





# Imaging of chemotherapy-induced liver toxicity: an illustrated overview

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## Hepatic Oncology

### Practice points

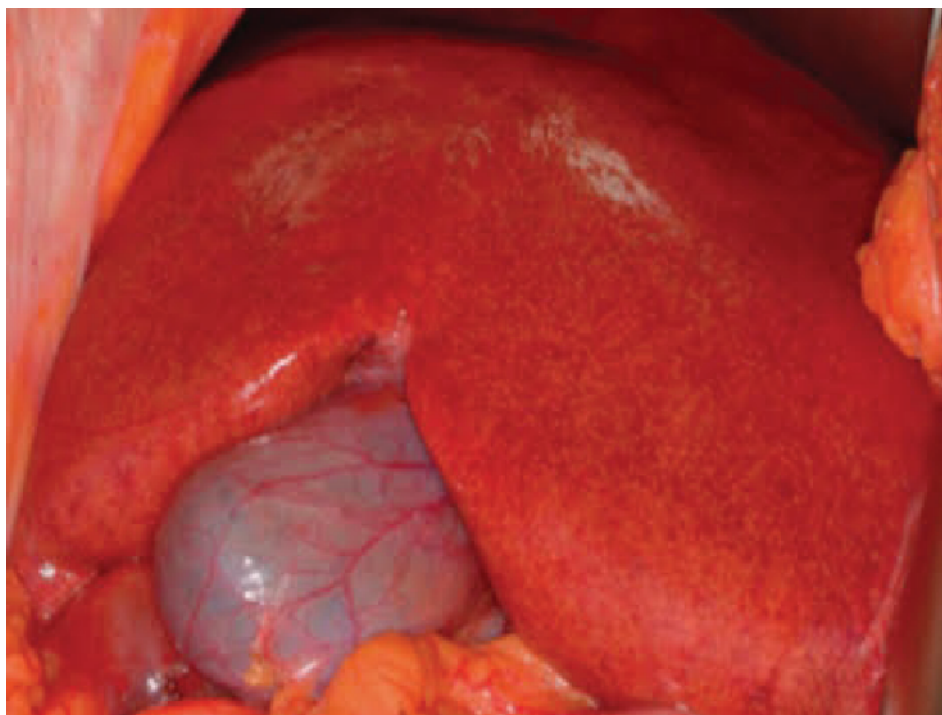
- Chemotherapeutic agents induce toxicity in multiple organs, including the liver. Many of these hepatic alterations can be detected on imaging, especially MRI.
- Knowledge about these lesions can reduce the risk of erroneously diagnosing them as neoplastic progression or relapse.
- Steatosis/steatohepatitis is mainly related to the use of irinotecan, tamoxifen and 5-fluorouracil, among other agents, and is associated with an increased risk of postoperative hepatic failure.
- Sinusoidal obstruction syndrome occurs when there is damage to the hepatic sinusoidal endothelium, usually after the administration of oxaliplatin, cyclophosphamide and vincristine. This condition is associated with an increased risk of bleeding and hepatic failure.
- Pseudocirrhosis presents with a strikingly nodular appearance and is usually observed in patients undergoing treatment for breast cancer, with or without hepatic metastases. The condition may be complicated by portal hypertension in some patients.
- Focal nodular hyperplasia is thought to result from microvascular alterations in the liver and is related to oxaliplatin use. Oncologists must be aware of this focal lesion, as it may be falsely considered as hypervascular metastasis. MRI with hepatospecific contrast media provides crucial information for the differential diagnosis of focal nodular hyperplasia.

Chemotherapy is a potential cause of focal and diffuse hepatobiliary lesions. Many of these lesions may be demonstrated on imaging, especially computed tomography and MRI. Some of these lesions, especially those of steatosis and sinusoidal obstruction syndrome, are associated with a worse prognosis and risk of hepatic failure in the context of surgical management. Notably, some chemotherapy-induced hepatic alterations, such as sinusoidal obstruction syndrome, pseudocirrhosis and focal hepatopathies, may be mistakenly interpreted as signs of cancer progression, misguiding the therapeutic planning for patients receiving chemotherapy.

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The use of chemotherapeutic agents in the oncologic setting is related to a better prognosis, increased resectability when used in neoadjuvant therapy and improved overall survival. However, this widely used therapeutic option is also related to toxicity in multiple organs, including liver, pancreas, and gastrointestinal and genitourinary tracts, negatively affecting outcomes for some patients. Some hepatobiliary alterations are considered peculiar based on imaging findings, primary neoplastic site and chemotherapy regimen. For example, sinusoidal obstruction



**Figure 1. Yellow liver.** Intraoperative photograph of a steatotic liver.

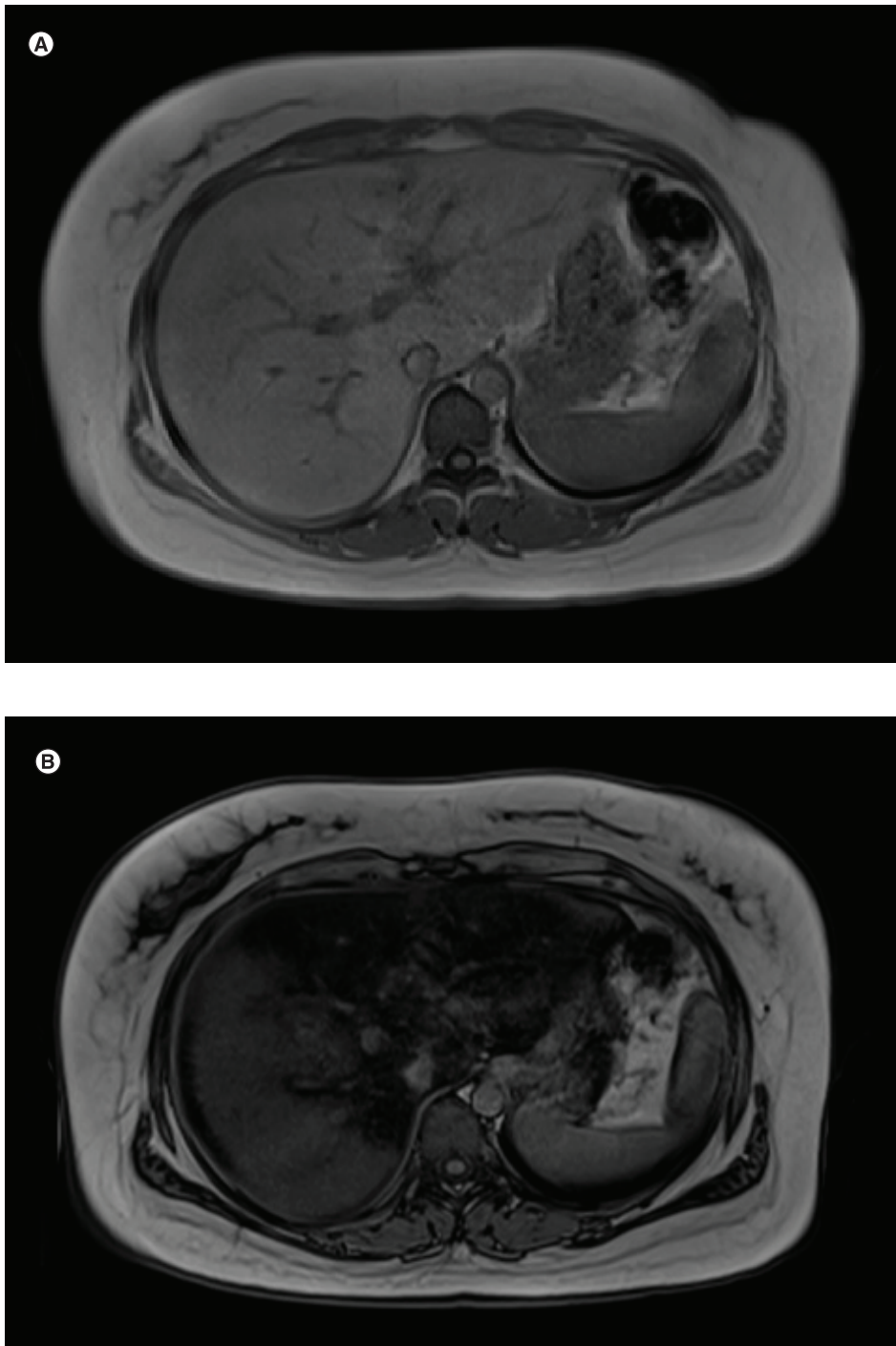
syndrome (SOS) presents with a diffuse heterogeneous reticular pattern in the hepatobiliary phase of MRI. Regarding the primary neoplastic site, pseudocirrhosis usually occurs in patients with metastatic breast cancer.

### Steatosis/steatohepatitis

Steatosis, which refers to an increased amount of fat in the live parenchyma, shows a peak incidence 3 to 12 months after the initiation of chemotherapy and usually regresses after treatment completion. Steatosis is particularly associated with the use of irinotecan, tamoxifen, 5-fluorouracil, doxifluridine, gemcitabine, methotrexate and platinum-based drugs [1–4]. Oxidative stress, mitochondrial injury and subsequent lipid accumulation are the key processes underlying the pathophysiology of this alteration [3]. The lesion distribution pattern may be diffuse, focal, multifocal or perivascular. Intraoperatively, a steatotic liver has a yellowish appearance (Figure 1). Although hyperechogenicity on ultrasound may suggest steatosis, this evaluation is subjective, with a positive predictive value of approximately 62–77%. On computed tomography (CT), a reduction in parenchymal attenuation in relation to the spleen is suggestive of steatosis. MRI has superior reliability in detecting and determining the amount of fat in the liver during the initial phases using in-phase and out-phase gradient-echo sequences (Figure 2), spectroscopy and elastography [3,5–7]. Possible complications include chronic cirrhosis and increased mortality in patients undergoing surgical resection [1,8].

### Sinusoidal obstruction syndrome

Previously called veno-occlusive disease, this disorder may present with acute (1–3 weeks), subacute and chronic phases. Chemotherapeutic regimens including oxaliplatin, cisplatin, cyclophosphamide and vincristine are associated with this condition. This pathology may occur in up to 10–60% of patients after chemotherapy for bone marrow transplant; it usually occurs 35 days after treatment initiation but may also occur later. Drugs inflict sinusoidal endothelial damage, with venular obstruction and hepatic congestion conferring a bluish appearance on the liver (Figure 3). Importantly, in contrast to Budd–Chiari syndrome, this condition is characterized by the patency of large veins (the hepatic veins and inferior vena cava). Clinically, patients with SOS present with jaundice, hepatomegaly, weight gain, abdominal pain and encephalopathy [3,4]. Chronic SOS may progress to cirrhosis. Nonspecific imaging findings include hepatosplenomegaly, ascites, gallbladder wall thickening and portosystemic shunts. The presence of portal hypertension signs in surgical patients is of significance, as these signs are

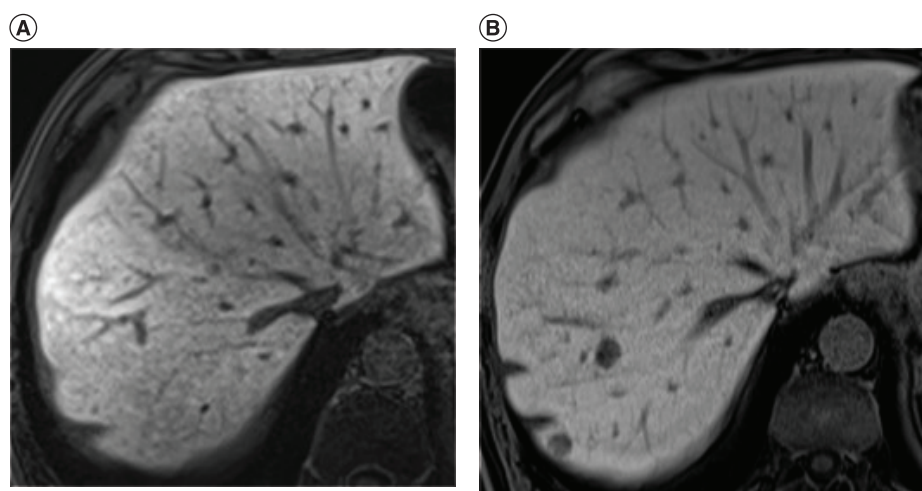


**Figure 2.** Axial T1-weighted gradient echo. MRI demonstrate loss of signal in the opposing-phase MRI predominantly in the left hepatic lobe after taxol and anastrozole use. (A) In phase. (B) Opposing phase.

potentially related to a worse prognosis due to an increased bleeding risk or hepatic failure after the procedure [4,9]. On contrast-enhanced CT, heterogeneous enhancement is observed, which is attributed to perfusion disturbances. It is important to note the presence of ascites in the context of SOS; otherwise, it may be mistaken for disease recurrence or progression [8]. A diffuse reticular pattern in the hepatobiliary phase of gadoteric acid-enhanced MRI in postchemotherapy patients is a characteristic feature of SOS (Figures 4 & 5) [4].



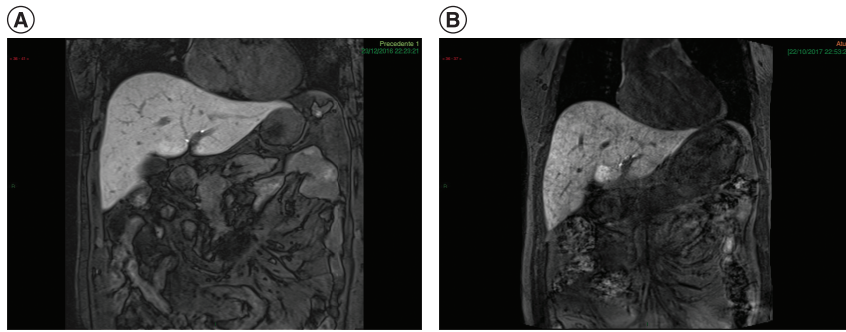
**Figure 3. Blue liver.** Intraoperative photograph of a liver with sinusoidal obstruction syndrome.



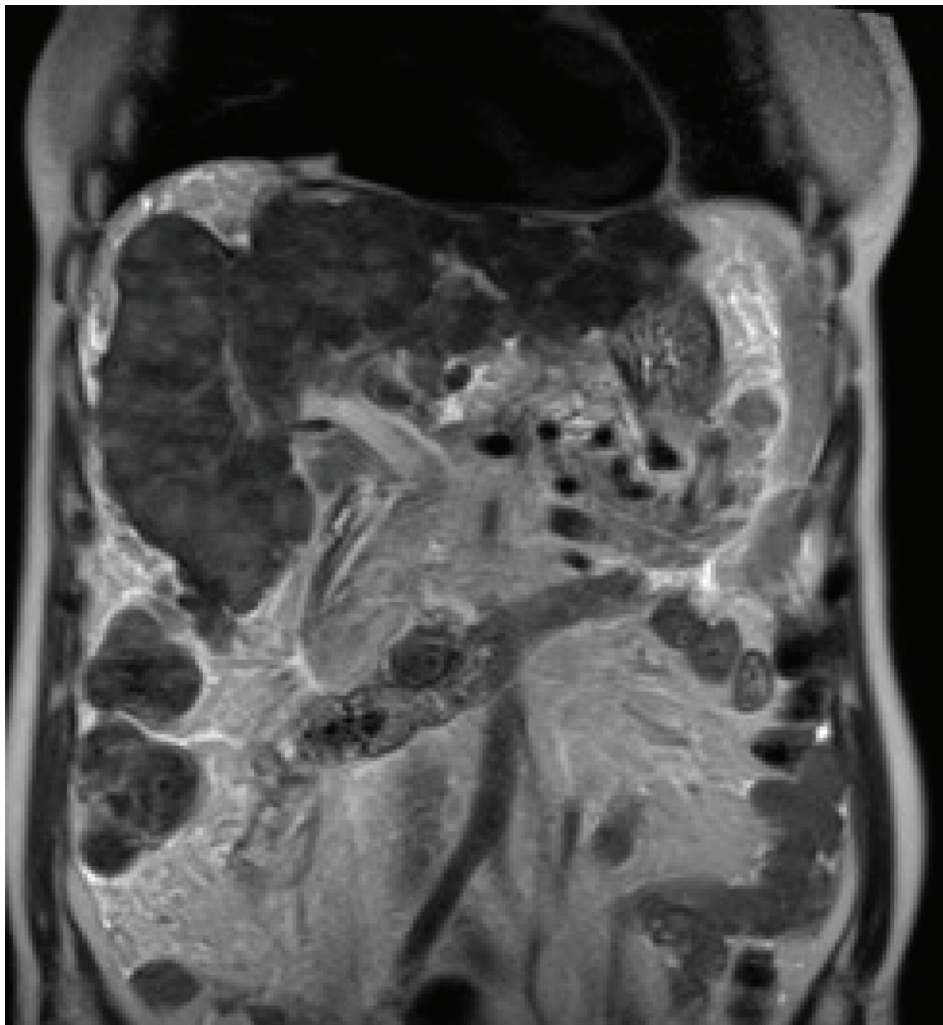
**Figure 4. Axial T1-weighted MRI obtained using hepatospecific contrast media in the hepatobiliary phase. (A)** Before chemotherapy. **(B)** After chemotherapy with the FOLFOX regimen in a patient with colon cancer; demonstrates a diffuse heterogeneous reticular pattern. Regarded to be the characteristic feature of sinusoidal obstructive syndrome.

### Pseudocirrhosis

Pseudocirrhosis is characterized by diffuse liver nodularity mimicking cirrhosis; however, histopathologically, pseudocirrhosis appears as nodular regenerative hyperplasia without significant fibrosis [10]. Pseudocirrhosis is usually seen in patients with hepatic metastasis, although it may occur in a liver without subjacent disease [4]. It is typically related to breast cancer in 50–75% of patients [1,9]. However, it can also occur in patients with primary cancers of the colon and pancreas, those with carcinoid tumors and those with Hodgkin lymphoma [1,4,9]. Rapid progression (usually 1 to 3 months after chemotherapy initiation), in contrast to true cirrhosis, is usually diagnostic of pseudocirrhosis. Tamoxifen and capecitabine are some of the offending drugs. Imaging findings include diffuse

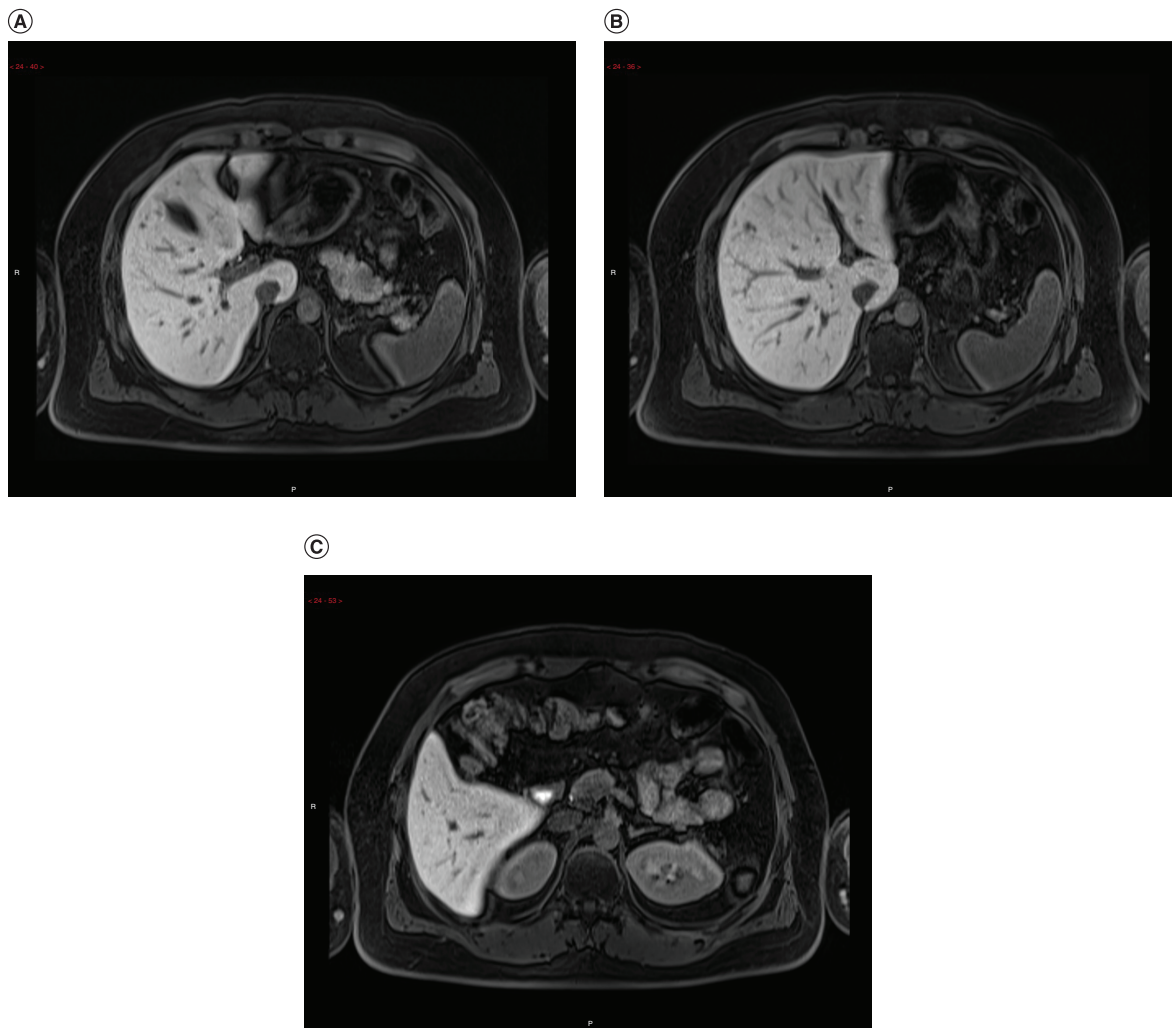


**Figure 5.** Coronal T1-weighted MRI obtained using hepatospecific contrast media in the hepatobiliary phase. They demonstrate onset of a diffuse heterogeneous reticular pattern after chemotherapy with the FOLFOX regimen for 8 months.



**Figure 6.** Coronal T2-weighted MRI. It demonstrates a diffuse nodular pattern with capsular retraction and hepatic parenchymal distortion.

nodularity, capsular retraction, reduced liver volume and caudate lobe enlargement (Figure 6). Portal hypertension signs, including portosystemic shunts (in 9% of the cases), may be present [1,8,9].



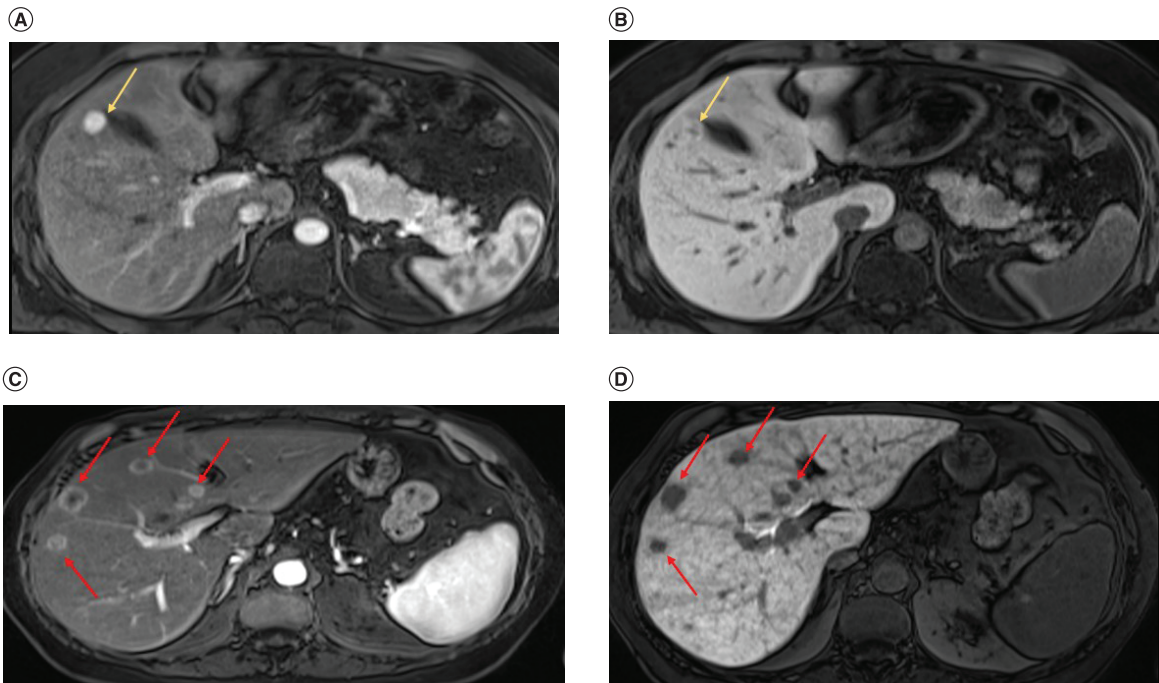
**Figure 7.** T1-weighted MRI postcontrast with hepatospecific contrast agent in the hepatobiliary phase. They demonstrate subtle focal enhancing lesions in a patient who received oxaliplatin.

### Focal nodular hyperplasia

Focal nodular hyperplasia (FNH) is a benign hepatocytary lesion with an unknown pathogenesis, although intrahepatic vascular disorders are potentially implicated. FNH may even have a pathogenesis similar to that of focal SOS [11,12]. This alteration is usually associated with oxaliplatin use, and in one study, up to 15% of patients with colorectal cancer presented with FNH [13]. The lesions may be solitary or multinodular. On CT, FNH classically presents as a homogeneous, isodense or slightly hypodense lesion in relation to the liver parenchyma. On contrast-enhanced CT, arterial hyperenhancement is observed; in cases where a central scar is evident, late enhancement may be observed. The detection and characterization of this type of lesion are essential considering its worrisome differential diagnosis with hypervascular metastasis. The most independent discriminant feature for differentiating FNH from metastases is the presence of a nonspherical shape, poorly defined margins, and especially, areas of hypercaptation in the hepatobiliary phase with hepatospecific contrast media (Figures 7 & 8). Additional features favoring FNH diagnosis include signal isointensity on T1- and T2-weighted images, absence of halo enhancement (early enhancement) and absence of restriction to water diffusion in the echo-planar sequence [11].

### Conclusion

Chemotherapy is one of the main treatment modalities for neoplasia and is administered as a neoadjuvant or adjuvant therapy. Although it increases patient survival, drug-induced toxicity may hinder the continuation of a specific regimen in many cases. In this report, the authors focused on reviewing and describing different types



**Figure 8. Axial MRIs of nodules.** (A) Axial MRI shows a hypervascular nodule (arrow) that is predominantly hyperintense in the hepatobiliary phase (arrow in [B]). The imaging findings are consistent with FNH. (C) In another contrasting example the arrows indicate several nodules with peripheral arterial hyperenhancement (arrows) and central hypointensity in the hepatobiliary phase (arrow in [D]), suggesting metastases. The pattern of reticular enhancement associated with sinusoidal obstruction syndrome is also visible.

Table 1. Take-home messages.		
Adverse effects in the liver	Radiological findings	Common agents
Sinusoidal obstruction syndrome	US: Ascites, gallbladder wall thickening and hepatosplenomegaly. CT: Ascites, decreased right hepatic vein diameter (<0.45 cm), paraesophageal varices, hepatosplenomegaly and recanalization of the umbilical vein. MRI: Diffuse hypointense reticular pattern on postcontrast delayed hepatobiliary phase T1-weighted imaging.	Oxaliplatin, 6-MP, dacarbazine, azathioprine, cyclophosphamide, fluorouracil and vincristine
Pseudocirrhosis	US, CT, MRI: Segmental volume loss, capsular retraction, fibrosis and caudate lobe enlargement mimicking macronodular cirrhosis on CT; occurs in patients with metastatic breast and colon cancers.	Gemcitabine, FOLFOX, oxaliplatin, irinotecan, fluorouracil and methotrexate
Steatosis	US: Increased echogenicity and beam attenuation. CT: Reduced liver attenuation. MRI: Reduced liver signal intensity in out-of-phase imaging observed in acutely ill patients with steatohepatitis.	Irinotecan, oxaliplatin, cetuximab, tamoxifen and antivascular endothelial growth factor therapy
Focal nodular hyperplasia	MRI: Signal isointensity on T1- and T2-weighted images, absence of halo enhancement (early enhancement) and absence of restriction to water diffusion in the echo-planar imaging sequence.	Oxaliplatin-based chemotherapy

of chemotherapy-related liver toxicities. An oncologist aware of these potential complications is better suited for optimal patient care (Table 1).

### Future perspective

Chemotherapy-related changes observed on liver imaging are increasingly being described in the literature, and they have important implications for therapeutic planning. Sensitive imaging methods help determine safe treatment regimens and enable prompt intervention for adverse effects.

### Author contributions

MD Soldatelli authored the original presentation for the Radiological Society of North America (2019) on the same subject; GB Torri was responsible manuscript submission and processing; GF Luersen gave the final manuscript review and; CLA Ghezzi accounted for cases and illustration selection.

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### Ethical conduct of research

The authors state that they have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. Informed consent was obtained for the use of patients' photographs.

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