorouracil therapy. Fluorouracil-induced acute cerebellar syndrome remains largely a clinical diagnosis, as workup with imaging (including CT and MRI) and CSF analysis is typically unrevealing [52].

Acute neurotoxicity manifesting as diffuse encephalopathy has also been reported in patients undergoing treatment with fluorouracil, usually presenting within the first week of treatment initiation [53]. Classic MR imaging findings of 5-FU encephalopathy involve primarily the deep white matter and corpus callosum. Cases of 5-FU-induced leukoencephalopathy have demonstrated imaging findings of symmetrical high signal intensity on T2W images and DWI in the deep white matter of the cerebral hemispheres, including symmetrically increased signal intensity in the corpus callosum [54]. FLAIR images typically also demonstrate high signal intensity in these regions (Fig. 8) [55]. Other cases of 5-FU encephalopathy have reported findings of high signal intensity on T2 and diffusion-weighted images in the bilateral basal ganglia and thalami [56]. CT is less sensitive for detection of white matter abnormalities but can demonstrate symmetrical hypoattenuation in the periventricular region.

Delayed neurotoxicity can also occur with fluorouracil administration and usually presents as a subacute multifocal leukoencephalopathy. Cases of delayed neurotoxicity have been reported within several months after initiation of fluorouracil and levamisole. Reported MRI findings in these cases have included the development of multiple small enhancing white matter lesions bilaterally throughout the cerebral hemispheres and brain stem [57]. In other cases, CT and MRI evaluation of the brain have revealed no abnormalities [58]. This form of delayed neurotoxicity is postulated to be immune mediated and typically responds to corticosteroid treatment [59].

Vascular toxicity

In terms of vascular complications, gemcitabine carries a particularly high risk of venous thrombosis [60]. There have also been numerous cases reported of capillary leak syndrome associated with gemcitabine, which classically presents as diffuse interstitial pulmonary edema on imaging. Patients developing capillary leak syndrome while on gemcitabine can present with lung infiltrates, lower extremity edema, and dyspnea. Severe cases can present with diffuse interstitial lung disease with respiratory distress syndrome [61].

Small-vessel and large-vessel vasculitis have been documented in patients receiving gemcitabine treatment [62]. Common CT findings of vasculitis include vessel wall thickening with increased contrast enhancement of vascular walls [63]. While angiography is often negative in cases of vasculitis, occlusions, and smooth long areas of stenoses can occur in later stages of severe vasculitis. Findings on ultrasound often include the classic “halo sign” consisting of a circumferential hypoechoic thickened wall of an artery [64].

Conclusion

The landscape of treatment for metastatic pancreatic cancer has substantially evolved in the past decade, and with it, so has knowledge of radiological assessment of disease and treatment responses. Despite the low survival rates traditionally seen in patients with pancreatic cancer in prior years, there is an ongoing effort in the medical community to develop novel first- and second-line therapeutics to treat advanced stages of this disease. Recent clinical trial data from the past several years have led to the development of new second-line therapy regimens which provide options for patients with metastatic disease who have failed initial first-line treatment. For radiologists tasked with interpreting imaging from these often-complex oncology patients, it is critical to have an understanding of the clinically relevant features of these systemic therapies. Knowledge of the specific toxicity profiles of these modern anticancer agents has become increasingly important, as many of these potentially harmful side effects have identifiable imaging findings. Imaging-based evaluation of response patterns and toxicities is an essential component of the modern approach to managing patients with metastatic pancreatic cancer.

References

1. National Cancer Institute: Surveillance Epidemiology, (SEER) ERP. Cancer Stat Facts: Pancreatic Cancer [Internet]. [cited 2018 Nov 3]. Available from: https://seer.cancer.gov/statfacts/html/pancreas.html
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018 Jan;68(1):7–30.
3. Saad AM, Turk T, Al-Husseini MJ, Abdel-Rahman O. Trends in pancreatic adenocarcinoma incidence and mortality in the United States in the last four decades; a SEER-based study. BMC Cancer. 2018 Dec;18(688).
4. Anderson CW, Bennett JJ. Clinical Presentation and Diagnosis of Pancreatic Neuroendocrine Tumors. [cited 2018 Nov 4];25(2):363–74. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1055320715001398

5. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017 Aug;15(8):1028–61.
6. Lopez NE, Prendergast C, Lowy AM. Borderline resectable pancreatic cancer: definitions and management. World J Gastroenterol [Internet]. 2014/08/21. 2014 Aug 21;20(31):10740–51. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25152577
7. Abou-Khalil J, Rocha FG. Surgical strategies and novel therapies for locally advanced pancreatic cancer. J Surg Oncol. 2017 Jul;116(1):16–24.
8. Peixoto RD, Speers C, McGahan CE, Renouf DJ, Schaeffer DF, Kennecke HF. Prognostic factors and sites of metastasis in unresectable locally advanced pancreatic cancer. Cancer Med [Internet]. 2015/04/18. 2015 Aug;4(8):1171–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25891650
9. Go PH, Klaassen Z, Meadows MC, Chamberlain RS. Gastrointestinal cancer and brain metastasis. Cancer [Internet]. 2011;117(16):3630–40. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/cncr.25940
10. Sohal DPS, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, et al. Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. [cited 2018 Nov 4];34(23):2784–96. Available from: http://ascopubs.org/doi/10.1200/JCO.2016.67.1412
11. Sohal DPS, Kennedy EB, Khorana A, Copur MS, Crane CH, Garrido-Laguna I, et al. Metastatic Pancreatic Cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol. 2018 Aug;36(24):2545–56.
12. Macherla S, Laks S, Naqash AR, Bulumulle A, Zervos E, Muzaffar M. Emerging Role of Immune Checkpoint Blockade in Pancreatic Cancer. Int J Mol Sci [Internet]. 2018 Nov 7;19(11):3505. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30405053
13. Shin S, Park CM, Kwon H, Lee K-H. Erlotinib plus gemcitabine versus gemcitabine for pancreatic cancer: real-world analysis of Korean national database. BMC Cancer [Internet]. 2016 Jul;16(1):443. Available from: https://doi.org/10.1186/s12885-016-2482-z
14. Sinn M, Bahra M, Liersch T, Gellert K, Messmann H, Bechstein W, et al. CONKO-005: Adjuvant Chemotherapy With Gemcitabine Plus Erlotinib Versus Gemcitabine Alone in Patients After R0 Resection of Pancreatic Cancer: A Multicenter Randomized Phase III Trial. J Clin Oncol [Internet]. 2017;35(29):3330–7. Available from: https://doi.org/10.1200/JCO.2017.72.6463
15. Chi D-C, Brogan F, Turenne I, Zelonis S, Schwartz L, Saif MW. Gemcitabine-induced Pulmonary Toxicity. Anticancer Res. 32:4147–50.
16. Boiselle PM, Morrin MM, Huberman MS. Gemcitabine Pulmonary Toxicity: CT Features: J Comput Assist Tomogr. 2000 Nov;24(6):977–80.
17. 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. [cited 2018 Nov 3];258(1):41–56. Available from: http://pubs.rsna.org/doi/10.1148/radiol.10092129
18. Vahid B, Marik PE. Pulmonary Complications of Novel Antineoplastic Agents for Solid Tumors. [cited 2018 Nov 3];133(2):528–38. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0012369215491044
19. Shitara K, Ishii E, Kondo M, Sakata Y. Suspected paclitaxel-induced pneumonitis. Gastric Cancer. 2006 Nov;9(4):325–8.
20. Sotiriou C, van Houtte P, Klastersky J. Lung fibrosis induced by paclitaxel. Support Care Cancer. 1997 Dec;6(1):68–71.
21. Suzaki N, Hiraki A, Takigawa N, Ueoka H, Tanimoto Y, Kozuki T, et al. Severe Interstitial Pneumonia Induced by Paclitaxel in a Patient with Adenocarcinoma of the Lung. 60(5):295–8.
22. Pontes LB, Armentano DPD, Soares A, Gansl RC. Fatal Pneumonitis Induced by Oxaliplatin: Description of Three Cases. [cited 2018 Nov 3];5:104–9. Available from: https://www.karger.com/Article/FullText/337030
23. Wilcox BE, Ryu JH, Kalra S. Exacerbation of pre-existing interstitial lung disease after oxaliplatin therapy: A report of three cases. Respir Med. 2008 Feb;102(2):273–9.
24. Balaji A, Verde F, Sures K, Naido J. Pneumonitis From Anti–PD-1/PD-L1 Therapy. Oncol (willist Park. 2017;31(10):739–46, 754.
25. Leroy V, Templier C, Faivre J-B, Scherpereel A, Fournier C, Mortier L, et al. Pembrolizumab-induced pneumonitis. [cited 2018 Nov 3];3. Available from: http://openres.ersjournals.com/lookup/doi/10.1183/23120541.00081-2016
26. Kuint R, Lotem M, Neuman T, Bekker-Milovanov E, Abutbul A, Laxer U, et al. Organizing pneumonia following treatment with pembrolizumab for metastatic malignant melanoma – A case report. [cited 2018 Nov 3];20:95–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213007117300126
27. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 Inhibitor-Related Pneumonitis in Advanced Cancer Patients: Radiographic Patterns and Clinical Course. Clin Cancer Res. 2016 Dec;22(24):6051–60.
28. Gadducci A, Gargini A, Palla E, Fanucchi A, Genazzani AR. Neutropenic Enterocolitis in an Advanced Epithelial Ovarian Cancer Patient Treated with Paclitaxel/Platinum-based Chemotherapy: A Case Report and Review of the Literature. 25:2509–14.
29. Li Z, Ibrahim NK, Wathen JK, Wang M, Mante Menchu RP, Valero V, et al. Colitis in patients with breast carcinoma treated with taxane-based chemotherapy. [cited 2018 Nov 3];101(7):1508–13. Available from: http://doi.wiley.com/10.1002/cncr.20546
30. Sassi C, Pasquali M, Facchini G, Bazzocchi A, Battista G. Pneumatosis intestinalis in oncologic patients: when should the radiologist not be afraid? BJR|case reports [Internet]. 2017;3(1):20160017. Available from: https://doi.org/10.1259/bjrcr.20160017
31. Lee KS, Hwang S, Hurtado Rua SM, Janjigian YY, Gollub MJ. Distinguishing benign and life-threatening pneumatosis intestinalis in patients with cancer by CT imaging features. AJR Am J Roentgenol. 2013 May;200(5):1042–7.
32. Stein A, Voigt W, Jordan K. Review: Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management. Ther Adv Med Oncol. 2010 Jan;2(1):51–63.
33. Nesher L, Rolston KVI. Neutropenic Enterocolitis, a Growing Concern in the Era of Widespread Use of Aggressive Chemotherapy. [cited 2018 Nov 3];56(5):711–7. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/cis998
34. Machado NO. Neutropenic enterocolitis: A continuing medical and surgical challenge. 2(7):293–300.
35. So ACP, Board RE. Real-world experience with pembrolizumab toxicities in advanced melanoma patients: a single-center experience in the {UK}. [cited 2018 Nov 3];5(1). Available from: https://www.futuremedicine.com/doi/10.2217/mmt-2017-0028
36. Widmann G, Nguyen VA, Plaickner J, Jaschke W. Imaging Features of Toxicities by Immune Checkpoint Inhibitors in Cancer Therapy. Curr Radiol Rep. 2017 Nov;5(59).
37. Vauthey J-N, Pawlik TM, Ribero D, Wu T-T, Zorzi D, Hoff PM, et al. Chemotherapy Regimen Predicts Steatohepatitis and an Increase in 90-Day Mortality After Surgery for Hepatic Colorectal Metastases. J Clin Oncol. 2006 May;24(13):2065–72.
38. Sharma A, Houshyar R, Bhosale P, Choi J-I, Gulati R, Lall C. Chemotherapy induced liver abnormalities: an imaging perspective. [cited

2018 Nov 3];20(3):317–26. Available from: http://e-cmh.org/journal/view.php?doi=10.3350/cmh.2014.20.3.317
39. Hamer OW, Aguirre DA, Casola G, Lavine JE, Woenckhaus M, Sirlin CB. Fatty Liver: Imaging Patterns and Pitfalls. [cited 2018 Nov 3];26(6):1637–53. Available from: http://pubs.rsna.org/doi/10.1148/rg.266065004
40. Behrns KE. Hepatobiliary cancer and pyogenic liver abscess: when poking the skunk is not enough: invited commentary on Chen, et al. Am J Surg 2013;205:52-7. Am J Surg [Internet]. 2013/01/31. 2013 Apr;205(4):479–80. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23375754
41. D'Haese J, Michalski C, Holzapfel K, Kleeff J. CASE REPORT Liver Abscesses Mimicking Metastatic Disease in a Patient with Pancreatic Cancer Following Neoadjuvant FOLFIRINOX Therapy. JOP J pancreas. 2015;16:613–5.
42. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey J-N, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. [cited 2018 Nov 3];94(3):274–86. Available from: http://doi.wiley.com/10.1002/bjs.5719
43. Han NY, Park BJ, Yang KS, Kim MJ, Sung DJ, Sim KC, et al. Hepatic Parenchymal Heterogeneity as a Marker for Oxaliplatin-Induced Sinusoidal Obstruction Syndrome: Correlation With Treatment Response of Colorectal Cancer Liver Metastases. Am J Roentgenol. 2017 Nov;209(5):1039–45.
44. Cayet S, Pasco J, Dujardin F, Besson M, Orain I, De Muret A, et al. Diagnostic performance of contrast-enhanced CT-scan in sinusoidal obstruction syndrome induced by chemotherapy of colorectal liver metastases: Radio-pathological correlation. Eur J Radiol. 2017 Sep;94:180–90.
45. Choi J-H, Won Y-W, Kim HS, Oh Y-H, Lim S, Kim H-J. Oxaliplatin-induced sinusoidal obstruction syndrome mimicking metastatic colon cancer in the liver. [cited 2018 Nov 3];11(4):2861–4. Available from: https://www.spandidos-publications.com/10.3892/ol.2016.4286
46. Overman MJ, Maru DM, Charnsangavej C, Loyer EM, Wang H, Pathak P, et al. Oxaliplatin-mediated increase in spleen size as a biomarker for the development of hepatic sinusoidal injury. J Clin Oncol. 2010 May;28(15):2549–55.
47. El Chediak A, Haydar AA, Hakim A, Massih SA, Hilal L, Mukherji D, et al. Increase in spleen volume as a predictor of oxaliplatin toxicity. Ther Clin Risk Manag [Internet]. 2018 Apr 11;14:653–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29695909
48. Kim KW, Ramaiya NH, Krajewski KM, Jagannathan JP, Tirumani SH, Srivastava A, et al. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. [cited 2018 Nov 3];31(4):1071–7. Available from: http://link.springer.com/10.1007/s10637-013-9939-6
49. Pirzada NA, Ali II, Dafer RM. Fluorouracil-Induced Neurotoxicity. 34:35–8.
50. Riehl J-L, Brown WJ. Acute cerebellar syndrome secondary to 5-fluorouracil therapy. Neurology. 1964 Oct;14(10):961.
51. Gottlieb J, Luce J. Cerebellar ataxia with weekly 5-Fluorouracil administration. 16(1):138–9.
52. Schiff D, Arrillaga I, Wen PY, editors. Cancer Neurology in Clinical Practice: Neurological Complications of Cancer and its Treatment. Springer International Publishing;
53. Kwon KA, Kwon H-C, Kim MC, Kim S-H, Oh SY, Lee S, et al. A Case of 5-Fluorouracil Induced Encephalopathy. [cited 2018 Nov 3];42(2):118–20. Available from: http://e-crt.org/journal/view.php?id=10.4143/crt.2010.42.2.118
54. Akitake R, Miyamoto S, Nakamura F, Horimatsu T, Ezoe Y, Muto M, et al. Early Detection of 5-FU-induced Acute Leukoencephalopathy on Diffusion-Weighted MRI. Jpn J Clin Oncol. 2011 Jan;41(1):121–4.
55. Lee W-W, Kim J-S, Son KR, Kwon H-M. Atypical Diffusion-Restricted Lesion in 5-Fluorouracil Encephalopathy. Am J Neuroradiol [Internet]. 2012;33(7):E102–E103. Available from: http://www.ajnr.org/content/33/7/E102
56. Lee W-W, Kim J-S, Son KR, Kwon H-M. Atypical Diffusion-Restricted Lesion in 5-Fluorouracil Encephalopathy: Fig 1. Am J Neuroradiol. 2012 Aug;33(7):E102–3.
57. Kimmel DW, Schutt AJ. Multifocal Leukoencephalopathy: Occurrence During 5-Fluorouracil and Levamisole Therapy and Resolution After Discontinuation of Chemotherapy. [cited 2018 Nov 3];68(4):363–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0025619612601323
58. Yi HJ, Hong KS, Moon N, Chung SS, Lee R-A, Kim KH. Acute hyperammonemic encephalopathy after 5-fluorouracil based chemotherapy. [cited 2018 Nov 3];90(3):179–82. Available from: http://synapse.koreamed.org/DOIx.php?id=10.4174/astr.2016.90.3.179
59. Han R, Yang YM, Dietrich J, Luebke A, Mayer-Pröschel M, Noble M. Systemic 5-fluorouracil treatment causes a syndrome of delayed myelin destruction in the central nervous system. J Biol. 2008;7(12).
60. Barni S, Labianca R, Agnelli G, Bonizzoni E, Verso M, Mandalà M, et al. Chemotherapy-associated thromboembolic risk in cancer outpatients and effect of nadroparin thromboprophylaxis: results of a retrospective analysis of the PROTECHT study. J Transl Med. 2011;9(179).
61. Casadei Gardini A, Aquilina M, Oboldi D, Lucchesi A, Carloni S, Tenti E, et al. Separate episodes of capillary leak syndrome and pulmonary hypertension after adjuvant gemcitabine and three years later after nab-paclitaxel for metastatic disease. [cited 2018 Nov 3];13(542). Available from: http://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-13-542
62. Ramsay LB, Stany MP, Edison JD, Bernstein SA, Schlegal KE, Hamilton CA. Gemcitabine-Associated Large Vessel Vasculitis Presenting as Fever of Unknown Origin: [cited 2018 Nov 3];16(4):181–2. Available from: https://insights.ovid.com/crossref?an=00124743-201006000-00009
63. Bendix N, Glodny B, Bernathova M, Bodner G. Sonography and CT of Vasculitis During Gemcitabine Therapy. Am J Roentgenol. 2005 Mar;184(3_supplement):S14–5.
64. Czihal M, Lottspeich C, Hoffmann U. Ultrasound imaging in the diagnosis of large vessel vasculitis. Vasa. 2017 Jun;46(4):241–53.
65. de Sousa Cavalcante L, Monteiro G. Gemcitabine: Metabolism and molecular mechanisms of action, sensitivity and chemoresistance in pancreatic cancer. [cited 2018 Nov 3];741:8–16. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0014299914005780
66. Yardley DA. nab-Paclitaxel mechanisms of action and delivery. J Control Release. 2013 Sep;170(3):365–72.
67. Longley DB, Harkin DP, Johnston PG. 5-Fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003 May;3(5):330–8.
68. Ko A. Nanomedicine developments in the treatment of metastatic pancreatic cancer: focus on nanoliposomal irinotecan. Int J Nanomedicine. 2016 Mar;11:1225–1235.
69. Alcindor T, Beauger N. Oxaliplatin: a review in the era of molecularly targeted therapy. [cited 2018 Nov 3];18(1):18–25. Available from: http://www.current-oncology.com/index.php/oncology/article/view/708
70. Keytruda (pembrolizumab) for injection [prescribing information].
71. Weiss GJ, Waypa J, Blaydorn L, Coats J, McGahey K, Sangal A, et al. A phase Ib study of pembrolizumab plus chemotherapy in patients with advanced cancer (PembroPlus). Br J Cancer. 2017 Jun;117:33–40.