

R E V I E W

Diagnostic value/performance of radiological liver imaging during chemotherapy for gastrointestinal malignancy: a critical review

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Summary. This article reviews the main toxic effect, complications and relative imaging findings of the liver that may appear during the oncologic follow up among patients affected by gastrointestinal malignancy. Awareness of the causative chemotherapeutic agent and regimens, pathophysiology and relative characteristic imaging findings of hepatic injuries is critical in order to obtain an accurate diagnosis especially when these parenchymal lesions are focal. An accurate synergic radiological diagnosis with Computed Tomography (CT) and Magnetic Resonance (MR) techniques may induce a potential termination of ineffective/toxic chemotherapy during early phases of treatment, changing the therapeutic plan in order to avoid first unnecessary liver biopsy and then invasive treatment as hepatic resection if not required. (www.actabiomedica.it)

Key words: colorectal cancer-chemotherapy-induced focal hepatopathy, steatosis, steatohepatitis, sinusoidal obstruction syndrome, liver MR - hepatobiliary phase-Liver CT

1. Introduction

Nearly one in two men and one in three women in the United States will be affected by cancer during the lifetime (1). Colorectal cancer is the third most common type of cancer diagnosed in men and the second in women. The liver is the most frequent site of colorectal cancer metastases and up to 25% of patients present hepatic metastases at the time of diagnosis of the primary tumour (synchronous); another 25% will develop metachronous ones during the follow up (2) (3-6).

Ultrasonography (US), Magnetic Resonance Imaging (MRI) (7-17) and computed tomography (CT) (18-30) are widely used in the diagnostic setting, with or without the use of contrast agents (23, 31-33), and as guidance in many interventional radiology proce-

dures (34-40). US is the least invasive imaging examination, well tolerated by patients (41-43).

Liver hepatectomy still represents the best curative therapeutic option for patients with colorectal metastases even if it is often preceded by chemotherapy in the preoperative setting (neoadjuvant chemotherapy) because only 15-25% of patients are fit for the curative metastasectomy at the time of presentation (44).

This medical treatment can reduce the size of colorectal liver metastases, downsize the present metastases and may provide to a presumptive treatment of micro metastases (45).

Unfortunately, micro metastases (less than 10 mm) are nearly undetectable using radiological imaging being the major cause of recurrence during follow up. Differentiation of small haemangiomas and cysts

smaller than 1 cm from metastases can be difficult due to volume averaging. The sensitivity of CT for detecting lesions less than 1 cm decreases from 65%-95% to 31%-38% (46, 47).

This article reviews the toxic effect, complications and relative imaging findings of the liver that may appear during the oncologic follow up among patients affected by gastrointestinal malignancy. Radiologists should know that in addition to the desired effects on malignancy, systemic oncological therapy could determine toxic effects whose are often visible first at imaging (48, 49).

2. Background

Any type of drug is able to induce changes in biological function and so to modify cell and organs function.

This modify can be positive or negative/toxic: it depends on concentration, dose and patient's own characteristics determining eventually drug adverse reaction that are predictable in most of cases.

Drug arrive to the target organs by steps. Pharmacokinetics studies processes that follow the administration of the drugs: absorption, metabolism and excretion. Through distribution, drugs arrive to the target organs to make its pharmacological effect (50).

Each of these steps is influenced by drug molecular structure (e.g. lipophilia), physiological characteristic such as pregnancy, age or nutritional state and patient pathologies such as hepatic or kidney's injury, cardiovascular disease or neoplastic ones.

Hepatic metabolism represents a crucial step because in most of cases drugs have to be transformed into more hydrophilic compounds in order to be eliminated easily by kidney and/or liver.

Chemotherapy traditionally includes cytotoxic agents because their own mechanism of action consists in the capacity of induction a cell damage that can be lethal for sensible cells, through a direct damn or interference in the replicative process of the proliferating cells. These agents have low therapeutic index because they're not specific for tumoral cells and they can cause toxicity especially to normal proliferating tissues (e.g. bone marrow).

Unfortunately, solid tumors (like colorectal malignancy) aren't sensible to these types of drugs compared with lymphoma or testis tumor so they should be associated to others in order to improve the therapeutic effect.

Nowadays newer agents such as molecular targeted therapies and immunological agents are available in clinical practice as monotherapy or in combination with each other.

2.1 Chemotherapy for gastrointestinal malignancy

Patients with advanced stage disease could require different types of chemotherapy (preoperative, postoperative or palliative chemotherapy) (51). Preoperative therapy, so called neoadjuvant chemotherapy, offers the potential advantage of eradicating micro metastatic disease preoperatively improving progression free survival especially through innovative associations of agents with the aim to ensure a multimodal treatment for colorectal liver metastases (2). In selected patients, unresectable metastatic disease can be rendered resectable by administering "conversion chemotherapy" in order to downsize the tumor and make possible a surgical resection increasing the number of patients undergoing curative hepatectomy. The duration of both these regimens of chemotherapy should be assessed as short as possible because of the risk of hepatic injury associated (52).

2.1.1 Alchilant agents (*oxaliplatin*)

They have the ability to react with DNA creating irreversible damage and lethal effect to the cell. One of these drugs called oxaliplatin is frequently used in combination with 5-FU/leucovorin or capecitabine for the treatment of gastrointestinal tumors. Toxicity, generally dose dependent, is represented by peripheral neuropathy and impose dose reduction. Oxaliplatin-based chemotherapy regimens (FOLFOX, CapeOX and FLOX) are recommended by NCCN for adjuvant treatment in colorectal cancer patients (8) and as neoadjuvant therapy in combination with 5-FU in patients with colorectal liver metastases.

2.1.2 Antimetabolite agents (*fluorouracil and capecitabine*)

Because of their similitude with physiological

metabolites, fluoropyrimidine such as fluorouracil (5-FU) can interfere with RNA synthesis and function and determine myelotoxicity as adverse reaction. 5-FU is administered intravenously while capecitabine is a prodrug that is converted in the intestine into the active 5-FU and it's given orally (53).

2.1.3 Topoisomerase inhibitor (irinotecan)

Irinotecan reversibly stabilizes the topoisomerase. I complex, blocking DNA synthesis with a double-strand DNA break. This event induces arrest of the cell cycle in the S-G2 phase and ultimately cause cell death (53).

2.1.4 Target therapy (bevacizumab)

Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) in the circulation and inhibits its connection to the receptor VEGFR. This complex prevents new vessel formation, reduces capillary leak and normalizes tumour vasculature (54).

3. Hepatic adverse injuries

Chemotherapy induces many undesirable effects against the hepatic parenchyma that may reduce and/or make difficult the detection of the hepatic tumor burden in patients with liver metastases. As patients with metastatic tumors undergo chemotherapy with curative intent with increasing frequency, it is mandatory therefore to understand the pathophysiology of these therapy-induced liver injury in order to be familiar with their imaging features .

3.1 Sinusoidal obstruction syndrome (SOS): pathophysiology and imaging features

Rubbia et al. observed that the neoadjuvant administration of oxaliplatin in patients with colorectal liver metastases was a risk factor for the development of a specific liver injury called sinusoidal obstruction syndrome (55, 56). Bevacizumab seems to have a protective effect against oxaliplatin-related sinusoidal lesions(57). This sinusoidal injury occurred for 19–52% of patients treated by oxaliplatin-based chemotherapy

(58–61). Patients could present abdominal pain, swelling, and weight gain, with or without elevation in serum enzyme levels (62).

SOS includes several pathologic conditions such as sinusoidal dilatation, peliosis, and nodular regenerative hyperplasia.

The major component initiating SOS seems to be the depolymerization of the F-actin and the increased expression of matrix metalloproteinase-9 in sinusoidal endothelial cells.

The sinusoidal wall integrity is then disrupted causing red blood cells migration into the space of Disse and deposition of collagens determining respectively peliosis and perisinusoidal fibrosis (63–66). Furthermore, the obstruction and increased pressure in the sinusoid determine presence of atrophic hepatocytes and also enlarged ones forming nodular regenerative hyperplasia (67). The discover and relative diagnosis of SOS could be important clinically for at least three reasons. First it is associated with an increased risk of morbidity after liver resection and bleeding. Particularly SOS has been associated with an increased risk for intraoperative blood transfusions, early recurrence after resection and a short overall survival after resection due to liver insufficiency (60, 68). Recently another interesting reported side effect is the development of liver nodules mimicking liver metastases (69, 70) misinterpreted as hepatic metastasis (71). Finally radiologists have to consider the development of oxaliplatin-induced SOS to avoid mistaking new-onset ascites for evidence of recurrent disease (72).

However, US findings include ascites, gallbladder wall thickening, and hepatosplenomegaly. Doppler US may show decreased flow in the portal vein (73). Common signs of a new-onset portal hypertension on CT examination could appear, including ascites, splenomegaly, periesophageal varices, and recanalization of the umbilical vein. Increased volume of the spleen has been reported to suggest sinusoidal injury(74–76); however, increased spleen size indicates portal hypertension and it is not specific for SOS(77). Han et al. reported that post-oxaliplatin “heterogeneity” of liver parenchyma, appearing as diffuse and heterogeneous hypoattenuation of the hepatic parenchyma on contrast-enhanced CT, is frequently observed in patients treated with oxaliplatin (45, 77). These findings are

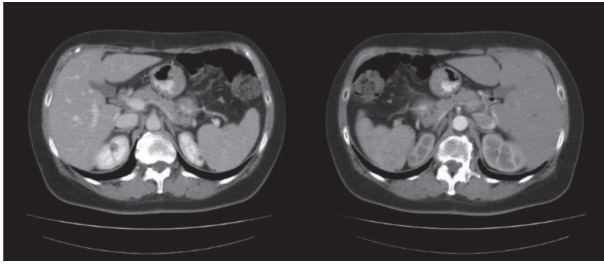


Figure 1. 55-year old woman affected by left colon adenocarcinoma who undergoes to left hemicolectomy. We may observe in this preoperative CT diffuse low attenuation of the liver

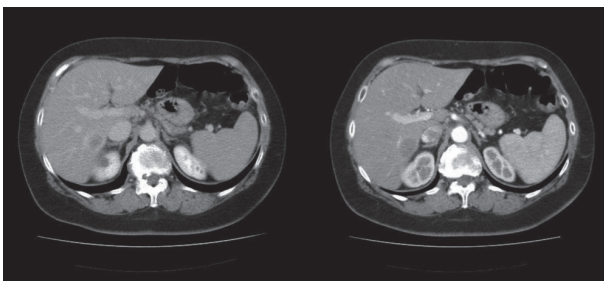


Figure 2. After the surgical resection of the primary tumor, the histological staging is pT3N1M1 for the presence, in the first post-operative CT, of a nodular hypodense lesion surrounded by rim enhancement with the appearance of a colorectal liver metastases

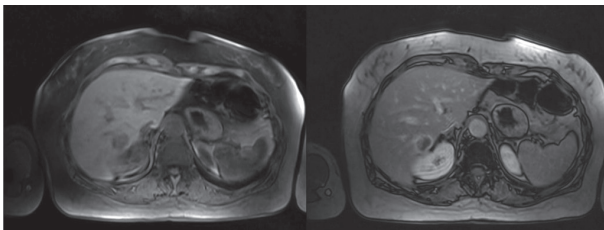


Figure 3. MR dynamic imaging confirms CT diagnosis of a colorectal metastase. This lesion is hypointense in T1w images before and after administration of contrast agent compared to the surrounding liver

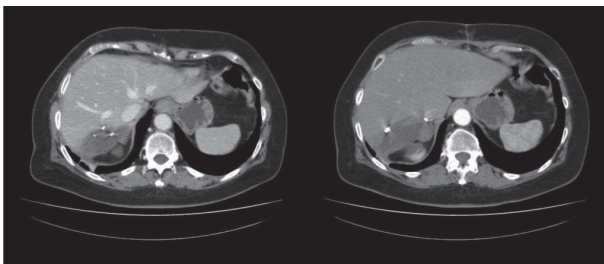


Figure 4. After a six-cycles-Folfox neoadjuvant regimen, these CT post-operative imaging shows common findings after surgical resection. The hepatic malignant lesion is conformed with the addition of “blue liver” as chemotherapeutic liver adverse reaction

especially observed at the peripheral area and right hepatic lobe. At MR, diffused SOS is detectable by T2-weighted images showing a heterogeneous liver with areas of increased signal intensity corresponding to edema (47). Heterogeneous reticular pattern are also found in the hepatic parenchyma on hepatobiliary phase (HBP) MRI of the liver using gadoxetate disodium (78, 79). However morphological imaging modalities, such as CT or US, are not enough suitable for the diagnosis of a pseudotumor caused by SOS (80). Focally lesions of SOS show an ill-defined margin (considered as the most valuable feature), non-spherical shape, isointensity on T1-weighted images, iso or hyper-signal intensity on T2-weighted images, unlike of a metastatic nodule. Gd-EOB MRI nevertheless displays a defect in the hepatocyte phase, similar to imaging findings of colorectal liver metastasis (47). Therefore, diffusion-weighted MRI, may be fundamental because the cellular density is higher in cancer than in pseudotumor (81).

3.2 Focal nodular hyperplasia-like lesions

Chemotherapeutic regimens with OXP may lead to the appearance of focal nodule hyperplasia (FNH) like lesions. It is very important to differentiate this type of pseudo metastases from the real ones during follow-up. This kind of diagnosis seems to be more suitable with MR images. Commonly FNH-like lesions appear as solitary or multiple nodular and well demarcated peripherally located liver lesions exhibiting significant contrast enhancement on hepatobiliary phase (77).

Images similarly to FNH ones, representing a benign hyperplasia of the hepatic parenchyma, may be linked to a vascular injury with increased arterial perfusion in areas with absent portal blood flow (77). In these lesions' overexpression of OATP8 that is the uptake transporter of gadoxetic acid may be due to increased hepatocyte function to compensate diffuse liver injury (82, 83).

3.3 Pseudocirrhosis: pathophysiology and imaging features

Pseudocirrhosis describes diffuse and heterogenic hepatic parenchyma due to the contemporary presence

of capsular retraction and nodular regenerative hyperplasia. This setting is however more common in patients undergoing chemotherapy for breast cancer (up to 50%) of patients (84-87). CT imaging shows first initial loss of the normal convex edge of the liver, with the presence of metastases followed by capsular retraction. It is very important to discontinue therapy in order to avoid progression in fibrosis, especially when this structural liver morphological change becomes severe with the occurrence of ascites, varices and splenomegaly, similar to true cirrhosis signs of portal hypertension. A recent case report shows the singular diagnosis of esophageal varices without liver dysfunction, after 3.5-year follow-up of the oxaliplatin-based chemotherapy (88).

3.4 Portal vein thrombosis

Portal vein branch thrombosis may appear after chemotherapy regimens with 5-FU and irinotecan (FOLFIRI) and bevacizumab (89, 90). The latter binds to the VEGF receptor and decreases the healing capacity of endothelial cells, determining bleeding and thrombosis. The mechanism by which irinotecan may determine thrombosis is not known. Patients with portal vein thrombosis are usually asymptomatic so the first diagnosis is often reached by imaging. Portal vein thrombosis is seen as a filling defect in the portal vein branch. In the arterial phase this wedge-shaped area shows increased enhancement that becomes isoattenuating compared to the liver in the further phases (90).

3.5 Steatosis and steatohepatitis: pathophysiology and imaging features

Many studies show that some chemotherapeutic agents, such as 5-FU and irinotecan, may determine chemotherapy-induced steatosis (51). The form of nonalcoholic steatohepatitis linked to chemotherapy is called chemotherapy-associated steatohepatitis (CASH) (91). The frequency of this occurrence is unknown (65, 92, 93). The combination of irinotecan and 5-fluorouracil (FOLFIRI) should be used carefully therefore in patients who are predisposed to fatty liver, mainly for those who can be eligible for liver resection. Hepatic steatosis increases morbidity after liver

resection and the presence of steatohepatitis has been associated with a higher 90-day mortality rate (93, 94). It is difficult to distinguish between steatosis and steatohepatitis through imaging features. However hepatic steatosis is characterized by deposition of lipid vesicles in hepatocytes while steatohepatitis is marked by ballooning of hepatocytes, lobular inflammation, or degeneration of hepatocytes (95). At imaging, steatosis can be focal or diffuse. At ultrasonography (US), the hepatic parenchyma shows increased echogenicity while at CT low attenuation compared to the spleen (at least 10 HU at unenhanced CT) (90). At MR imaging with in-phase and out-of-phase gradient-echo sequences, the presence of signal loss (dropout) on out-of-phase images when compared with in-phase images confirms the presence of steatosis. The pattern of fatty deposition may be also focal mimicking metastases. However, in this case MRI allows to obtain a more reliable diagnosis because unlike steatosis there is no signal drop on the opposed phase in the images of metastasis (95). According to Unal et al., focal steatosis liver parenchyma may show decreased hepatocyte function and signal on MRI Gd-EOB-DTPA-enhanced liver while fat spared areas may demonstrate compensatory increased hepatocyte function on the same phase similarly to FNH-like lesions. Anyway, in the latter case diagnosis could be easily reached with T1w in- and out-of-phase (77)

4. Discussion

Follow up in oncology represents the period of time that starts after the first treatment with a curative intent. Follow up for colorectal cancer has become much longer because of the increased median overall survival of these patients due principally to the improving efficacy of modern chemotherapeutic regimens (96).

The current concept of multidisciplinary treatment and management of patient affected by colorectal malignancy has been decisive to reach optimal outcomes.

In this team, radiologists must be aware of their crucial role. Mainly during chemotherapy, imaging diagnosis is necessary to evaluate:

- treatment response;
- detection of metastases and recurrence;

- restaging of the malignancy.

CT is currently the most commonly used first-line imaging modality for oncologic monitoring because of its wide availability and reproducibility (97). CT, is also a valuable diagnostic tool for the diagnosis and the guidance of interventional procedures in a wide range of organs and in the in gastrointestinal systems (98-103).

Regarding treatment response during follow up, the effects of conventional chemotherapeutic agents are assessed generally after three to four cycles of chemotherapy (after about 1 to 2 months into the therapy) and changes in lesion sizes, as classified according to Response Evaluation Criteria in Solid Tumor (RECIST) are used to planning further decision (104, 105). However, it is already known that new imaging criteria are needed to better characterize tumor response actually. Hepatic lesions, when treated through regimens with molecularly targeted therapeutic agents, may be responding to treatment even without change in size .

Regarding the detection of metastases (hepatic tumor burden) , we should remember indeed the effect of chemotherapy first on the hepatic metastases itself and then on the surrounding liver parenchymal.

Han et al demonstrated a correlation between treatment response of colorectal liver metastases and SOS in patient who have undergone oxaliplatin-based chemotherapy: the more severe is SOS, evaluated by CT parenchymal heterogeneity, the worse the tumor response is expected to be (45).

Hepatic hypoperfusion due to sinusoidal obstruction syndrome might induce hepatic hypoxia, reducing the response to chemotherapy and increasing instead the invasiveness of the tumor in the surrounding stroma (106).

Until now, in a patient with a story of gastrointestinal malignancy, radiologists have considered the appearance of each new hepatic nodule first as a new metastatic lesion (51). This possible setting could indicate progression disease and change in therapeutic planning. It is important to recognize therefore parenchymal changes due to systemic therapy in order to make differential diagnosis especially from metastases when these structural changes are focal (pseudo metastases) (96).

During follow up with CT examination it might be possible to discover new indeterminate hepatic lesion or diffuse changes in the hepatic parenchyma that make difficult the detection of malignancy. Radiologists should be aware of the possibility that a new developing liver lesion is not always a new metastasis.

Multi-detector row CT represents the modality of choice for oncologic surveillance thanks to its availability and efficiency (23, 97, 107, 108); nowadays, for the complexity of the questions that radiologists have to answer, morphological CT study should be more often associated with other emerging functional and molecular imaging techniques.

CT perfusion parameters for example seems to predict properly the presence and extent of tumor vessels (109-112). Even if CT perfusion is a technique actually available mainly in research studies, it should be considered in future to improve earlier detection of liver malignancies and more individualized monitoring of patients during treatment, especially for molecular targeted therapies that act on on tumor perfusion.

In order to assess a better diagnosis and to quantify properly the hepatic tumor burden, liver dynamic MR examination with DWI/ADC (113) and contrast-hepatobiliary phase should be recommended. Multi-detector CT has a specificity of 67% in characterizing lesions as benign or malignant, compared with 81% for MR imaging (47). The use of heavily T2-weighted images may help differentiate solid malignant lesions from hemangiomas and cysts (46).

Furthermore hepatocyte-specific contrast-enhanced MR imaging detects more metastatic lesions than does conventional MR imaging and should be used particularly for the follow-up of metastases after systemic or liver-directed therapies (114). Hepatic metastases typically appear hypointense relative to the surrounding liver parenchyma on delayed images, whereas "pseudo metastases" lesions such as focal nodular hyperplasia are visible as iso- or hyperintense. DW imaging helps the detection of small lesions and apparent diffusion coefficient (ADC) values can be useful to estimate diffusion restriction, differentiating metastatic lesions whose show high-signal-intensity with low ADC values (46, 114). Multiparametric MR examination seems to be necessary also for the pre-operative planning after neoadjuvant chemotherapy

regimens with the aim to obtain the most reliable re-staging of the hepatic tumor burden. Systemic chemotherapy in the preoperative setting improves the potential benefit of surgery (115, 116) and this downsizing therapy represent the major reason for the yearly increase in the number of liver resections for colorectal liver metastases (44). Nowadays surgeons estimate that future liver remnant volume after hepatectomy can be as low as 20% if there is no evidence of injury in the remaining liver tissue (117). MR should be recommended therefore also to estimate the quality of the future remnant parenchyma.

MR pre-operative imaging features should be accurately considered because after curative resection in the context of liver surgery, chemotherapy-induced liver injury could increase the risks of intra- and postoperative complications and postoperative liver insufficiency (118). Preoperative diagnosis of these hepatic injuries seems to be important in order to choose the optimal timing for hepatic resection. Karoui et al. demonstrated that morbidity after liver resection was associated with the number of preoperative chemotherapy cycles: patients who received more than 6 cycles of chemotherapy increased morbidity (61). Another issue to consider is that the time interval between cessation of last chemotherapy predicts the possibility to have post-operative liver failure: an interval of less than four weeks was associated with more complications (59, 119).

The desirable aim would be avoiding liver needle biopsy as much as possible because of its invasive nature of carries inherent risks such as infection, requiring local anesthesia or patient sedation (104). In addition, biopsies can potentially stimulate neoangiogenesis by damaging tumor tissue and increase metastatic risk by increasing the number of circulating tumor cells (120).

5. Conclusion

It seems to be necessary to establish common standard radiological findings criteria first to recognize and assess chemotherapy liver adverse injuries (121-125) with the aim to achieve early and accurate diagnosis, especially when these parenchymal lesions are focal. An accurate synergic radiological diagnosis with CT and MR techniques may induce a potential termi-

nation of ineffective/toxic chemotherapy during early phases of treatment, changing the therapeutic plan in order to avoid first unnecessary liver biopsy and then invasive treatment as hepatic resection if not required. A more personalized approach of cancer treatment would be desirable by assessment of CT/MR imaging biomarker determining treatment response where the aim is to demonstrate that drugs may have an effect on tumor biology.

Conflict of interest: None to declare

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Received: 26 March 2019

Accepted: 4 April 2019

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