Review

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Insights into the diagnosis of hepatocellular carcinomas with hepatobiliary MRI

Valérie Vilgrain[1,2], Bernard E. Van Beers[1,2,3], Catherine M. Pastor[2,4,*]

[1]*Department of Radiology, University Hospitals Paris Nord Val-de-Seine, Beaujon, 100 Boulevard du Général Leclerc, 92118 Clichy, France;* [2]*University Paris Diderot, Sorbonne Paris Cité, Paris, France;* [3]*Inserm U1149, Centre de Recherche sur l'Inflammation, Paris, France;* [4]*Département d'imagerie et des sciences de l'information médicale, Hôpitaux Universitaires de Genève, Geneva, Switzerland*

Summary

The incidence of hepatocellular carcinomas (HCCs) has increased worldwide in line with an improved screening by high-resolution imaging of cirrhotic livers. Besides abdominal ultrasonography and computerised tomography, magnetic resonance imaging (MRI) is an important tool to detect HCCs. With commercialisation of MR hepatobiliary contrast agents that cross membrane transporters in hepatocytes or tumour cells, MRI adds new information to detect and characterise HCCs. When tumour cells lose organic anion transporting polypeptides (OATP1B1/B3) in cell membranes facing sinusoidal blood, tumours appear hypointense (decreased contrast agent concentrations) in comparison to surrounding normal or cirrhotic liver that retains OATP1B1/B3 expression. However, expression, regulation, and prognostic significance of transporter evolution along carcinogenesis are not completely known. Moreover, understanding signal intensities in focal lesions also relies on transport functions of cellular efflux transporters. This manuscript reviews all the publications that associate liver imaging with hepatobiliary contrast agents and expression of transporters. The regulation of transporters along carcinogenesis to anticipate the prognosis of focal lesions is also included.

Keywords: Hepatocellular carcinoma; Hepatobiliary MRI; Hepatocyte transporters.

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* Corresponding author. Address: Département d'imagerie et des sciences de l'information médicale, Hôpitaux Universitaires de Genève, Rue Gabrielle-Perret-Gentil, 4, 1205 Geneva, Switzerland. Tel.: +41 22 372 38 36.

E-mail address: catherine.pastor@hcuge.ch (C.M. Pastor).

Abbreviations: HCCs, hepatocellular carcinomas; MRI, magnetic resonance imaging; HB-MRI, Hepatobiliary MRI, images acquired during the hepatobiliary phase; DN, dysplastic nodule; LGDN, low grade dysplastic nodule; HGDN, high grade dysplastic nodule; BOPTA, gadobenate dimeglumine, MultiHance®, Bracco Imaging SpA, Milan, Italy; EOB-DTPA, gadoxetate dimeglumine, Primovist® or Eovist®, Bayer Health Care Pharmaceuticals, Berlin, Germany; Hypointense HCCs, lower signal intensities (darker) than surrounding parenchyma at HB-MRI; Hyperintense HCCs, higher signal intensities (brighter) than surrounding parenchyma at HB-MRI; OATP, Organic Anion Transporting Polypeptide; MRP, Multiple Resistance-associated Protein.

Introduction

Over the past decade, the incidence of hepatocellular carcinomas (HCCs) has increased worldwide in line with an improved screening by high-resolution imaging of cirrhotic livers [1–3]. Besides abdominal ultrasonography and computerised tomography, magnetic resonance imaging (MRI) is an important tool to detect HCC [4–6], while the use of positron emission tomography is increasing [7].

For typical advanced HCC, MRI following the injection of extracellular contrast agents shows tumour angiogenesis (development of isolated arteries) and a disappearance of portal triads (decreased portal perfusion of tumour). With commercialisation of MR hepatobiliary contrast agents that cross membrane transporters in hepatocytes or tumour cells, hepatobiliary MRI (HB-MRI or imaging acquired during the hepatobiliary phase) adds new information to detect and characterise HCCs [4,5,8]. When tumour cells lose organic anion transporting polypeptides (OATP1B1 and OATP1B3) in cell membranes facing sinusoidal blood, the tumour appears hypointense during the hepatobiliary phase (decreased signal intensities or decreased contrast agent concentrations) in comparison to surrounding normal or cirrhotic liver that retains OATP1B1/B3 expression (Fig. 1). Early HCCs can be diagnosed more accurately when hepatobiliary contrast agents do not accumulate in focal lesions, confirming the disappearance of uptake membrane transporters in tumour cells. However, expression, regulation, and prognostic significance of transporter evolution along carcinogenesis are not completely known. Moreover, understanding of signal intensities in focal lesions relies on transport functions of efflux transporters: multiple resistance-associated protein 2 (MRP2) located in the canalicular membrane of hepatocytes or tumour cells and MRP3 or MRP4 located in the sinusoidal membrane (return of contrast agents back to sinusoids). This manuscript reviews all the publications that are associated to liver imaging with hepatobiliary contrast agents and expression of transporters. The regulation of transporters along carcinogenesis to anticipate the prognosis of focal lesions is also included [9].

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Key points

- Drug transporters present on hepatocyte membranes modify their expression along hepatocarcinogenesis with important implications for liver imaging
- Several reviews suggest that OATP1B1/B3 expression decreases from normal hepatocytes to tumour cells but few studies show the transporter expression along carcinogenesis
- Potential factors regulating OATP and MRP transporters in hepatocellular carcinomas are β-catenin, hepatic nuclear factors, and protein kinase C
- Most HCCs are hypointense at HB-MRI in comparison to surrounding parenchyma because OATP expression on the membrane of tumour cells is low and EOB-DTPA uptake into hepatocytes is decreased
- Hyperintense HCCs have OATPs on tumour cells located in tissue or pseudogland. High signal intensities are generated by low canalicular MRP2 expression (EOB-DTPA cytosolic trapping), closed canaliculi (EOB-DTPA bile canaliculi trapping), or MRP2 expression in apical membrane of tumour cells inside pseudoglands (EOB-DTPA trapping in pseudogland lumen)

Pathology: from dysplastic nodules to HCCs

Progression of tissue injury from dysplastic nodules (DN) to HCCs is summarised because histological structures such as pseudoglands interfere with signal intensities at HB-MRI (Fig. 1). Most HCCs develop from clonal cells and expand into foci or DN, before evolving into a true carcinoma with exclusive arterial blood supply as well as stromal and vascular invasion [10,11]. Classification of these lesions was rationalised during several international meetings and is briefly summarised [10,12].

Dysplastic nodules

DNs range between 1 and 3 cm and are either low (LGDNs) or high (HGDNs) grade dysplastic nodules (Fig. 1A). Hepatocytes in LGDNs show minimal nuclear atypia. Cytoplasm is normal but clonal cells (dysplastic foci) may accumulate fat, hemosiderin, or copper. DNs are often identified by the presence of a peripheral fibrous scar, accumulation of fat, and increased cell density. The vascular supply is identical to surrounding tissues. LGDNs do not contain pseudoglands, which are rosettes of hepatocytes that secrete bile into a closed space. Unpaired (isolated or not triadal) arteries are sometimes present, spreading outside portal tracts. They are not associated with portal vein or bile ductules and

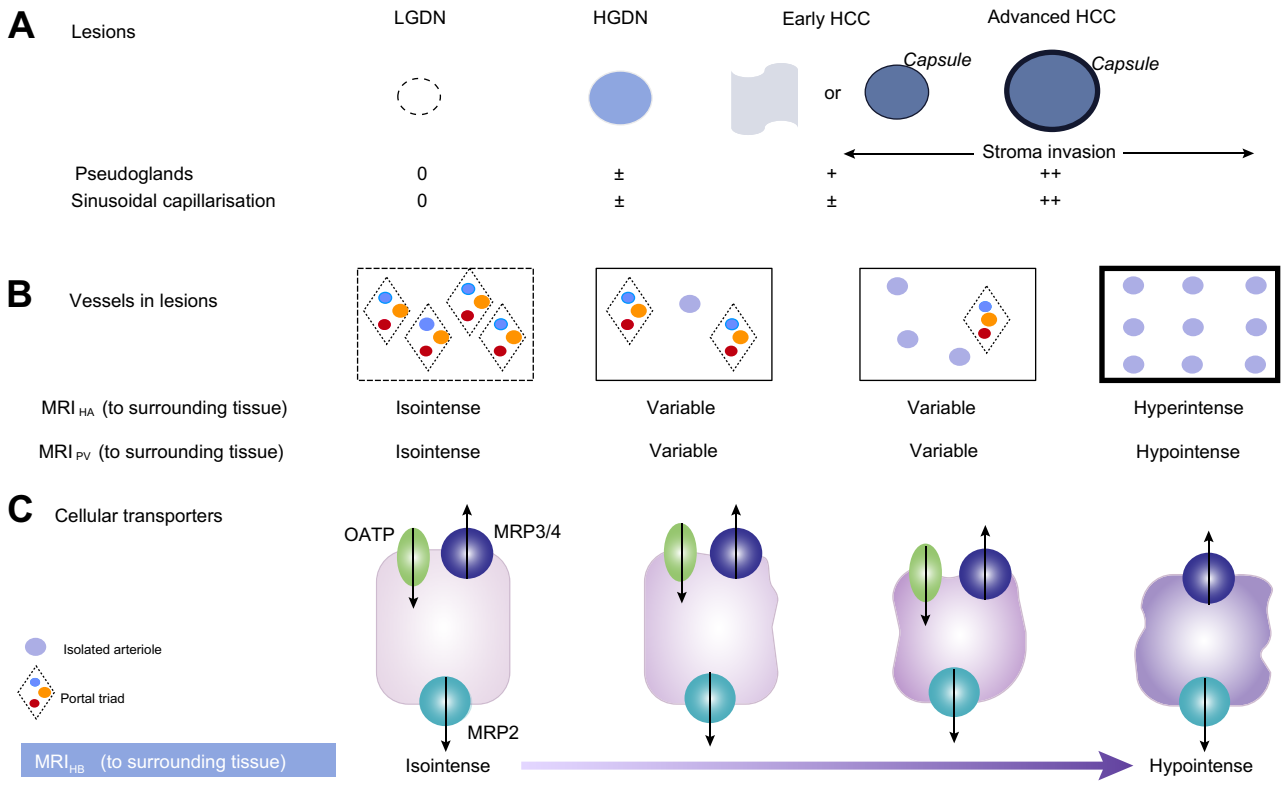

Fig. 1. Carcinogenesis evolution from dysplasic nodules to hepatocellular carcinomas with corresponding signal intensities at liver magnetic resonance imaging (MRI) following hepatobiliary contrast agents. (A) Macroscopic evolution of focal lesions, presence of pseudoglands and sinusoidal capillarisation are illustrated. (B) Evolution of arterioles and venules in focal lesions with corresponding signal intensities at MRI following injection of extracellular contrast agents in comparison to surrounding tissues. Hyperintense lesion during the hepatic artery phase (MRI_{HA}) reflects the presence of numerous isolated arterioles. Hypointense lesion during the portal vein phase (MRI_{PV}) reflects the disappearance of portal triads. (C) Putative evolution of transporter expression from hepatocyte to tumour cell and corresponding signal intensities during the hepatobiliary phase (MRI_{HB}). Adapted from [47]. LGDN, low grade dysplastic nodule; HGDN, high grade dysplastic nodule; OATP, organic anion transporting polypeptide; MRP, multiple resistance-associated protein.