European Review for Medical and Pharmacological Sciences 2019; 23: 9697-9706

Liver radiologic findings of chemotherapy-induced toxicity in liver colorectal metastases patients

V. GRANATA[1], R. FUSCO[1], S. VENANZIO SETOLA[1], M. MATTACE RASO[1], A. AVALLONE[2], A. DE STEFANO[2], G. NASTI[2], R. PALAIA[3], P. DELRIO[3], A. PETRILLO[1], F. IZZO[3]

[1]Division of Radiology, [2]Division of Abdominal Oncology, [3]Division of Hepatobiliary Surgical Oncology; "Istituto Nazionale Tumori – IRCCS, Fondazione G. Pascale", Naples, Italy

Abstract. – There are a number of chemotherapy-effects that should be assessed with liver imaging since they have an influence on surgical morbidity. Chemotherapy-related complications, steatosis, chemotherapy-associated steatohepatitis (CASH), and SOS might impair the hepatic parenchyma, thus reducing the functionality and influencing the outcome following resection. The main role of a radiologist is to provide an accurate diagnosis of the lesion. With constant advances in medicine, a radiologist's role should extend beyond just reporting the data of tumor, providing additional information that may greatly improve patient care. Radiologists should assess both chemotherapy effects on the hepatic metastasis itself, as well as chemo-induced focal and diffuse modifications of non-tumor hepatic parenchyma, since it is important to avoid impaired hepatic function after hepatic resection.

Key Words:
Colorectal liver metastases, Chemotherapy-toxicity, Imaging.

Introduction

Colorectal cancer is the third most common cancer in the world, with 774,000 deaths worldwide[1]. The most common site of metastases is the liver; colorectal liver metastases (mCRC) can be synchronous in 15% to 25% of patients or metachronous in 25% to 30%[1,2]. Currently, the standard of care of patients with mCRC is surgical resection[2]. Unfortunately, not all patients are candidates for surgery owing to factors, such as the number, size, or location of the metastases. For these patients, neoadjuvant chemotherapy is often used to decrease the tumor burden; if patients have an adequate response, they may undergo to surgical resection. As a matter of facts, the current median overall survival for patients with mCRC in large observational series is 30 months, more than double that of 20 years ago[2]. The features involved are a closer patient follow-up to obtain an earlier detection of metastatic disease, an improvement in the efficacy of systemic therapies based on a better patient selection[2,3] and an increase in the number of patients underwent to resection[3], thanks to a more strategic approach, which saw the spread of percutaneous ablative techniques[4,5] and of chemotherapeutic target therapies[6-8]. Systemic therapy is given to convert unresectable liver metastases into resectable and is known as conversion therapy[2]. During treatment, resectability is evaluated after 2 months and again after 4 months from neoadjuvant therapy, when the maximal tumor shrinkage is deemed to occur in most patients[2]. Surgical liver resection has enhanced the survival[2]. Some characteristics should be considered when is planned a liver resection, such as the number of hepatic segments involved, the lesions contiguity to vascular or biliary tree, and the residual liver volume after treatment[3]. The size and functionality of residual liver had an impact on the success rate, influencing surgical mortality and morbidity[3] and the occurrence probability of parenchymal injury secondary due to hepatotoxic chemotherapy[9-11]. Liver volumetry, obtained by imaging, generally performed using Computed Tomography (CT), allows an accurate assessment of major hepatic resections[11]. However, this method only evaluates the size and not the function, so more appropriate techniques are requested. Dynamic Contrast Enhanced-Magnetic Resonance Imaging (DCE-MRI) with hepatospe-

Corresponding Author: Roberta Fusco, MD; e-mail: r.fusco@istitutotumori.na.it

cific contrast medium (CM) has been proposed for the assessment of liver function and staging of liver fibrosis[12-14]. The hepatobiliary function can be assessed evaluating the hepatospecific CM uptake in the normal hepatocytes. Regional CM uptake measurement may be useful for pre-surgical quantification of liver function in patients schedule for hepatic surgery. Also parenchymal injury should be assessed in order to define the proper strategical approach[12-14].

Chemotherapy-Related Complications

The most commonly used chemotherapy regimens include FOLFOX (5-fluorouracil/leucovorin and oxaliplatin) and FOLFIRI (5-fluorouracil/leucovorin and irinotecan), which often achieve excellent treatment responses[2]. Biologic agents, such as bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, and cetuximab, an anti-epidermal growth factor receptor agent, have contributed to improve systemic therapy for mCRC, without an increase of major complication rates after hepatectomy[2]. However, the practice of multi-agent regimens, the systemic therapies duration and the introduction of new treatments have increased the risk for drug-induced liver injury (DILI)[15]. These agents can determine hepatocyte and biliary ducts toxicity altering lipid metabolism or causing hepatic vascular tree damage. Drug toxicity provokes hepatocytes injury in in terms of mild or severe hepatitis with possibility of the evolution to cirrhosis and fibrosis[16-20]. As a consequence of the lipid metabolism alteration, a deposition of fat within the hepatocytes can be present, determining steatosis or steatohepatitis. Lastly, drug-induced vascular damages may lead to sinusoid obstructive syndrome (SOS), portal vein thrombosis, and peliosis hepatis[19]. Therefore, there are a number of chemotherapy-effects that should be assessed with liver imaging since they have an influence on surgical morbidity. The chemotherapy-related complications, steatosis, chemotherapy-associated steatohepatitis (CASH), and SOS might impair the hepatic parenchyma, thus reducing the functionality and influencing the outcome following resection. Either CASH and SOS are associated with an increase of morbidity but not mortality after hepatic surgery[3,20]. Traditionally, the main role of a radiologist, in the assessment of liver metastases, is to provide an accurate diagnosis of the lesion/s. With constant advances in medicine, including radiology, a radiologist's role should extend beyond just reporting the data of tumor, including side, diameter, vascular, and biliary involvement. Although in some cases these may be the only components to report, we should provide additional information that may greatly improve patient care[3]. Radiologists should also assess both the effects of chemotherapy on the hepatic metastasis itself, as well as the chemo-induced focal and diffuse modifications of non-tumor hepatic parenchyma, since it is important to differentiate mimickers from hepatic metastasis and avoid impaired hepatic function after hepatic resection. Therefore, additional features that are often not evaluated in the report include the presence or absence of chemotherapy related injury in the non-neoplastic liver parenchyma[3]. The most efficient means to communicate these diagnostic details to the multidisciplinary team is for radiologist to include them in their radiological report. The non-neoplastic liver parenchyma should be assessed for underlying or superimposed liver disease, such as steatohepatitis or other diseases that might affect liver function or its ability to respond to chemotherapy after hepatic resection[3,17]. In patients with chronic liver disease, fibrosis is often the most important prognostic factor, that may affect a patient's ability to tolerate hepatic resections, and should be included in all liver reports whenever possible[3]. The non-neoplastic liver is also susceptible to chemotherapy-induced sinusoidal injury. Liver injury may occur with chemotherapy regimens, such as irinotecan, which may cause steatohepatitis and oxaliplatin, which may cause nodular regenerative hyperplasia or sinusoidal obstruction syndrome. If steatohepatitis is identified in the pre-surgical imaging, the radiologist should assess the inflammation and fibrosis. If a patient has received FOLFOX and the background liver shows sinusoidal dilatation, congestion, nodular regenerative hyperplasia changes, and/or venous obstruction, a diagnosis of chemotherapy induced sinusoidal injury and/or sinusoidal obstruction syndrome should be reported[3].

Hepatitis

Hepatitis due to chemotherapy can be classified histologically in three groups: hepatocellular, cholestatic (Figure 1), or mixed. Radiologist role is the identification and the classification of hepatitis severity grading, as well as the detection of other increasing causes of liver function tests (LFT)[21]. Different agents have been linked with hepatitis, including 5-fluorouracil (FU), cisplatin, VEFG tyrosine kinase inhibitors (TKI), non-VEGF TKI, epithelial growth factor receptors (EGFR) in-

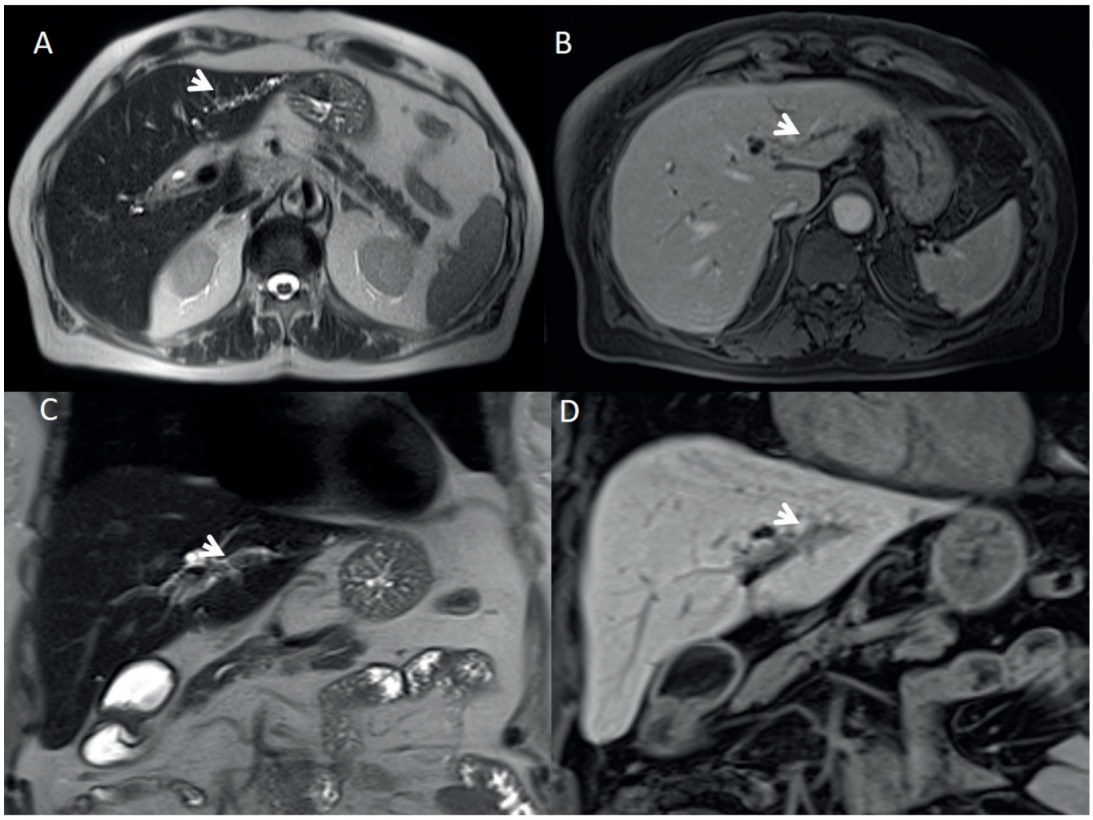

Figure 1. Woman 45 y with colon cancer. Chemotherapy-induced cholestatic hepatitis that appears as peribiliary hypointense (perisinusoidal fibrosis) tissue (*arrow*) in T2-W sequences (**A** and **C**). In portal phase of contrast study (**B**) it is present an indirect sign of perisinusoidal fibrosis, that appears as a distrectual biliary tree dilatation (*arrow*). During EOB phase (**D**) the tissue (*arrow*) shows hypointense signal.

hibitors, and immune checkpoint inhibitors. Radiological characteristics include hepatomegaly, perihepatic fluid, lymphadenopathy, and periportal edema[21]. The main feature is the gallbladder wall thickening or gallbladder fossa edema. On ultrasound (US) imaging, typical findings are a parenchymal echogenicity decreasing with an increase of the portal vein conspicuity (known as "starry sky")[16,22]. Hepatitis on Multi-detectors CT (MDCT) or MRI appears as liver attenuation decreasing or diffuse hyper-intensity in T2-weigthed (T2-W) scans, with heterogeneous enhancement during the contrast phase. Severe cholestatic hepatitis on MR cholangiopancreatography (MRCP) can appear as a decreasing of the tertiary bile ducts number[16,21-23].

Chemotherapy-Induced Focal Steatosis/ Steatohepatitis

Liver steatosis is due to lipids accumulation. Fatty accumulation may be typical when the hepatic fat content surpasses the 5% of the liver wet weight and the steatosis severity is measured as a percentage of fatty hepatocytes, compared to the total hepatocytes seen[19,24,25]. Hepatic steatosis could be steatohepatitis, as long as there is ballooning of hepatocytes, lobular inflammation, or degeneration of hepatocytes. Both 5-fluorouracil and irinotecan have been shown to determine steatosis, probably through an oxidative stress-mediated injury[26]. In literature many cases of steatosis have been reported (Figure 2) in patients treated with bevacizumab, alone or in combination with other agents[24-26]. Liver steatosis decreases the difference in contrast between hepatic parenchyma and lesions, influencing the assessment of hepatic metastasis[3]. Chemotherapy- induced steatohepatitis (called as CASH) may limit hepatic reserve for regeneration and place patients, who subsequently undergo resection of hepatic metastases, at risk for postoperative hepatic failure[26,27]. Although examining pathologic specimens can only distinguish the two histologic subtypes of steatosis, development of fatty changes on imaging studies

is an important observation to report[3]. In fact, the presence of a diffuse and severe fatty liver (Figure 3) should suggest alternative therapeutic approaches, including more minimally invasive therapies[26,27]. Radiologist should identify steatosis in asymptomatic patients, severity, and should exclude other causes of liver aminotransferases increasing. Imaging diagnosis of steatosis/steatohepatitis is relatively easy. On ultrasound, hepatic steatosis/steatohepatitis appears as diffuse or focal increased echogenicity. Focal fat deposition or sparing may simulate hepatic metastases, but can be differentiate by its location, shape, and mass effect absence on vasculature. On unenhanced MDCT, a reduced hepatic-to splenic attenuation ratio confirms the presence of fat deposition, while an increased cranio-caudal liver diameter and an increased caudate-to-right lobe ratio are findings of steatohepatitis. Focal steatosis could mimic metastasis. However, MRI is a problem solving, confirming the diagnosis because steatosis appears as signal loss on opposed-phase T1-W scans, respect to in-phase scans. By contrast, there is no signal drop on the opposed phase images of metastasis[16,21-23].

Sinusoid Obstructive Syndrome

Sinusoidal obstruction syndrome (SOS), also called veno-occlusive disease (VOD), is due to severe toxic injury of the hepatic sinusoidal endothelial cells (SECs) related to the fibrous material deposition within venule walls and liver sinusoids leading to histological changes varying from sinusoidal dilation to occlusion[19]. SOS has been reported to be significantly more common in patients receiving oxaliplatin before resection than patients receiving no chemotherapy[28]. Macroscopically, the affected liver typically has a bluish-red marbled appearance and therefore, has been called "blue liver syndrome"[29]. Histologically, distinct areas of dilated sinusoids with congestion determined the SOS, which may be associated with liver cell plate atrophy. In severe cases, it can also be associated with perisinusoidal fibrosis, nodular regenerative hyperplasia (NRH) (Figure 4), obstruction of centrilobular veins, and peliotic

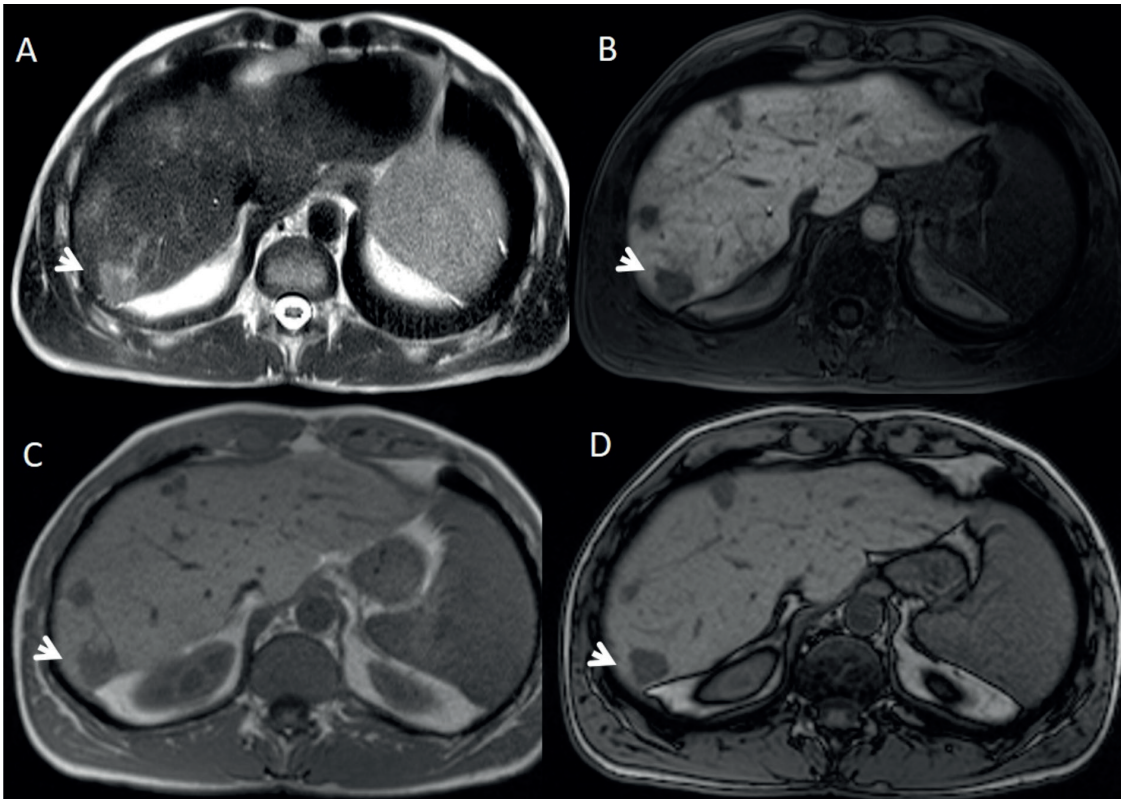

Figure 2. Woman 63 y with rectal cancer. Chemotherapy-induced steatohepatitis that appears as inhomogeneous signal of parenchymal liver in T2-W sequences (**A**), in EOB-T1-W sequence (**B**) and in in (**C**) and out (**D**) phase, in patients with necrotic mCRC (*arrow*).

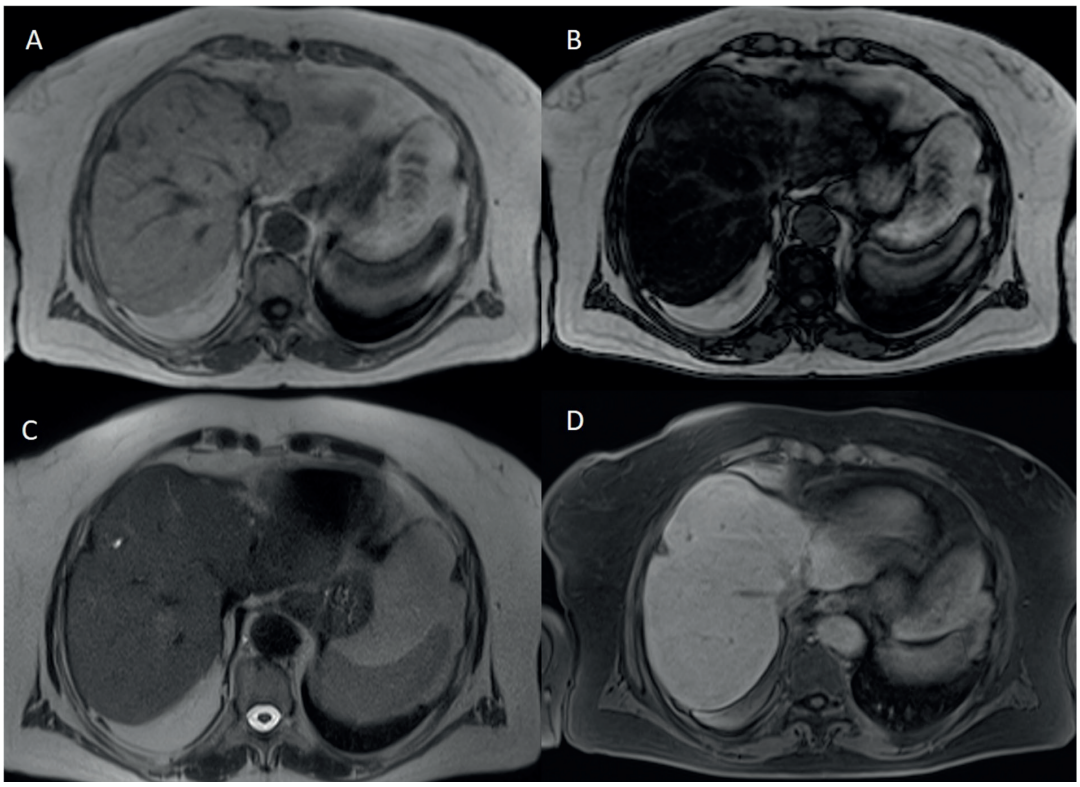

Figure 3. Woman 61 y with colon cancer. In in (**A**)/out (**B**) phase T1-W sequences is evident the severe steatohepatitis of hepatic parenchymal. In T2-W sequence (**C**) is evident the reduced hepatic-to splenic signal ratio and in EOB phase (**D**) the parenchymal signal is lower than we expected with hepatospecific contrast medium.

change (Figure 5). Rubbia-Brandt et al[28] reported SOS in patients undergoing hepatic resection following oxaliplatin treatment. Perisinusoidal injuries, including dilatation and congestion with fibrosis and venous occlusion, were present in 78% of patients[28]. These authors reported a scoring system to grade the histological features from 0 (absent) to 3 (severe). Liver structure pathological changes may cause portal hypertension resulting in the clinical presentation of SOS that includes symptoms, such as hepatomegaly, jaundice, and ascites[28-30]. SOS is correlated to an increase of the postoperative morbidity, since SOS is linked to the increase of the risk for intraoperative blood loss and the need for perioperative transfusions[30-35]. Moreover, recent researchers[36,37] have proven a defensive effect of bevacizumab with regard to the SOS development. Considering the need to conserve liver regenerative capacity following hepatectomy, the reduction of the SOS effect is very essential for surgical practicability and postoperative outcome. Ribero et al[37] observed that bevacizumab in combination to oxaliplatin in mCRC increased neoadjuvant chemotherapy pathologic response and shown a protective effect against the SOS development. To date, the bevacizumab protection against SOS effect is not adequately understood. Sinusoidal obstruction syndrome appears on imaging with various degrees of portal hypertension, hepatosplenomegaly, recanalization of paraumbilical vein, ascites, gallbladder wall thickening, and portal vein thrombosis (Figure 6)[21-23]. The radiologist should report the presence of SOS in the radiological report to guide a proper patient's management. MDCT and US findings of hepatic SOS includes hepatosplenomegaly, ascites, gallbladder wall thickening, periesophageal varices, and recanalization of umbilical veins. On Doppler ultrasound, decreased flow in the portal vein can be noted. During dynamic studies, "post-oxaliplatin heterogeneity of liver parenchyma" presenting as diffuse and heterogeneous hypo-attenuation of the hepatic parenchyma on contrast-enhanced MDCT is frequently observed in patients who underwent oxaliplatin based chemotherapy, and is

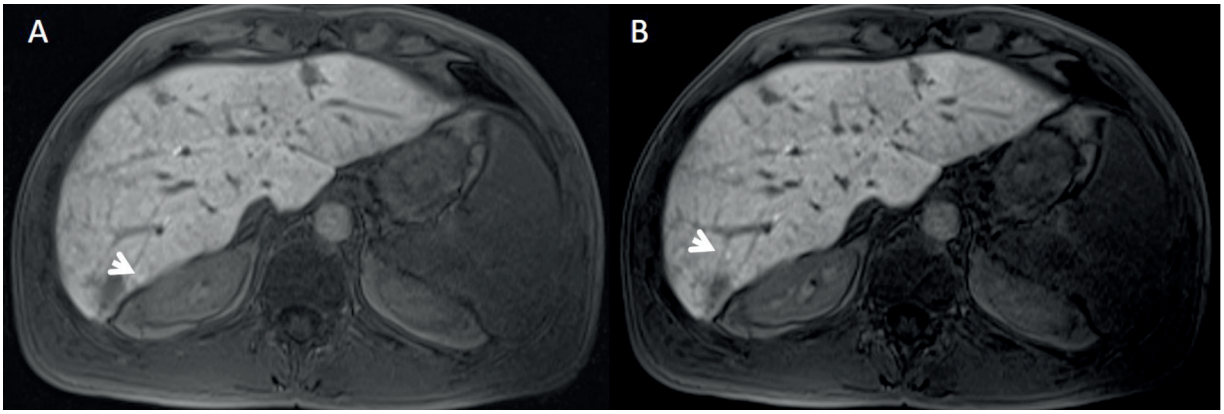

Figure 4. Man 57 y with colon cancer. SOS syndrome. The signal of hepatic parenchymal appears inhomogeneous during hepatospecific phase of contrast study (**A,** VIBE T1-W sequence; flip angle 10; **B,** VIBE T1-W sequence, flip angle 30). The arrow shows little nodule FNH like.

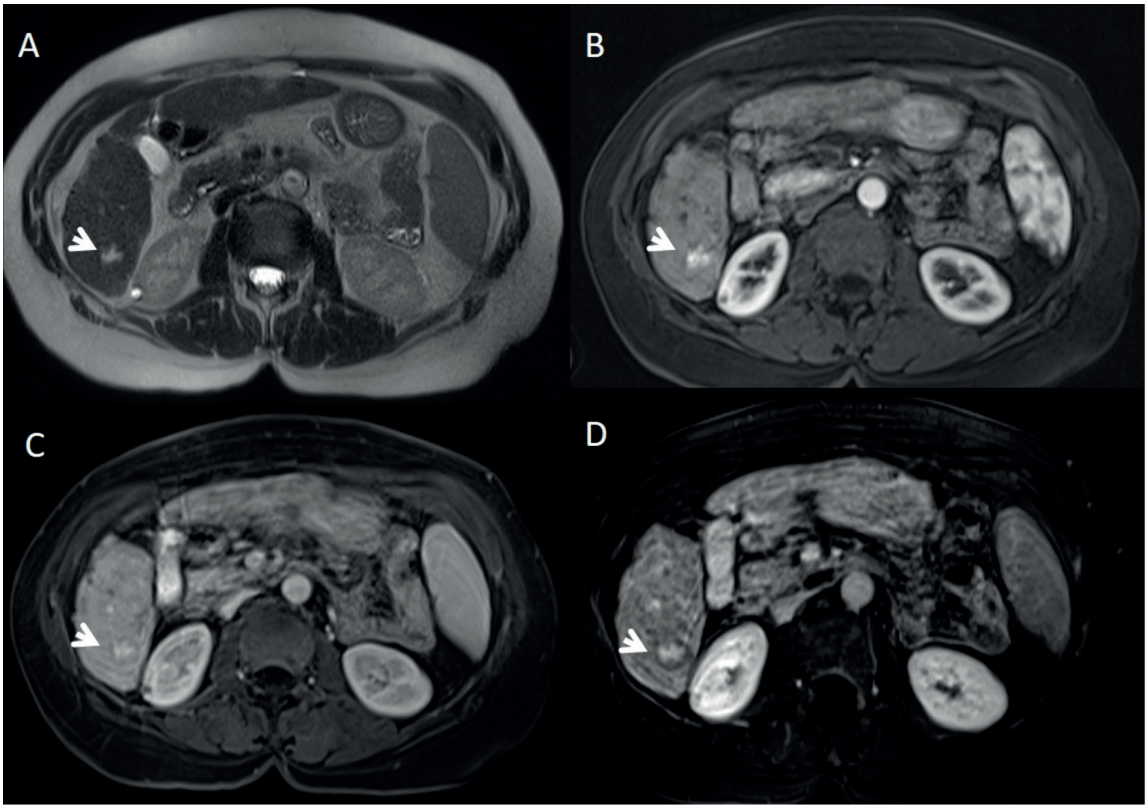

Figure 5. Woman 58 y with rectal cancer. Pseudo-cirrhosis. The arrow shows peliotic change in T2-W (**A**), during arterial (**B**), portal (**C**), and EOB (**D**) phase of contrast study.

predominantly located at the peripheral area and right hepatic lobe. This finding is also reported in MR contrast studies. Heterogeneous reticular pattern is found in the non-tumor parenchyma on hepatobiliary phase (HBP) MRI of the liver using liver-specific contrast agents gadoxetate disodium (Eovist or Primovist; Bayer Healthcare, Berlin, Germany) (Figure 7). The following action mechanisms are suggested: obstruction and high pressure in the sinusoid modify the hepatic blood flow and damage hepatocytes, which results in the low reticular signal intensity on HBP imaging

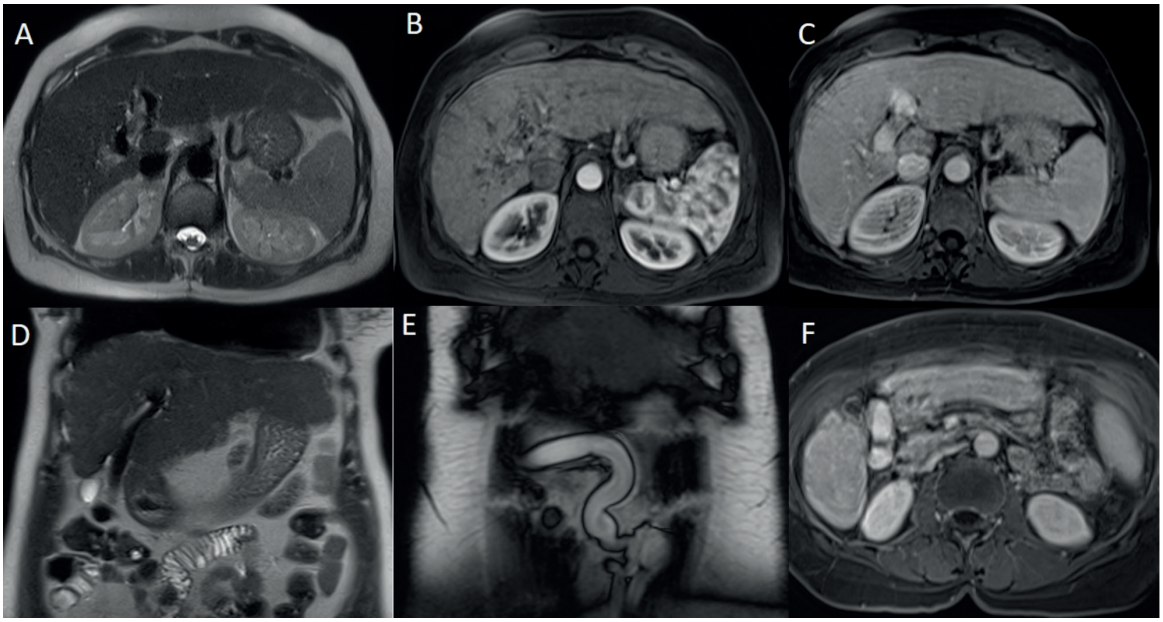

Figure 6. The same case of 5. Portal vein thrombosis (**A**-**B**, and **C**) and recanalization of paraumbilical vein (**D**-**E**, and **F**).

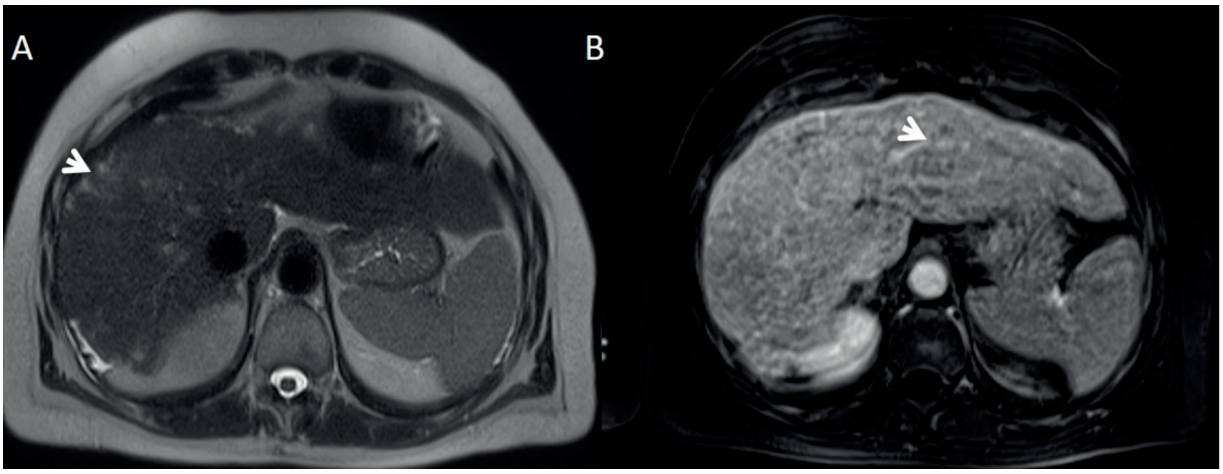

Figure 7. Man 73 y with rectal cancer. Heterogeneous reticular pattern in the non-tumor parenchyma (*arrow*) on T2-W sequence (**A**) and more evident in hepatobiliary phase (**B**) of contrast study.

due to disturbed uptake of gadoxetate disodium into the dysfunctional hepatocytes and modified portal flow. Until now, few cases of chemotherapy-induced focal hepatopathies mimicking a metastatic tumor on imaging are reported[17,38,39]. Granata el al[17] reported multiple lesions in a patient with history of rectal cancer (Figure 8). On US imaging, the lesions showed isoechoic or hypoechoic heterogeneity. On MDCT portal phase, some lesions showed isodense aspect while other lesions had hypodense signal. On MRI scan performed using hepatospecific CM, some lesions showed hyper-intense signal on T2-W images and hypo-intense signal on T1-W images. During arterial phase, the authors found hyper-vascular lesions that in the portal and transitional phase became isointense or hypo-intense. During the hepatobiliary phase, the lesions accumulated the CM, with consequential isointense signal with a hyper-intense rim or hyper-intense signal[17].

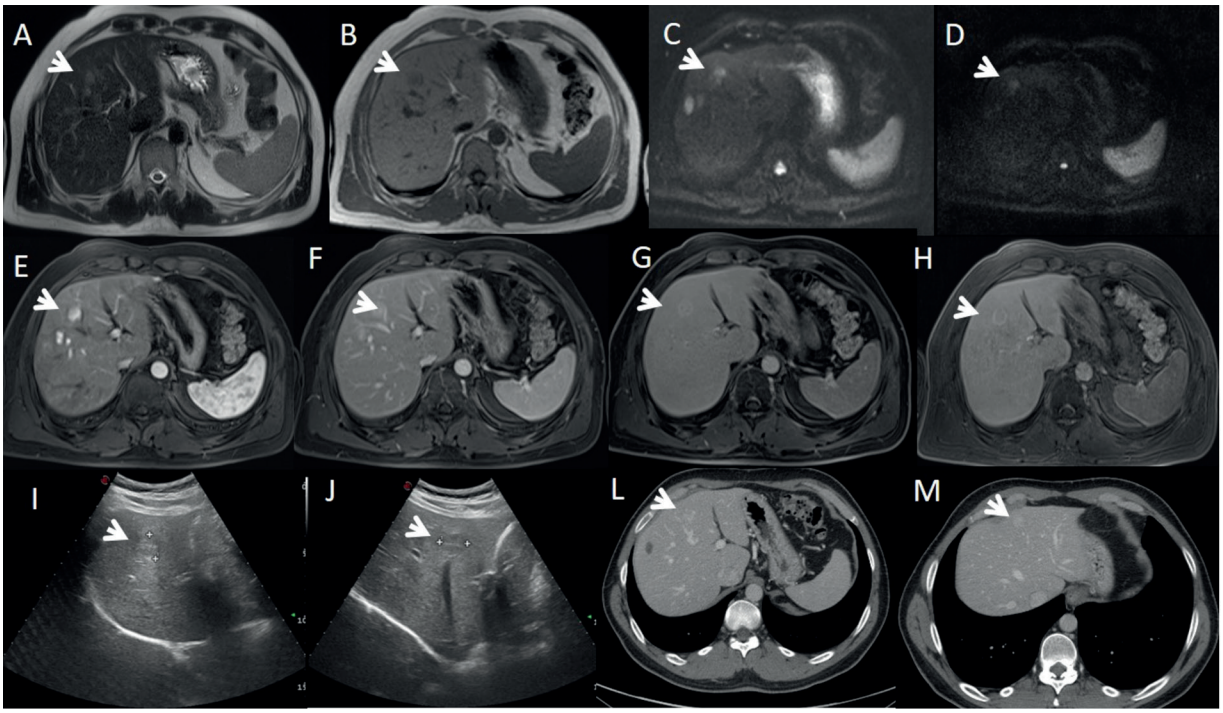

Figure 8. 42-year-old male with history of rectal cancer. Oxaliplatin-induced lesions. Liver lesions appear hyperintense (*arrow*) on T2 W sequence (**A**) hypointense (*arrow*) on T1-W in-of-phase sequence (**B**), with restricted diffusion (*arrow*) on b 50 s/mm^2 (**C**) and b800 s/mm^2 (**D**). During contrast study the lesions show hyperintense signal (*arrow*) on arterial phase (**E**) and portal phase (**F**), isointense signal with hyperintense peripheral rim (arrow) on transitional (**G**) and EOB phase (**H**). US (**I** and **J**) show solid, isoechoic to hypoechoic lesions (*arrow*). In (**L-M**) CT scan on portal phase of dynamic study: the lesion is hyperdense or isodense with hyperdense peripheral rim (*arrow*).

Conclusions

Hepatic resection is the standard care of patients with mCRC. Some features should be considered when a liver resection is planned, such as the number of hepatic segments involved, the proximity of the lesions to vascular and biliary structures, the amount of residual liver after the resection, and the parenchymal injury secondary to hepatotoxic chemotherapy. Therefore, there are a number of chemotherapy-effects that should be assessed with liver imaging since they have an influence on surgical morbidity. The chemotherapy-related complications, steatosis, CASH and SOS might impair the hepatic parenchyma, thus reducing the functionality and influencing the outcome following resection. The radiologist's role should extend beyond just reporting the data of metastases, providing additional information that may greatly improve patient care. Radiologists should assess both the effects of chemotherapy on the hepatic metastasis itself, as well as the chemo-induced focal and diffuse modifications of non-tumor hepatic parenchyma, since it is important to avoid impaired hepatic function after hepatic resection. The most efficient means to communicate these diagnostic details to the multidisciplinary team for radiologist is to include them in their radiological report.

Conflict of Interests

The Authors declare that they have no conflict of interests.

Research Involving Human Participants and/or Animals

No human participants and/or animals were involved.

References

1) World Health Organization. Cancer. http://www.who.int/mediacentre/factsheets/fs297/en/. Accessed September 2, 2017.
2) Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D'Hoore A,

Diaz-Rubio E, Douillard JY, Ducreux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hoff P, Köhne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Österlund P, Oyen WJ, Papamichael D, Pentheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmoll HJ, Tabernero J, Taïeb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold D. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016; 27: 1386-1422.

3) Granata V, Fusco R, Avallone A, Catalano O, Piccirillo M, Palaia R, Nasti G, Petrillo A, Izzo F. A radiologist's point of view in the presurgical and intraoperative setting of colorectal liver metastases. Future Oncol 2018; 14: 2189-2206.

4) Izzo F, Palaia R, Albino V, Amore A, di Giacomo R, Piccirillo M, Leongito M, Nasto A, Granata V, Petrillo A, Lastoria S. Hepatocellular carcinoma and liver metastases: clinical data on a new dual-lumen catheter kit for surgical sealant infusion to prevent perihepatic bleeding and dissemination of cancer cells following biopsy and loco-regional treatments. Infect Agent Cancer 2015; 10: 11.

5) Izzo F, Piccirillo M, Palaia R, Albino V, Di Giacomo R, Mastro AA. Management of colorectal liver metastases in patients with peritoneal carcinomatosis. J Surg Oncol 2009; 100: 345-347.

6) Scaife CL, Curley SA, Izzo F, Marra P, Delrio P, Daniele B, Cremona F, Gershenwald JE, Chase JL, Lozano RD, Patt YZ, Fornage BD, Vauthey JN, Woodall ML, Gonzalez KB, Ellis LM. Feasibility of adjuvant hepatic arterial infusion of chemotherapy after radiofrequency ablation with or without resection in patients with hepatic metastases from colorectal cancer. Ann Surg Oncol 2003; 10: 348-354.

7) Fanotto V, Ongaro E, Rihawi K, Avallone A, Silvestris N, Fornaro L, Vasile E, Antonuzzo L, Leone F, Rosati G, Giuliani F, Bordonaro R, Scartozzi M, De Maglio G, Negri FV, Fasola G, Aprile G. HER-2 inhibition in gastric and colorectal cancers: tangible achievements, novel acquisitions and future perspectives. Oncotarget 2016; 7: 69060-69074.

8) Rosati G, Cordio S, Aprile G, Butera A, Avallone A, Di Lucca G, De Pauli F, Parra HS, Reggiardo G, Bordonaro R. Discontinuation of bevacizumab and FOLFIRI administered up to a maximum of 12 cycles as first-line therapy for metastatic colorectal cancer: a retrospective Italian study. Invest New Drugs 2012; 30: 1978-1983.

9) de Graaf W, van Lienden KP, van Gulik TM, Bennink RJ. (99m)Tc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. J Nucl Med 2010; 51: 229-236.

10) de Graaf W, van Lienden KP, Dinant S, Roelofs JJ, Busch OR, Gouma DJ, Bennink RJ, van Gulik TM. Assessment of future remnant liver function using hepatobiliary scintigraphy in patients undergoing major liver resection. J Gastrointest Surg 2010; 14: 369-378.

11) Cieslak KP, Huisman F, Bais T, Bennink RJ, van Lienden KP, Verheij J, Besselink MG, Busch ORC, van Gulik TM. Future remnant liver function as predictive factor for the hypertrophy response after portal vein embolization. Surgery 2017; 162: 37-47.

12) Tamada T, Ito K, Higaki A, Yoshida K, Kanki A, Sato T, Higashi H, Sone T. Gd-EOB-DTPA-enhanced MR imaging: evaluation of hepatic enhancement effects in normal and cirrhotic livers. Eur J Radiol 2011; 80: 311-316.

13) Motosugi U, Ichikawa T, Oguri M, Sano K, Sou H, Muhi A, Matsuda M, Fujii H, Enomoto N, Araki T. Staging liver fibrosis by using liver-enhancement ratio of gadoxetic acid-enhanced MR imaging: comparison with aspartate aminotransferase-to-platelet ratio index. Magn Reson Imaging 2011; 29: 1047-1052.

14) Utsunomiya T, Shimada M, Hanaoka J, Kanamoto M, Ikemoto T, Morine Y, Imura S, Harada M. Possible utility of MRI using Gd-EOB-DTPA for estimating liver functional reserve. J Gastroenterol 2012; 47: 470-476.

15) Azad A, Chang P, Devuni D, Bichoupan K, Kesar V, Branch AD, Oh WK, Galsky MD, Ahmad J, Odin JA. Real world experience of drug induced liver injury in patients undergoing chemotherapy. J Clin Gastroenterol Hepatol 2018; 2: pii: 18.

16) Alessandrino F, Tirumani SH, Krajewski KM, Shinagare AB, Jagannathan JP, Ramaiya NH, Di Salvo DN. Imaging of hepatic toxicity of systemic therapy in a tertiary cancer centre: chemotherapy, haematopoietic stem cell transplantation, molecular targeted therapies, and immune checkpoint inhibitors. Clin Radiol 2017; 72: 521-533.

17) Granata V, Fusco R Md, Catalano O, Filice S, Avallone A, Piccirillo M, Leongito M, Palaia R, Grassi R, Izzo F, Petrillo A. Uncommon neoplasms of the biliary tract: radiological findings. Br J Radiol 2017; 90: 20160561.

18) Dhanasekaran R, Kwo PY. The liver in oncology. Clin Liver Dis 2017; 2: 697-707.

19) Moreno Prats M, Sasatomi E, Stevenson HL. Colorectal liver metastases: a pathologist's guide to creating an informative report and improving patient care. Arch Pathol Lab Med 2019; 143: 251-257.

20) Duwe G, Knitter S, Pesthy S, Beierle AS, Bahra M, Schmelzle M, Schmuck RB, Lohneis P, Raschzok N, Öllinger R, Sinn M, Struecker B, Sauer IM, Pratschke J, Andreou A. Hepatotoxicity following systemic therapy for colorectal liver metastases and the impact of chemotherapy-associated liver injury on outcomes after curative liver resection. Eur J Surg Oncol 2017; 43: 1668-1681.

21) Torrisi JM, Schwartz LH, Gollub MJ, Ginsberg MS, Bosl GJ, Hricak H. CT findings of chemotherapy-induced toxicity: what radiologists need to know about the clinical and radiologic manifestations of chemotherapy toxicity. Radiology 2011; 258: 41-56.

22) Alessandrino F, Krajewski KM, Tirumani SH, Braschi-Amirfarzan M, Jagannathan JP, Ramaiya NH, Di Salvo DN. Biliary and pancreatic complications of

molecular targeted therapies in cancer imaging. Abdom Radiol (NY) 2017; 42: 1721-1733.

23) Shanbhogue AK, Virmani V, Vikram R, Prasad SR, Shanbhogue DK, Nagar A, Fasih N. Spectrum of medication-induced complications in the abdomen: role of cross-sectional imaging. AJR Am J Roentgenol 2011; 197: W286-W294.

24) Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002; 346: 1221-1231.

25) Kooby DA, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS, DeMatteo RP, D'Angelica M, Blumgart LH, Jarnagin WR. Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg 2003; 7: 1034-1044.

26) Adam R, De Gramont A, Figueras J, Guthrie A, Kokudo N, Kunstlinger F, Loyer E, Poston G, Rougier P, Rubbia-Brandt L, Sobrero A, Tabernero J, Teh C, Van Cutsem E; Jean-Nicolas Vauthey of the EGOSLIM (Expert Group on OncoSurgery management of Liver Metastases) group. The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. Oncologist 2012; 17: 1225-1239.

27) Khan AZ, Morris-Stiff G, Makuuchi M. Patterns of chemotherapy-induced hepatic injury and their implications for patients undergoing liver resection for colorectal liver metastases. J Hepatobiliary Pancreat Surg 2009; 16: 137-144.

28) Rubbia-Brandt L, Audard V, Sartoretti P, Roth AD, Brezault C, Le Charpentier M, Dousset B, Morel P, Soubrane O, Chaussade S, Mentha G, Terris B. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004; 15: 460-466.

29) Stevenson HL, Prats MM, Sasatomi E. Chemotherapy-induced Sinusoidal Injury (CSI) score: a novel histologic assessment of chemotherapy-related hepatic sinusoidal injury in patients with colorectal liver metastasis. BMC Cancer 2017; 17: 35.

30) Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B, Rougier P, Nordlinger B. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006; 243: 1-7.

31) Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P, Bechstein WO, Primrose JN, Walpole ET, Finch-Jones M, Jaeck D, Mirza D, Parks RW, Mauer M, Tanis E, Van Cutsem E, Scheithauer W, Gruenberger T; EORTC Gastro-Intestinal Tract Cancer Group; Cancer Research UK; Arbeitsgruppe Lebermetastasen und–tumoren in der Chirurgischen Arbeitsgemeinschaft Onkologie (ALM-CAO); Australasian Gastro-Intestinal Trials Group (AGITG); Fédération Francophone de Cancérologie Digestive (FFCD). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol 2013; 14: 1208-1215.

32) Aloia T, Sebagh M, Plasse M, Karam V, Lévi F, Giacchetti S, Azoulay D, Bismuth H, Castaing D, Adam R. Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases. J Clin Oncol 2006; 24: 4983-4990.

33) Malik HZ, Farid S, Al-Mukthar A, Anthoney A, Toogood GJ, Lodge JP, Prasad KR. A critical appraisal of the role of neoadjuvant chemotherapy for colorectal liver metastases: a case-controlled study. Ann Surg Oncol 2007; 14: 3519-3526.

34) Welsh FK, Tilney HS, Tekkis PP, John TG, Rees M. Safe liver resection following chemotherapy for colorectal metastases is a matter of timing. Br J Cancer 2007; 96: 1037-1042.

35) Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, Dematteo RP, Tuorto S, Wuest D, Blumgart LH, Fong Y. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg 2003; 237: 860-869.

36) Hubert C, Lucidi V, Weerts J, Dili A, Demetter P, Massart B, Komuta M, Navez J, Reding R, Gigot JF, Sempoux C. Impact of biological agents on the prevalence of chemotherapy associated liver injury (CALI): multicentric study of patients operated for colorectal liver metastases. Eur J Surg Oncol 2018; 44: 1532-1538.

37) Ribero D, Wang H, Donadon M, Zorzi D, Thomas MB, Eng C, Chang DZ, Curley SA, Abdalla EK, Ellis LM, Vauthey JN. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer 2007; 110: 2761-2767.

38) Arakawa Y, Shimada M, Utsunomya T, Imura S, Morine Y, Ikemoto T, Hanaoka J, Sugimoto K, Bando Y. Oxaliplatin-related sinusoidal obstruction syndrome mimicking metastatic liver tumors. Hepatol Res 2013; 43: 685-689.

39) Alexandrino H, Oliveira D, Cipriano MA, Ferreira L, Tralhão JG, Castro E Sousa F. Oxaliplatin toxicity presenting as a liver nodule - case report. BMC Cancer 2015; 15: 247..