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Complications of loco-regional therapy in the liver—spectrum of imaging findings by CT and MRI

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Abstract

The aim of this study was to discuss the appearance of common complications from loco-regional therapy of primary and secondary malignant liver neoplasms on cross-sectional imaging. Knowledge of common complications is important for the safe performance of loco-regional therapy (LRT) and for the interpretation of post-LRT follow-up imaging. With careful patient selection, LRT represents an effective and safe treatment of primary and secondary hepatic

malignancies; however, complications related to LRT methods infrequently lead to additional morbidity.

Keywords

Liver; Loco-regional therapy; Complications; Transarterial chemoembolization; Hepatocellular carcinoma

Introduction

For the majority of patients with primary and metastatic malignant liver tumors, potentially curative surgical resection or transplantation is not possible. Hepatocellular carcinoma (HCC) is one of the most common lethal malignancies worldwide and its incidence is steadily and rapidly increasing due to the rising prevalence of hepatitis C infection in the USA [1]. The majority (80–85%) of patients with HCC at presentation have unresectable disease. Nearly 50% of colorectal cancers present with liver metastases, usually too numerous and too large to be managed surgically or with transcutaneous techniques. Up to 78% of neuroendocrine tumors present with liver metastases, less than 10% of which are resectable.

Loco-regional therapy (LRT) improves survival of patients with unresectable primary malignancies of the liver or metastatic disease compared to conservative therapy [2–4]. Transarterial chemoembolization (TACE) has been extensively studied since the early 1990s and has changed the management of HCC [2]. The normal liver derives 75% of its blood supply from the portal vein and only 25% from the hepatic artery [5]. In hypervascular liver tumors, such as HCC and in neuroendocrine metastases, this relationship is reversed. The response of HCC to systemic chemotherapy is poor, due to the inability to generate effective chemotherapy concentrations over a sufficient time without causing prohibitive systemic toxicity. The paradigm of LRT is to concentrate the treatment to the targeted tumor while minimizing the systemic toxicity or effects on normal hepatic parenchyma. Promising newer techniques for the treatment of malignant liver tumors are yttrium-90 radioembolization, interstitial laser photocoagulation, and drug-eluting beads (DEBs) [6]. Combinations of these techniques with each other or with targeted radiation therapy are being examined. Building on evidence of increased vascular endothelial growth factor activity in patients with HCC, increased stimulation of angiogenic activity following TACE, and both the survival advantage and synergy seen with the combination of doxorubicin and sorafenib, the current work is focused on combination therapies. For example, bevacizumab and TACE, sorafenib and TACE and TACE with DEBs are currently in clinical trials (Reyes DK, et. al. #208 and #254, American Society of Clinical Oncology. Orlando, Florida, 2010).

The safety of LRT must be assessed for each tumor–agent combination. TACE has been shown to be a safe procedure when patients are selected carefully [7,8]. For TACE, the complication rates in most series are reported between 4% and 5% [8,9]. The most common complications are post-embolization syndrome requiring extended stay or readmission (4.6%) and liver failure (2.3%). Most other complications occur in less than 1% of cases [9].

Complications from loco-regional therapy

Non-target embolization

Non-target embolization (NTE) is the inadvertent reflux of chemotherapeutic agents and/or embolic material into unintended territories. Careful examination of the diagnostic angiogram obtained before administration of treatment is essential to minimize the risk of NTE. Common anatomic variants include the hepatic falciform artery and origin of the left phrenic artery from the left hepatic artery, exposing extrahepatic structures including the diaphragm and the anterior abdominal wall to risk for ischemia from embolization. Although prophylactic embolization of accessory vessels prior to TACE can be used, at our institution, embolization is rarely necessary, as superselective catheterization is usually sufficient to avoid NTE. Proper injection technique ensures forward flow of the embolization material. This is usually easy to perform using oil-based embolization. However, in the case of yttrium-90 radio-embolization and drug-eluting beads, inadvertent backflow may occur, resulting in NTE. If tumor involvement requires the cystic artery to be treated, this can usually be performed to reduce the tumor burden, since the majority of cases are without consequences. In rare cases, backflow to the cystic artery may lead to gallbladder ischemia, (hemorrhagic) cholecystitis (Fig. 1), surgical cholecystitis (Fig. 2), and gallbladder gangrene. Backflow to the gastroduodenal artery or pancreaticoduodenal artery may lead to acute pancreatitis (Fig. 2) or duodenal ulcer formation (Fig. 3) with possible subsequent duodenal perforation [10]. Similarly, gastric ulcers may rarely occur as a result of stasis in the feeding artery leading to possible reflux of a few microspheres into the gastric or gastrointestinal arteries. Overall, gastrointestinal ischemia has been reported in <1% of patients [9].

Liver capsular rupture/tumor rupture

Tumor rupture after TACE is rare and occurs in less than 1% of cases [9]. Subcapsular location of liver tumors, large tumor size, and exophytic growth may contribute to this complication (Fig. 4). The etiology of tumor rupture is presumably capsular necrosis due to ischemia or secondary infection or inflammation due to chemotherapeutic agents [9]. Tumor hemorrhage and necrosis raise the intratumoral pressure and increase the risk of rupture. Hemoperitoneum may occur, but is uncommon (<1%) [9] (Fig. 4).

Arterial injury

Direct mechanical arterial injury during LRT may occur anywhere from the access site to the selectively accessed visceral artery. LRT shares local access site complications with any other angiographic technique, including groin hematoma, arteriovenous fistula, and pseudoaneurysm formation. Patients who receive systemic chemotherapy are predisposed to vascular dissection (Fig. 5) because the vessels become more fragile. Therefore, guidewires with extra flexible atraumatic tips are recommended to reduce this risk. Post-treatment vascular thrombosis, dissection, stenoses, or occlusions may occur.

With LRT of the liver, complications of spasm of the hepatic artery and hepatic artery occlusion have been described [10]. If collateral pathways are not sufficient, focal liver

infarction may occur. Vasospasm can be induced either due to mechanical irritation by the catheter or as a reaction to the drug treatment.

Bile duct injury

Bile ducts are known to be exquisitely sensitive to ischemia and, for example, may indicate ischemia in liver transplants. They derive their blood supply from the hepatic artery, and it is therefore not surprising that transarterial therapy has a disproportionate effect on them. A biloma is an accumulation of hepatic secretions due to compromise of the biliary drainage (Fig. 6). TACE may cause duct necrosis by directly damaging the sensitive peribiliary capillary plexus. Interestingly, the bile ducts have been found to be more sensitive to ischemic injury in less severe liver disease (Child-Pugh class A) when compared to more advanced cirrhosis, likely due to hypertrophy of the peribiliary capillary plexus [9]. This may also explain the higher incidence of bile duct necrosis after TACE in liver metastatic disease, which often occurs to a liver without the presence of chronic liver disease. Non-target embolization can potentially lead to damage of extrahepatic bile ducts with the result of strictures, obstruction, or even free perforation, although such cases are rare.

Infection/inflammation

The risk of formation of a hepatic abscess (Fig. 7) after TACE has been found to be 1.8% with biliary dilation alone and 7.4% in patients with biliary stents or biliary-enteric anastomoses [11]. Antibiotic prophylaxis, for example with cephalexin, has not been found effective for preventing liver abscesses, although the occurrence of fatal sepsis was reduced [12]. Aggressive antibiotic prophylaxis with a preprocedural bowel-cleansing regimen was shown to reduce the incidence of liver abscess in patients with bilioenteric anastomosis [13]. The risk of fatal sepsis can be reduced by careful patient selection and adjustment of the chemotherapeutic dose on the basis of the patient's risk profile [7]. Secondary infection and inflammation may occur due to non-target embolization, such as cholecystitis, acute pancreatitis, or pulmonary embolism with secondary pneumonia.

Conclusion

Knowledge of possible complications is important for safe performance of LRT of the liver and for the interpretation of post-LRT follow-up imaging. Overall, LRT-related complications infrequently lead to additional morbidity, and LRT represents an effective and safe treatment of primary and secondary hepatic malignancies. Future extension of the LRT methodology includes concurrent therapy with anti-angiogenesis agents and gene therapy. These applications are currently in clinical trials to assess safety and efficacy.

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Fig. 1.

A 47-year-old female patient with metastatic carcinoid underwent TACE #1 via the right hepatic artery. **a** CT immediately after TACE depicts lipiodol deposition in the right lobe surrounding the gallbladder fossa. **b–d** T1-weighted image (T1W) with fat saturation (+FS) (**b**), T1W with intravenous contrast administration (+C) in the arterial phase (**c**) and T2-weighted image (T2W) (**d**) 1 month after TACE show thickening of the left anterior gallbladder wall with precontrast T1 hyperintensity and T2 hypo-intensity compatible with hemorrhage. **e** Review of the angiogram shows the difficulty in this case of treating a central liver tumor (*arrowheads*) supplied by central branches of the right hepatic artery. Cystic artery branches (*feathered arrow*) can be seen to arise in close vicinity

Fig. 2.

A 58-year-old female with right hepatic lobe large HCC underwent TACE with doxorubicin eluting beads (DEBS) #1 without complication. TACE with DEBS #2 was performed subsequently. **a** Gadolinium-enhanced T1W MRI of the liver 1 month before TACE #1 demonstrates a large heterogeneously hypoenhancing mass replacing a large portion of the right hepatic lobe, representing HCC. **b–c** Axial CT images 1 day after TACE with DEBS #2 show edema and stranding of the pancreas (*arrows in b*). Hemorrhage is noted in the large right hepatic mass (*arrow in c*). **d** MRI T1W with contrast 6 days later shows development of pancreatic pseudocysts (*arrows*). **e** Ultrasound 22 days later shows sloughing of the gallbladder mucosa (*arrow*) and pericholecystic fluid (*open arrow*), compatible with gallbladder mucosal necrosis. **f, g** MRI T2W (**f**) and T1W+C (**g**) at the same time show gallbladder mucosal sloughing (**f, g**—*open arrow*) and multiple pancreatic pseudocysts (**f, g**—*arrows*). The patient underwent right hepatectomy 2 months later. Histologic examination with H&E stained slides (**h** magnification $\times 4$, **i** magnification $\times 20$)

showed remains of DEBS in lamina propria, gallbladder vessels (stained blue, *arrows*), and extensive transmural coagulative necrosis. Complete breach of the mucosa was evident by intramural bile (*asterisk*). The letter “L” in the figure identifies the luminal side of the gallbladder. (Images courtesy of Dr. Robert A. Anders, Pathology, JHH). Pancreatitis resolved on subsequent imaging, and at the time of this report, the patient is without further complication or recurrence for several years

Fig. 3.

A 53-year-old male with metastatic colon cancer presented with persistent vomiting 50 days after radioembolization through the left hepatic artery. **a** Post-contrast MR image shows diffuse thickening compatible with edema of the antrum and pylorus with mild hyperemia (*arrowhead*). **b** Contrast-enhanced CT: diffuse thickening compatible with edema of the antrum and pylorus with focal asymmetric oral contrast collection (*arrowhead*), which may in retrospect represent the ulcer crater. Imaging findings are subtle in this case and lack specificity in the underdistended stomach. There is no mesenteric fat stranding. **c** Endoscopy demonstrated a 4-cm ulcer in the distal antrum. (A small portion of the image to the left of the ulcer has been retouched to remove patient information). Non-target embolization of the left gastric artery was the likely cause. Pathology showed ulcerated antral mucosa and absence of *Helicobacter pylori*, cytomegalovirus, or herpes simplex virus. No embolic particles were found in the biopsy specimen

Fig. 4.

A 59-year-old female with HCC in the dome of the right liver (segment VIII). **a** Arterial phase CT examination 1 month before TACE shows a hypervascular well-defined, round mass (*arrow*) in the liver dome. **b, c** Diagnostic angiogram (**b**), performed immediately before TACE demonstrates a tumor blush (*arrows*) in the dome of the right liver lobe (segment VIII). Replaced right gastric artery (*open arrow*) arising from the celiac axis is noted. Selective catheter position for TACE (**c**, *black arrow*) is shown. Injection shows large feeder supplying the tumor vessels. Venous phase (not shown) showed rapid washout from the tumor. The exophytic tumor bulges the liver capsule and right hemidiaphragm (*arrowhead* in **c**). **d–f** Unenhanced CT, 24 h after TACE. Appearance of a crescent of hyperdense blood adjacent to the right liver lobe, representing hemoperitoneum (*arrowhead* in **d**). This is most prominent over the tumor site. In place of the previously seen well-defined mass, there is now a heterogeneous large area of mixed hyper- and hypodensity representing ruptured tumor, blood clot, and acute hemorrhage (*arrows* in **d** and **e**). Hemoperitoneum accumulates dependently in the pelvis (**f**). Immediate surgical exploration was undertaken with removal of necrotic tumor and blood clot from the liver. The peritoneal cavity was irrigated. On pathology, approximately 25% of the removed tumor tissue was found viable. The patient recovered and had stable disease for the following 2 years under sorafenib therapy.

Fig. 5.

A 56-year-old female with history of islet cell tumor metastatic to the liver. After pre-radioembolization angiogram performed to evaluate for the possibility of shunting to the lungs, she developed right lower extremity pain, heaviness, and claudication. **a** Dissection flap (*arrow*) can be seen in the right external iliac artery, which is small in caliber compared to the left external iliac artery (*open arrow*). **b** Volume rendering demonstrates narrow caliber of the right external iliac artery over a long segment, compatible with dissection (*arrow*). The patient was able to receive radioembolization via the left femoral artery and had a good response. She did not opt for vascular repair, and her right leg symptoms completely resolved without further intervention

Fig. 6.

A 76-year-old male. The patient had a history of metastatic neuroendocrine tumor (VIPoma) and underwent left hepatectomy and splenectomy for metastatic disease. The patient then again developed metastatic disease to the liver and was referred for TACE. He developed a biloma after the fourth TACE procedure. **ac**, Axial T2W (**a**), coronal incoherent gradient echo (**b**), and arterial phase contrast-enhanced fat-suppressed T1W (**c**) MR images. The biloma presents as a well-defined lobulated cystic non-enhancing lesion without septa, calcifications, or encapsulation (*arrows*). Minimal peripheral enhancement is due to compression of normal liver parenchyma (*arrows* in **c**). This biloma was drained transcutaneously. It subsequently became infected and led to the development of an abscess, requiring additional drainage

Fig. 7.

A 57-year-old male with metastatic neuroendocrine tumor. **a** CT exam before TACE #1 shows two centrally necrotic neuroendocrine metastases in the right hepatic lobe (*arrows*). Additional metastases are noted, bulging the liver capsule (*open arrows*). After TACE #1, there was good response of the dominant liver lesion, but incomplete response of the adjacent metastasis on follow-up MRI, which prompted TACE #2. **b–d** Follow-up MRI after TACE #2 shows the development of a liver abscess: T1W + FS + C (**b**) and T2W (**c**) images show heterogenous and nonenhancing necrosis and liquefaction (*arrows*) of liver parenchyma surrounding the segment VII lesion (*arrowhead*), which is still well discernible. Diffusion-weighted MRI showed high signal on an image acquired with a *b* value of 700 mm²/s (not shown) with associated low ADC values (**d**) in the abscess (*arrows*), compatible

with diffusion restriction. The quality of the ADC image is limited, due to patient motion; however, the diffusion restriction can be appreciated. **e** Follow-up CT shows increased demarcation of the abscess, with development of internal air pockets and large air-fluid level (*arrowhead*). The abscess was drained and resolved subsequently