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Multidisciplinary Session for Colorectal Cancer Liver Metastasis (English Session)

Interpretation of CRLM Lesions

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Colorectal cancer (CRC) is the third cause of cancer related death worldwide. The liver is the most common site for colorectal cancer metastases. Liver metastases in CRC are already present at the time of diagnosis of primary tumor in 15-20% of cases, whereas 60% of patients who develop metastatic disease present liver metastases. In these patients, surgical resection of metastases remains the only treatment with potentially curative intent, achieving a 5-year survival rate of 30 and 15% at 10 years. Metastases must be differentiated from benign hepatic lesions. In oncologic patients, hepatic lesions measuring 1 cm or smaller are benign in 80%. Therefore, accurate detection and characterization of the hepatic lesion as well as meticulous assessment of tumor burden is important for selecting the optimal treatment method in patients with colorectal cancer liver metastasis (CRCLM).

Contrast-enhanced multi-phasic MDCT is a robust and accurate technique to assess liver and extrahepatic disease in patients with CRC. Most CRCLM are hypoattenuating on unenhanced CT. CRCLM from mucinous adenocarcinoma of the colon may contain amorphous calcified areas on unenhanced CT.Calcification may develop or change during chemotherapy. It is not certain whether the calcification of the tumor may carry any prognostic significance. CRCLM enhancesless than liver after administration of contrast agents and tend to be hypoattenuating compared to liver in both the arterial and venous phases. The difference in enhancement between the lesion and the liver usually is greatest in the portal venous phase - owing to the intense enhancement of the liver - and CRCLM characteristically are seen to best advantage in the portal venous phase after administration of extra-cellular agents. CRCLM may show ring-like enhancement in the arterial phase. The ring-like enhancement may correspond to the tumor edge or to non-tumoral perilesional tissue (desmoplastic reaction, inflammatory cell infiltration, vascular proliferation). Some CRCLM may have fibrotic cores that progressively enhance in the portal venous and more delayed phases; such metastases exhibit a target appearance on delayed images.

Generally, hepatic metastases are moderately hypointense to liver parenchymaon unenhanced T1-weighted images and moderately hyperintense on T2-weighted images. Although most metastases are hypointense to liver parenchyma on T1-weighted images, some are hyperintense. Metastases may appear hyperintense on unenhanced T1-weighted images because of intralesional substances with a short T1 relaxation time such as hemorrhage. On T2-weighted images, hepatic metastasesare hyperintense to liver, but less so than hemangiomas or cysts. Metastases from mucinous adenocarcinoma can appear similar to benign fluid-filled lesions on moderately T2-weighted images. Nearly half of CRCLM will show central areas of low T2 signal intensity, particularly in larger lesions. On T1-weighted images, these lesions

appear uniformly hypointense to liver parenchyma. Histologically, this central hypointensity corresponds to areas of desmoplastic stroma, coagulative necrosis, and mucin accumulation.The peripheral halos of T2 hyperintensity present in CRCLM reflect the tumor margin and variable tumor necrosis. Some large CRCLM will show central areas of very high T2 signal intensity secondary to liquefactive necrosis.

CRCLM may show thin rim enhancement on arterial phase images but are best detected on portal venous phase images on extracellular contrast agent (ECF agent)enhanced MRI. They may appear isovascular on dynamic imaging, particularly after chemotherapy. Enhancement extending beyond the border of hepatic metastases as defined on unenhanced images is termed perilesional enhancement. Perilesional enhancement of metastases is attributed to peritumoral desmoplastic reaction, inflammatory cell infiltration, and vascular proliferation.

Among recent advances in magnetic resonance (MR) imaging techniques, diffusion-weighted (DW) imaging and gadoxetic acid-enhanced MR imaging improved the effectiveness of liver MR imaging for evaluating focal hepatic lesions by providing images with high lesion-to-liver contrast, as well as information in regard to the lesion characteristics. Hepatobiliary contrast agents may improve the detection of tiny hypovascular metastases. These metastases may be too small to be detected reliably on vascular phase images of CT or MRI but may be visible as sharply demarcated hypointense lesions relative to the markedly hyperenhanced liver on T1-weighted MR images in the hepatobiliary phase after injection of such agents. As a result, these techniques have been increasingly used for clinical liver MR imaging.

Dramatic improvements in cytotoxic agents and the use of newer and more effective regimens have enabled downsizing of hepatic metastases, especially in patients with CRCLM. However, these newer agents have been associated with idiosyncratic side effects; therefore, increasing attention has been drawn to chemotherapy-induced hepatopathies because these may impair the hepatic parenchyma and deteriorate the postoperative outcome. Reported patterns of chemotherapy-induced hepatopathy of non-tumor-bearing hepatic parenchyma include steatosis, steatohepatitis, and sinusoidal obstruction syndrome (SOS). SOS has been recognized as a diffuse parenchymal change, showing a heterogeneous reticular pattern in non-tumor-bearing liver parenchyma, which is detectable with superparamagnetic iron oxide- and gadoxetic acid-enhanced MR imaging. SOS, also called hepatic venoocclusive disease or blue liver syndrome, is characterized pathologically by obliteration of small hepatic venules and clogging of dilated sinusoids with debris from endothelial cell necrosis and trapped red blood cells. Oxaliplatin-related sinusoidal dilatation is also associated with fibrosis, peliosis, and nodular transformation, and these findings are related to the severity of SOS.

The typical imaging findings of CRCLM are summarized below:

Colorectal cancer liver metastases (CRCLM)
CT
- Usually hypoattenuating. Some CRCLM may be calcified
- may show ring-like enhancement in the arterial phase
- Some CRCLM may exhibit a target appearance on delayed images due to fibrotic cores

MRI
- T1-weighted images: hypointense to liver
- T2-weighted images: solid lesions hyperintense to liver, isointense to spleen, mucinous tumors may appear hyperintense on T2WI
- Dynamic enhancement study
  - Hypovascular metastases such as CRC best shown on portal venous phase images when enhancement of the liver parenchyma is greatest on ECF-agent enhancement MRI
- DWI and gadoxetic acid-enhanced MRI provide images with high lesion-to-liver contrast

Indication for liver resection in CRCLM has been changed. Even patient with multiple lesions, large tumors, or extrahepatic disease will be considered

for treatment in multimodality programs with the ultimate aim to cure. To achieve this goal, meticulous preoperative assessment of tumor burden is important in patients with colorectal cancer liver metastasis (CRCLM). Preoperative imaging is essential for the evaluation of tumor burden, number of segments involved, tumor location, vascular anatomy, and estimation of the future liver remnant. In addition to the planning for surgery, imaging plays an important role in determining treatment strategies and monitoring response.

Reference

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How to optimize perioperative chemotherapy

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Patients with resectable liver metastases who are have a high chance of relapse as only about 30% - 40% of patients are enjoying long-term cure. Perioperative chemotherapy has therefore been utilised in order to improve the results. The EORTC EPOCH study used six cycles of FOLFOX preoperatively followed by operation and postoperatively another six cycles of FOLFOX. The progression-free survival was significantly prolonged as compared to patients receiving immediate surgery. The New-EPOCH study intensified the FOLFOX regimen adding cetuximab in patients with KRAS wild-type disease. Surprisingly patients receiving cetuximab had an inferior outcome as compared to patients receiving FOLFOX alone. The patient char-ac-teristics differed between EPOCH and New-EPOCH and may explain these surprising results. Also, in all of these studies the effect on long-term survival, which may need a ten-year follow-up, is unclear at the moment. Neoadjuvant chemotherapy in resectable liver metastases may be a disadvantage as invisible metastases may disappear even at the time of surgery and may not be resected, thus the place of early relapse of remaining microscopic deposits.

In patients with unresectable liver-limited disease the adjuvant chemotherapy in combination with an EGFR inhibitor in patients with KRAS wild-type disease increases the chance of resectability and significantly prolongs long-term survival according to a prospectively randomised trial giving important evidence for this kind of approach. Liver resection, although it may not be curative, does significantly