[SY07] Abdomen Symposium ll

SY07-01

EOB-MRI of multistep hepato-carcinogenesis: molecular background

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Gadoxetic acid (Gd-EOB-DTPA)-enhanced MRI (EOB-MRI) significantly improves the detectability of early hepatocellular carcinoma (HCC) with a higher sensitivity than dynamic CT or CT arterial portography/CT hepatic arteriography. Sano et al. reported 97% of early HCCs can be detected as slightly hypointense nodules on the hepatobiliary phase of EOB-MRI.

To elucidate the molecular mechanism behind the high detectability of early HCC by EOB-MRI, we evaluated the expression of organic anion transporting polypeptide 1B3 (OATP1B3), a main transporter of Gd-EOB-DTPA, in surgically resected dysplastic nodules, early HCCs, and advanced HCCs. Low-grade dysplastic nodules showed the same level of OATP1B3 expression as normal liver, while 40% of high-grade dysplastic nodules and 70% of early HCCs demonstrated decreased expression of OATP1B3. All poorly differentiated HCCs showed decreased or absent expression of OATP1B3. OATP1B3 expression significantly decreased with the decline of tumor differentiation from low grade dysplastic nodule to poorly differentiated HCC; however, 6% of moderately differentiated HCCs showed equivalent or increased expression of OATP1B3. The enhancement ratio on the hepatobiliary phase also decreased from well-differentiated HCC to poorly differentiated HCC, correlating with the decrease of OATP1B3. Decreased OATP1B3 expression, namely, decreased signal intensity on the hepatobiliary phase of EOB-MRI, is a sensitive biomarker reflecting the early stage of multistep hepatocarcinogenesis, resulting in high sensitivity in the detection of early HCCs.

De-differentiated foci show hypointensity in 20%, isointensity in 50%, and hyperintensity in 30% on the hepatobiliary phase relative to the surrounding borderline lesion. However, hyperintense de-differentiated foci arise at a considerable frequency and can develop into entirely hyperintense HCCs.

Most overt hypervascular HCCs show hypointensity on the hepatobiliary phase accompanying decreased expression of OATP1B3, whereas 10% of hypervascular HCCswith atypically increased expression of OATP1B3 show hyperintensity caused by some genetic alterations in carcinogenesis. These HCCs are a biologically less aggressive group, with lower serum levels of tumor markers and with a more favorable prognosis than hypointense HCCs. Hyperintense HCCs show a specific molecular expression pattern characteristic ofmature hepatocytes, with few stem cell features. Genetic analysis proves hepatocyte nuclear factor 4A (HNF4A) is highly activated in high-OATP1B3 hyperintense HCCs. HNF4A is a transcription factor playing important roles in the development, metabolism, and suppression of HCC growth. It is also reported that decreased HNF4A is the initiator of hepatocarcinogenesis, which may be the background mechanism of decrease of OATP1B3 expression in early HCC.

In conclusion, EOB-MRI is useful for the early diagnosis of HCC and the evaluation of multistep hepatocarcinogenesis, based on the fact that OATP1B3 begins to decrease in the early stage of carcinogenesis. In addition, the signal intensity on the hepatobiliary phase of EOB-MRI is useful for the evaluation of biological, molecular, and genetic characteristics of overt HCC.

Keywords : Hepatocellular carcinoma, Dysplastic nodule, Gd-EOB-DTPA

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SY07-02

The role of EOB-MRI for HCC diagnosis and predicting prognosis

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The principal objective of liver imaging in patients with chronic liver disease is early diagnosis of HCC and differentiation of HCC mimickers such as benign hepatocellular nodules and hypervascular pseudolesions. These will improve patient outcome with curative treatment and facilitate decision-making for therapeutic strategies. The development of liver specific MR contrast agent such as gadoxetic acid improved detection and characterization of focal liver lesions. Some studies including meta-analysis reported that the diagnostic performance of gadoxetic acid-enhanced MRI for the detection of HCC in patients with chronic liver disease is superior to those of MDCT, conventional gadolinium- or gadobenate dimeglumine-enhanced MRI, particularly for detection of smaller HCC (< 2 cm). Gadoxetic acid-enhanced hepatobiliary phase imaging is the most sensitive for the diagnosis of HCC and some studies have confirmed that hepatobiliary phase imaging in addition to dynamic MR imaging has apparent additional benefit for improving the diagnosis of HCC with increased sensitivity. Accurate diagnosis of smaller HCC with high diagnostic confidence enables us to determine proper management and thus patient’s outcome improves. Some studies reported that additional examination of gadoxetic acid-enhanced MRI to dynamic CT in patients with early staged HCC led to the detection of additional HCC nodules, reduced the risk of disease recurrence, and decreased overall mortality.

The prognosis of HCC patients has improved with advances in surgical and imaging technology including MR contrast agent such as gadoxetic acid. However, high intrahepatic recurrence rates after curative treatment still remain a major challenge in HCC treatment. A previous study reported that more than 80% of tumor recurrence develops in the remnant liver after hepatic resection, and can represent either intrahepatic metastasis from the initial HCC or de novo multicentric occurrence. Early recurrence within the first 2 years after HCC resection is more likely to be associated with poorer prognosis and tumor factors such as worse histological differentiation, microvascular invasion, and microsatellite nodules, while the late recurrence is more likely related to underlying liver conditions such as degree of cirrhosis.

Preoperative estimation of aggressive histological features of HCC non-invasively based on imaging findings is very important for reducing early recurrence after curative treatment. Imaging findings for predicting HCC invasiveness may help decide appropriate management strategy. Furthermore, patients with HCC with imaging findings that aggressive histologic behavior is expected may require intensive follow up after curative treatment. Earlier identification and treatment of early recurrence may improve the survival of patients.

This lecture will present the role of gadoxetic acid-enhanced MRI for diagnosis of HCC and prediction of prognosis.

Keywords : Diagnosis, Prognosis, Hepatocellular carcinoma, MRI

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SY07-03

Challenges of EOB-MRI for HCC diagnosis: cHCC-CC and IHCC

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Typical hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) are easy to diagnose. However, sometimes it is not easy to differentiate HCC from CC or the combined type. Simply classifying primary liver tumors into either HCC or CC has been challenged because malignant hepatic tumors that share features of both cell types are increasingly recognized. Recent studies indicate that hepatocytes are the source of HCC and dedifferentiate into precursor cells that can transform into HCC with progenitor cell markers or CC. Accordingly, imaging features of HCC, combined type and CC form a spectrum. Typical HCC and CC have radiological hallmarks. However, the combined type may have overlapping features of HCC and CC.

Typically, bile duct cancer is divided into 3 types based on morphology and location. Typical mass-forming CC are infiltrative hepatic masses with capsular retraction or peripheral ductal dilatation. They may show irregular rim-like enhancement around the periphery of the tumor on arterial phase and progressive enhancement on delayed phase images. Gadoxetic-acid enhanced MRI may be helpful for diagnosing mass-forming CC because of increased lesion conspicuity and better delineation of daughter nodules or intrahepatic metastases. Recently a new subclassification of CC has been proposed. Perihilar large duct ICCs are more likely to have ill-defined or infiltrating tumor margins and increased necrosis. Perineural, vascular, and lymphatic invasion and lymph node metastases are more frequently associated with perihilar large duct ICCs than with peripheral small duct ICCs. In contrast, peripheral small duct ICCs have more expansive tumor borders and are less likely to exhibit perineural or lymphatic invasion compared with the perihilar large duct type. They may be hypervascular or may show rim-enhancement.

Combined HCC-CC is a tumor with intermixed elements of HCC and CC. In the 2010 WHO classification, combined HCC-CC is classified into two types: the classical type and subtypes with stem cell features. The problem with the WHO classification is that there is no detailed terminology even though combined type can be comprised of various histological components with varying proportions. Another problem is that minor histologic components are common, especially in stem cell features. Therefore, a new terminology for combined HCC-CC (cHCC-CC) has been proposed for uniformity of histological approach and facilitating scientific studies. In this new terminology, primary liver cancer, not classic HCC or CC, are classified into three types: cHCC-CC, with varying degrees of hepatocytic and cholangiocytic architecture; primary liver cancer (PLC) purely comprised of “intermediate cells”; PLC comprised of cholangiolocarcinoma (CLC). Combined type has been described as demonstrating some form of arterial hyperenhancement, most commonly peripheral or rim-like on dynamic images. Washout appearance is common and is often peripheral in location. Delayed enhancement is frequently observed. These imaging features most commonly overlap with those of CC. Predominant imaging features of HCC or CC appear to correspond to the predominant histologic component.

In conclusion, imaging features of HCC, combined HCC-CC and CC form a spectrum. Typical HCC and CC have radiological hallmarks. However, the combined type may have overlapping features of HCC and CC.

Keywords : Hepatocellular carcinoma, Cholangiocarcinoma, Combined hepatocellular-cholangiocarcinoma

SY07-04

Quantitative Evaluation of Liver Function with use of MR Imaging.

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Quantitative evaluation of liver reserve is important to avoid post-hepatectomy liver failure (PHLF), especially in patients with chronic liver diseases because of/owing to impaired liver function.

The indocyanine green (ICG) clearance test is a valuable tool for quantitatively assessing liver reserve in excretory and detoxifying functions because ICG is removed from the circulation exclusively by the liver. Various indices obtained from the ICG clearance test and volumetry, such as the plasma disappearance rate of ICG (ICG-PDR), ICG retention rate at 15 minutes (ICGR15), future remnant liver volume (rV), and hepatic parenchymal resection rate (HPRR), are significant predictors of postoperative liver failure and mortality. The Makuuchi criteria that combines ICGR15 and HPRR is one of the most useful criteria to evaluate safety limits for parenchymal resection rates in patients without obstructive jaundice, which improved operative mortality and morbidity after liver resection. The ICG-Krem or ICG-PDR of the future remnant liver (rICG-PDR) is a quantitative index for predicting PHLF that combines ICG-PDR and volumetry. However, one disadvantage of the ICG clearance test is that regional heterogeneities of liver functions cannot be evaluated.

Conversely, gadoxetate disodium is a paramagnetic hepatobiliary contrast agent that combines features of extracellular agents with those of a hepatocellular contrast agent. The same transporting mechanisms (i.e., the organic anion transporting polypeptide [OATP]) may be responsible for gadoxetate disodium and ICG uptake in hepatocytes; therefore, gadoxetate disodium-enhanced magnetic resonance imaging (MRI) scans may be the basis of a useful method for quantitatively estimating postoperative liver failure similar to ICG clearance, but with anatomic delineation of hepatic function. Relative enhancement (RE)-based indices determined from preoperative gadoxetate disodium-enhanced MRI scans could be used to predict PHLF in patients who underwent major hepatic resection. However, RE-based indices have been determined from signal intensities of the liver on post-contrast-enhanced MRI scans without appropriate corrections using rV and extracellular fluid space of the liver. Yamada et al. (2011) reported that the liver function that is correlated with the ICG clearance test can be estimated quantitatively using the hepatocellular uptake index (HUI), which can be determined from the signal intensities and volumes of the liver and spleen on gadoxetate disodium-enhanced MRI scans with appropriate corrections using the volume and extracellular fluid space of the liver. The feasibility of using the segmental liver reserve prediction with HUI has been validated in patients who underwent preoperative portal vein embolization (PVE) and extended hemi-hepatectomy. Furthermore, the strong correlation between future remnant HUI (rHUI) and PHLF is better than other indices, including the ICG clearance test and RE-based indices previously reported. Because rHUI is determined directly from the volume and signal intensity of the future remnant liver, a more accurate quantitative estimation of PHLF is feasible.

Keywords : Gadoxetate disodium, Magnetic resonance imaging, Future remnant liver reserve, Post-hepatectomy liver failure

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SY07-05

Challenges of EOB-MRI acquisition & potential solutions

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Gadoxetic acid-enhanced magnetic resonance imaging (MRI) has been widely used for liver lesion detection and characterization for last decade. It has shown superior capability for detecting small hepatocellular carcinomas and metastases compared with computed tomography, and now regarded as a problem solving tool.

However, the acquisition of arterial phase with acceptable image quality is often challenging in practice. Gadoxetic acid is known to show higher incidence of transient motion than other extracellular contrast agent, and it is often not predictable before the event, due to a lack of clear risk factors. In addition, arterial window for late arterial phase is relatively short because the recommended dose is smaller than other extracellular contrast media. With regard this, arterial enhancement is relatively weak which raises concerns of insufficient arterial enhancement of focal liver lesions. Addressing those issues would be important because the most common indication of liver MRI is for HCC, and appropriate arterial timing is critical for its diagnosis.

In this talk, the attempts to overcome those shortcomings would be discussed, focusing on technical advantages for dynamic sequences. It includes multiphasic arterial phase acquisition with variable techniques, motion-resistant sequences, and free-breathing sequences with motion correction, and we would see how those techniques can change clinical practice and may widen the indication of gadoxetic acid-enhanced MRI.

Keywords : Gadoxetic acid; MRI; Liver; GRASP; Free breathing

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SY07-06

EOB-MRI at AI-era: upcoming challenge and potential opportunity

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Artificial intelligence (AI) is a rapidly growing in recent years, and has a great impact in radiology. Although the concept of the computer aided diagnosis (CAD) systems was introduced more about 20 years ago, deep learning differs greatly from previous CAD systems. Radiologists don’t have to define features based on domain knowledge. Deep learning can learn important features by itself through the training process. Recent studies in computer vision have shown that deep learning with big data works better than the other methods that depend on the domain knowledge. Many applications of deep learning on radiology have already been introduced in research and commercial level.

EOM-MRI plays an important role in evaluating liver function and diagnosing hepatocellular carcinoma. The dynamic contrast enhancement pattern provides us a variety of information including the shape and physiology of the lesion, but we cannot be sure that all information about the lesion are successfully utilized by visual inspection. The benefit of deep learning is to help radiologists better interpret EOB-MRI. Deep learning models trained using large scale datasets can provide important information for image interpretation. To be used successfully in practice, we should know that the strengths and limitations of deep learning. Also, Clinicians should be interested not only in algorithm development but also in clinical validation. As many algorithms have been introduced, clinician’s roles are becoming increasingly important in clinical validation of the algorithms.

Keywords : Liver MRI, Deep learning