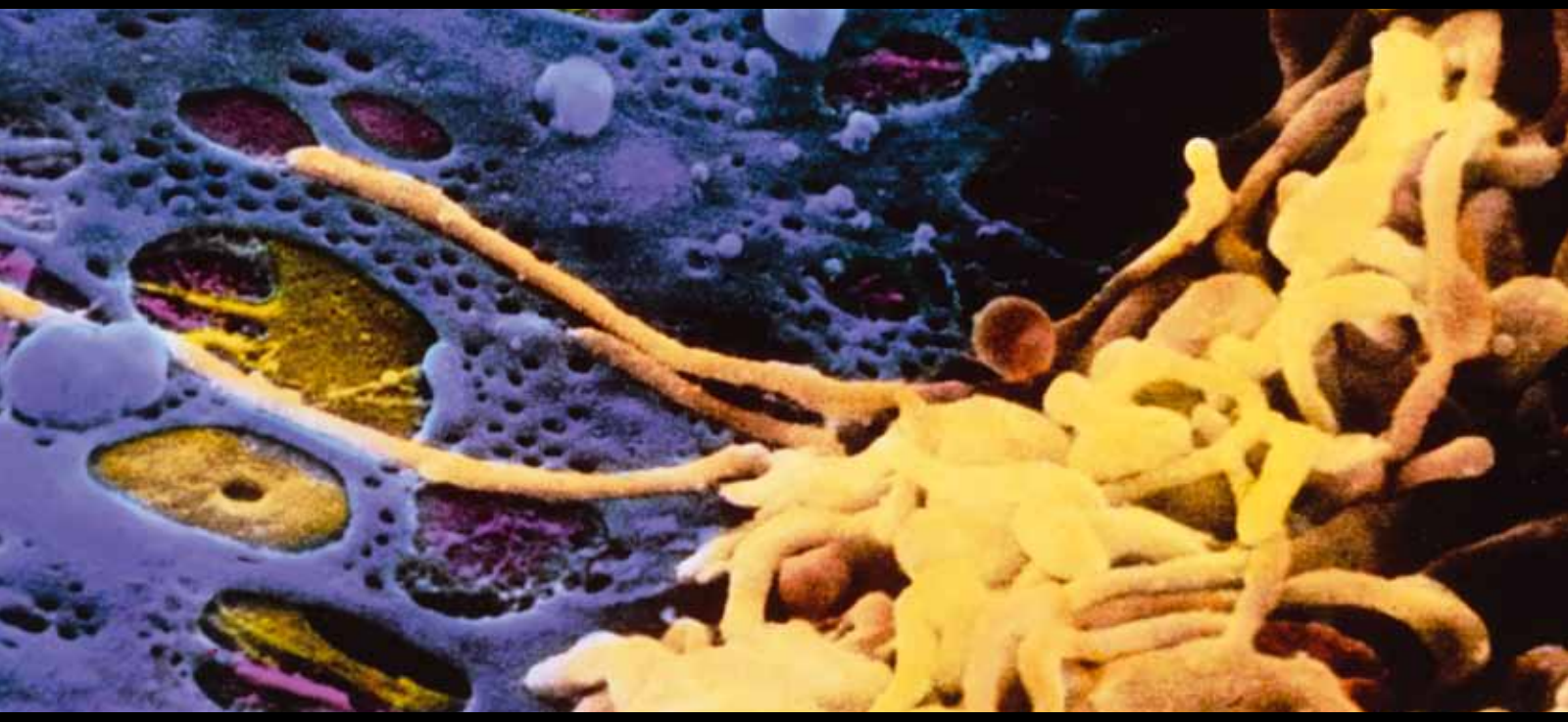
International Journal of Hepatology

# Hepatocellular Carcinoma: Current Management and Future Development

Guest Editors: Pierce Chow, Thomas Leung, Ryosuke Tateishi, and Huynh The Hung



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# Editorial Board

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*Clinical Study*

# Gadoxetate Acid-Enhanced MR Imaging for HCC: A Review for Clinicians

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Hepatocellular carcinoma (HCC) is increasingly being detected at an earlier stage, owing to the screening programs and regular imaging follow-up in high-risk populations. Small HCCs still pose diagnostic challenges on imaging due to decreased sensitivity and increased frequency of atypical features. Differentiating early HCC from premalignant or benign nodules is important as management differs and has implications on both the quality of life and the overall survival for the patients. Gadoxetate acid (Gd-EOB-DTPA, Primovist®, Bayer Schering Pharma) is a relatively new, safe and well-tolerated liver-specific contrast agent for magnetic resonance (MR) imaging of the liver that has combined perfusion- and hepatocyte-specific properties, allowing for the acquisition of both dynamic and hepatobiliary phase images. Its high biliary uptake and excretion improves lesion detection and characterization by increasing liver-to-lesion conspicuity in the added hepatobiliary phase imaging. To date, gadoxetate acid-enhanced MRI has been mostly shown to be superior to unenhanced MRI, computed tomography, and other types of contrast agents in the detection and characterization of liver lesions. This review article focuses on the evolving role of gadoxetate acid in the characterization of HCC, differentiating it from other mimickers of HCC.

## 1. Brief Overview of HCC

Hepatocellular carcinoma (HCC) is the fifth most common malignant neoplasm and the third most common cause of cancer-related death worldwide [1]. There has been a reported 41% increase in mortality from HCC over the last 2 decades [2], and HCC continues to be a major health concern. Many studies have shown that patients with early-stage HCC, as defined by the Milan criteria [3], treated either by resection [4, 5] or transplantation [3], do significantly better than those with advanced disease [6], with 5-year overall survival rate approximating 40–70% [6, 7] in such cases. The presence of microvascular invasion—an independent poor prognostic factor regardless of treatment—is more probable in larger tumors [8–10]. Thus, the detection and accurate characterization of early focal liver lesion in normal or cirrhotic livers is crucial so that appropriate treatment can be instituted [11–13].

## 2. The Evolution in Magnetic Resonance Imaging (MRI) of the Liver

MRI has become an established modality for the assessment of various types of focal liver lesions [14–18]. Nevertheless, up to 60% of small malignant nodules, particularly those less than 1 cm size in the background of cirrhotic liver, are missed at MRI [19]. Continued improvement in the MR sequences and hardware [20, 21], as well as the advent of liver-specific contrast agents [22, 23], which are only available for MRI, have led to the improved diagnostic performance of MRI. The broad arsenal of MR sequences and multiphasic post-contrast imaging provide comprehensive information on the liver lesion by elucidating different signal intensities that reflect the inherent properties of the lesion's composition, as well as blood flow dynamics, which gives each lesion type different MR characteristic appearances.

## 3. Liver-Specific Contrast Agents for MRI

*3.1. An Overview.* To increase the sensitivity and specificity of MRI in the detection and characterization of focal liver lesions and overcome some of the existing limitations of extracellular fluid (ECF) agents, which include suboptimal differentiation between benign and malignant liver lesions due to the contrast agents' non-specific nature and nephrotoxicity (nephrogenic systemic fibrosis) that can result with use of high doses of gadolinium contrasts [24], liver-specific contrast agents emerged. Currently, two major classes of liver-specific contrast agents exist: (1) hepatocyte-specific, or hepatobiliary, agents and (2) reticuloendothelial cell-specific, or nanoparticulate, agents. They are considered "liver-specific" as they all cause significant liver signal changes after intravenous administration, with resultant increased liver-to-lesion conspicuity. The first group of contrast agents, as the name implies, targets the functioning hepatocytes with varying degree of contrast uptake into them with subsequent biliary excretion. This is possible because of the addition of a lipophilic moiety to the gadolinium chelates [25]. Currently available contrast agents of this type include gadoxetate acid (Gd-EOB-DTPA or gadolinium ethoxybenzyl diethylene-triamine pentaacetic acid, Primovist®, Eovist® in the USA, Bayer Schering Pharma, Berlin, Germany) and gadobenate dimeglumine (Gd-BOPTA, Multihance®, Bracco, SpA, Milan, Italy), both of which are gadolinium-based. Manganese-based paramagnetic agent, mangafodipir trisodium (Mn-dipyridoxyl 5'phosphate, Teslascan®, GE Healthcare, Oslo, Norway), was another contrast agent belonging to this group; however, it has been removed for use in the United States [26] and will not be further discussed here.

The second group of contrast agents target the Kupffer cells of the reticuloendothelial system, where phagocytosis of contrast agents occur and, by the effects of iron ions, liver signal intensity decreases giving rise to a "black" liver [27], instead of "white" liver seen with hepatocyte-specific contrast agents.

### 3.2. Hepatobiliary Agents

*Gadoxetate Acid.* Gadoxetate acid is a gadolinium-based, paramagnetic, liver-specific MR contrast agent with combined perfusion- and hepatocyte-selective properties that is primarily developed for imaging of the liver to improve lesion detection and characterization. It has been found in preclinical studies to be safe and well tolerated with no major side effects [25, 28–30].

Several unique properties deserve mention. Upon intravenous administration of gadoxetate acid, it rapidly distributes itself in the vascular-interstitial compartment, enhancing the blood pool, providing acquisition of dynamic phase images that allows for lesion characterization based on perfusion. Approximately 50% of the injected dose of gadoxetate acid is then selectively taken up by the functioning hepatocytes and subsequently excreted into bile, allowing for the acquisition of the delayed, hepatocyte-specific phase that is optimal at 20 min post injection. This phase further improves diagnostic performance by increasing liver-to-lesion contrast, where lesions with absent or dysfunctional hepatocytes appear dark against the background white liver. Because of such high specificity for hepatocytes, the recommended dose of gadolinium is 4-fold less than the ECF agents [25, 29, 30].

The cellular mechanism underlying this high percentage of contrast volume uptake can be explained by the enhanced lipophilic property of gadoxetate acid due to the presence of EOB moiety that is linked to the gadolinium complex. Passive diffusion of contrast agent occurs via transporter molecules, organic anion transporting polypeptide 1 (OATP1), that are present on the basolateral membrane of the normal hepatocytes [31–33].

Following a relatively high hepatocyte uptake, studies have shown that gadoxetate acid is cleared in equal quantities via bile (50%) and urine (50%). At molecular level, its excretion into bile is as a result of another type of transporter molecule present at the canalicular membrane of the cell called multidrug resistance protein 2 (MRP2) [31–33]. In the event that one of these elimination pathways is impaired, the other elimination pathway compensates, according to animal studies [34, 35]. This theoretically allows patients with either renal or liver impairment to safely undergo examination by gadoxetate acid-enhanced MRI, although to date, there is no human studies to confirm this.

Gadoxetate acid is also highly water-soluble and thus is bolus-injectable [29, 30]. Previous non-gadolinium liver-specific contrast agents did not allow for a single examination of both the vascular- and the liver-specific phase to be performed after a single injection in a reasonable time-frame. However, gadoxetate acid-enhanced MRI is injected as a bolus and allows for the acquisition of the delayed (hepatocyte-specific) phase at 20 minutes post injection via the mechanism described above, with a total examination time possible in 35 min.

The diagnostic performance of gadoxetate acid-enhanced MRI versus other forms of imaging or other contrast agents for MRI will be discussed in a separate section below.

*Gadobenate Dimeglumine.* Gadobenate dimeglumine (Gd-BOPTA; Multihance®, Bracco SpA, Milan, Italy), like gadoxetate acid, is a gadolinium-based, dual-acting (with combined extracellular and liver-specific properties) contrast agent, that provides two-level information of a suspected lesion: its vascularity (from the dynamic phase imaging) and its cellularity (from the hepatobiliary phase imaging). It has been shown to be safe and well-tolerated in preliminary studies [36–38].

One of the main differences between the two contrast agents (see Table 1) is the degree of hepatocyte uptake. With gadobenate dimeglumine, only 2–4% (as compared to 50% of gadoxetate acid) is taken up by functioning hepatocytes; it is predominantly (96%) cleared by the kidneys [37]. This has several implications: (1) theoretically, the higher proportion of contrast elimination via the kidneys means patients with significant renal impairment should not be

Table 1: Major differences between gadoxetate acid and gadobenate dimeglumine.

| Properties in comparison | Gadoxetate acid | Gadobenate dimeglumine |
|---|---|---|
| % contrast uptake | 50% | 2–4% |
| Hepatobiliary phase image acquisition | 10–45 minutes postcontrast administration | 60–120 min postcontrast administration |
| Duration of liver enhancement | 2 hrs | 4 hrs |
| Clearance | 50% biliary excretion, 50% renal excretion | 2–4% biliary excretion, 96% renal excretion |
| Recommended dosage | 0.025 mmol/kg, bolus injection at 2 mL/sec | 0.1 mmol/kg bodyweight, bolus injection at 2 mL/sec |

Table 2

| Differences | SPIO | Hepatobiliary agents |
|---|---|---|
| Targeting cells | Kupffer cells | Functioning hepatocytes |
| Liver parenchyma | Black liver | White liver |
| Malignant liver lesion | White nodule | Black nodule |

advised to undergo MR studies with this contrast; (2) acquisition time of the hepatocyte-specific phase occurs later than that of gadoxetate acid (40 min versus 20 min), (3) recommended dosage of contrast volume is different (higher with gadobenate dimeglumine) [36–39]. Despite the differences in the degree of hepatocyte uptake and the time course of liver enhancement, it has been found that both agents, during their maximum enhancement, provide comparable enhancement of the liver parenchyma [40]. For gadobenate dimeglumine, this is achieved because OATP phosphorylation—occurs when the agent is taken up into the hepatocytes—causes changes in MRP2 location and expression, preventing the exit of contrast material into bile [41, 42].

Several studies have demonstrated superior diagnostic performance of gadobenate dimeglumine-enhanced MRI in the detection and characterization of benign and malignant liver nodules over non-specific extracellular agents and ferumoxides [43–48]. In the detection of HCC, Choi et al. [49] reported a sensitivity of 80–85% and a positive predictive value of 65-66%.

*3.3. Reticuloendothelial Cell-Specific Agents.* Superparamagnetic iron oxide (SPIO) is another class of liver-specific contrast agents for MR imaging of the liver. Ferucarbotran (Resovist®; Bayer Schering, Berlin, Germany), a commonly used SPIO, works by targeting the Kupffer cells of the reticuloendothelial system (RES), which are present in various organs, including the liver, spleen, and bone marrow [50]. It is also administered intravenously as a bolus [51]. Unlike gadoxetate acid that can evaluate a liver lesion by its function and vascularity, SPIO can only evaluate a lesion functionally.

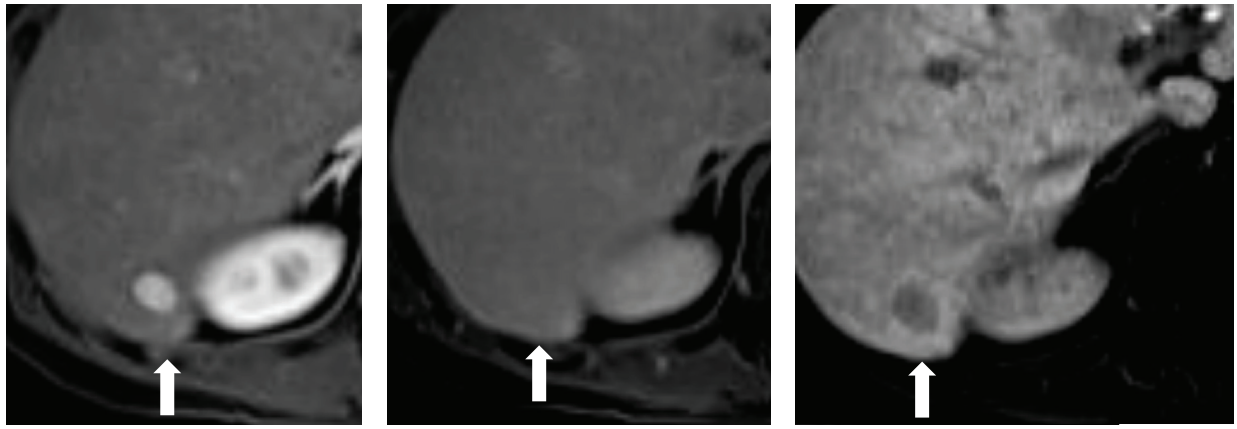
Generally, malignant lesions (HCC) are presumed to lack phagocytic activity and thus appear hyperintense with respect to the hypointense liver parenchyma on SPIO-enhanced MRI [27, 52]. This differs from findings of hepatocyte-specific contrast-enhanced MRI, where most HCC nodules appear hypointense with respect to the hyperintense liver parenchyma in the hepatobiliary phase. However, it is important to note that up to 60% of well-differentiated HCCs are not hyperintense on ferucarbotran-enhanced MRI possibly due to the fact that early HCCs may retain normal Kupffer cell function and counts [53–55].

Table 2 summarizes the major differences between the two types of liver-specific contrast agents.

## 4. Gadoxetate Acid for Detection and Characterization of HCC

The liver parenchyma enhances strongly in the hepatocyte phase on T1-weighted images, starting at 10–20 min after the intravenous injection of contrast. This forms the background against which various types of nodules, which do or do not contain functioning hepatocytes, stand out. Nodules that do not contain normal functioning hepatocytes, such as most HCC or liver metastases, lack contrast uptake and are usually depicted as low-intensity (hypointense) lesions. On the other hand, nodules that do contain (varying degrees of) functioning hepatocytes, such as regenerative nodules of focal nodular hyperplasia (FNH), appear enhanced, either to a similar or higher degree to the surrounding liver parenchyma.

*HCC.* Using AASLD criteria [56], HCC can be diagnosed noninvaively in at-risk patients with contrast-enhanced imaging, typically showing arterial phase enhancement and venous or delayed phase washout on CT or MRI [57, 58]. The presence of fat or late enhancing pseudocapsule are supportive features. Complementary features on MRI include mild-moderate hyperintensity on T2-weighted images and restricted diffusion on diffusion-weighted imaging (DWI) sequences. With the recent international consensus recognition of the early HCC nodule as a pathologic entity, their imaging correlates are also being increasingly recognized at hepatobiliary phase imaging as the decreased expression of anion transporters may predate the development of overt hypervascularity. At conventional dynamic contrast-enhanced imaging, a significant proportion of these early HCCs will not show typical diagnostic arterial phase hyperenhancement and would be potentially misdiagnosed as benign lesions, such as regenerative or dysplastic nodules. At hepatobiliary phase imaging post gadoxetate acid administration, 3 patterns of HCC have been described, depending on whether they express transporter molecules OATP1 [31] on their membranes: (1) typically, as arterial hypervascularized lesion and washout on a 3-min late phase MRI and hypointense lesion at 10–20-min hepatocyte phase



(a) (b) (c)

Figure 1: (a) Gadoxetate acid-enhanced MRI in the arterial phase in a 51-year-old male with alcoholic liver cirrhosis showing a hyperenhancing nodule in the liver segment 6. (b) Equilibrium phase imaging shows isointense appearance with no hypointense washout. The diagnosis of HCC is therefore not confirmed in the dynamic vascular phases. (c) Hepatobiliary phase imaging at 20 minutes after injection shows a hypointense nodule against the background of enhancing liver parenchyma, implying lack of lesional uptake. This additional information allowed more confident diagnosis of HCC. Final histopathology was a well-differentiated Edmondson-Steiner grade I HCC.

because most HCCs do not contain functioning hepatocytes and hence >80% of HCCs appear hypointense in relation to the surrounding enhanced liver parenchyma [59, 60]; (2) as isointense or hyperintense lesions at 10–20-min hepatocyte phase because some moderate or well-differentiated HCCs may overexpress anion transporters OATP1 resulting in uptake of contrast agent in 10–20% of cases [59, 60]; (3) occasionally in approximately 10% of HCCs especially small lesions may present as hypointense lesions on hepatocyte phase imaging without accompanying arterial hypervascularization or T2-weighted or DWI hyperintensity [61].

The following underlying cellular mechanism explains the above phenomena. In a normal liver, after intravenous administration, gadoxetate acid first reaches the extracellular space (the vasculature). It then enters the normal functioning hepatocytes via transporter molecule organic anion transporting peptides (OATPs) that are located in the hepatocyte's basolateral membrane. The contrast agents then exits the hepatocytes into bile (in 50% of injected contrast volume) through another transporter molecule located on the canalicular membrane, the multidrug resistance protein 2 (MRP2) [31–33]. In cirrhotics, these two transporter molecule expressions undergo modifications. It has been established that the presence of OATPs determines the uptake of gadoxetate acid in hepatocellular carcinoma [62]. In 2010, Tsuboyama et al. [63] found that when OATPs are present in HCC, the expression and location of MRP2 is the one ultimately responsible for the cellular accumulation or lack of it. If the MRP2 are present on the normal canalicular membrane, the contrast material will exit into bile and that HCC nodule will appear hypointense. Correspondingly, Tsuda and Matsui [64] found that the presence of liver cirrhosis upregulates MRP2, which promotes the elimination of gadoxetate acid. Thus, although some HCCs may contain OATPs, most still appear hypointense relative to the liver enhancement. On the contrary, if MRP2 is situated in the pseudoglands, the contrast agent will not be able to exit into bile, and its accumulation in the HCC lesion causes it to appear hyperintense [63]. A similar report regarding above findings with use of gadobenate dimeglumine has been described by Planchamp C and team in his animal study [41, 42].

Figures 1(a)–1(c) illustrate the features of a typical HCC on gadoxetate acid-enhanced MRI. Figures 2(a)–2(d) demonstrate how gadoxetate acid-enhanced MRI can assist in the characterization of a non-specific, non-enhancing lesion on triphasic CT scan. Figures 3(a)–3(f) demonstrate another HCC with hepatobiliary excretion on gadoxetate acid-enhanced MRI.

*4.1. Differentiating HCC from Regenerative or Dysplastic Nodules.* Regenerative or dysplastic nodules are theoretically not malignant and hence may be expected to exhibit normal expression of the uptake transporter OATP1 and the excretory transporter MRP2. They take up contrast material and appear enhanced unlike most HCC [65]. Kudo reported that the differentiation of HCC from premalignant lesion can be achieved with 93% accuracy when investigated with gadoxetate acid-enhanced MRI [66]. However, as hepatocarcinogenesis is a stepwise continuum, a variable proportion of high-grade dysplastic nodules will begin to show lack of uptake of gadoxetate acid, resulting in overlap with early HCCs [67]. This highlights the potential pitfall in these borderline category cases. Currently, the Japan Liver Oncology Group (JLOG) is conducting a clinical trial to address this issue, to determine the frequency of dysplastic lesions appearing as hypointense, isointense, or hyperintense lesion in the hepatocyte phase [68]. Preliminary data from an Italian study suggests that a proportion of hypointense nodules on hepatocyte phase are high-grade dysplastic nodules and not always specific for HCCs [67]. From a practical standpoint, it may be appropriate to follow

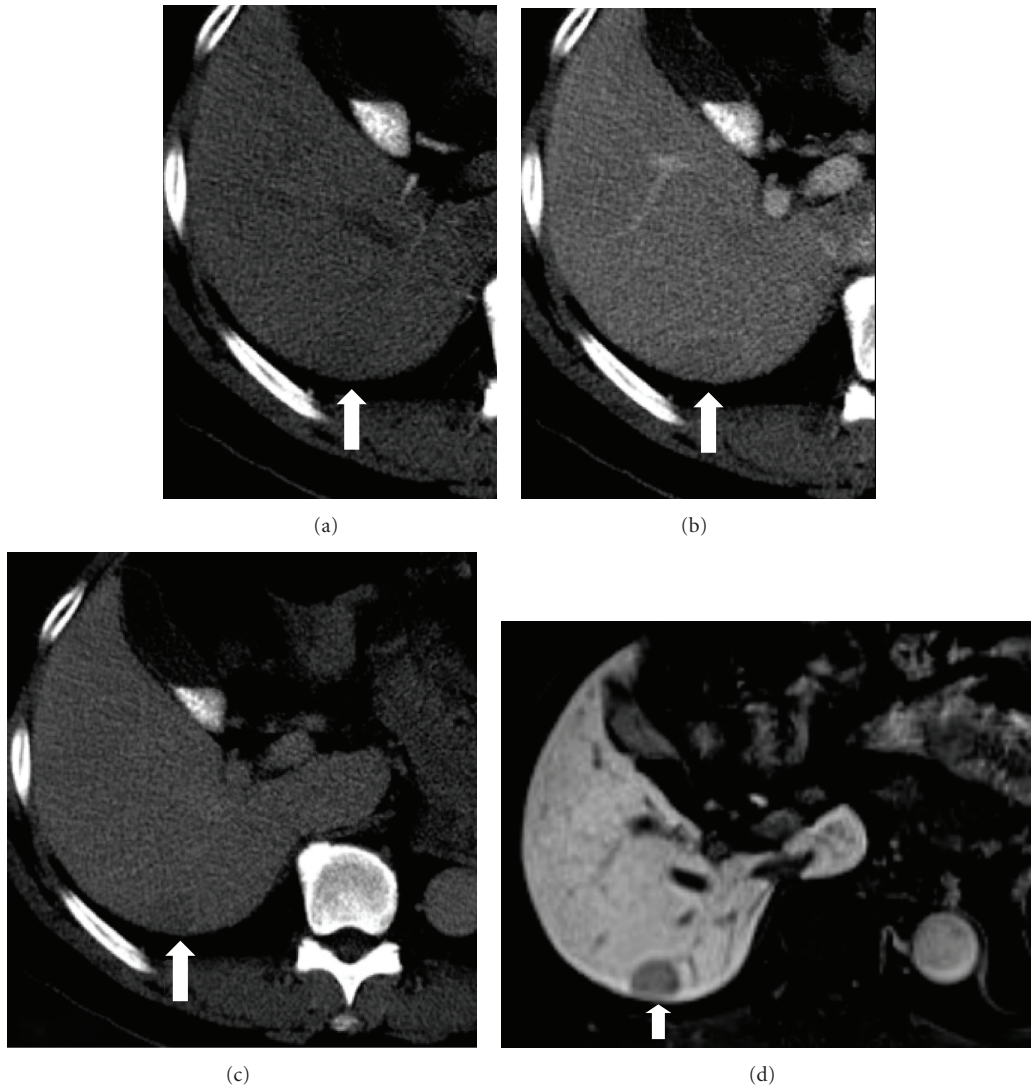



Figure 2: (a–c) Contrast-enhanced CT in the arterial, venous and equilibrium phases of a 75-year-old male Hepatitis B virus carrier showing an indeterminate slightly hypodense nonhypervascular nodule in the liver segment 6. (d) Gadoxetate acid-enhanced MRI in the hepatobiliary phase 20 minutes after injection showing a hypointense nodule against the background of enhancing liver parenchyma, implying lack of lesional uptake, suspicious for HCC or high-grade dysplastic nodule. Final surgical histopathology was a well-differentiated Edmondson-Steiner grade I HCC.

up these difficult nodules with interval imaging if they are smaller than 1.5 cm, whilst a more proactive approach such as biopsy may be advocated if lesions are larger than 1.5 cm since larger lesions tend to have a higher risk of malignancy or show microvascular invasion [69, 70].

*4.2. Differentiating HCC from Hypervascular/Arterial Enhancing Pseudolesions.* Arterioportal shunts are also one of the main mimickers of hypervascular HCCs on conventional dynamic contrast-enhanced CT and MRI [71, 72]. These are relatively of higher prevalence in the cirrhotic liver and appear as flash-enhancing lesions ranging from 5 to 20 mm and are typically not visible on other phases or sequences. However, as up to 50% of all flash-enhancing foci are eventually found to be HCCs, confident diagnosis at a single time-point is difficult without the benefit of serial followup. However, Motosugi and Sun et al. recently reported that gadoxetate acid-enhanced hepatocyte-phase MR images and diffusion weighted images are useful for distinguishing hypervascular pseudolesions from hypervascular HCCs [72, 73].

*4.3. Differentiating HCC from Focal Nodular Hyperplasia (FNH).* Although regarded as the second most common benign tumor of the liver, FNH is less of a consideration in the cirrhotic liver. Nonetheless, they can be confidently distinguished from adenomas/metastases on gadoxetate acid-enhanced MRI as they typically appear as isointense or hyperintense on hepatocyte-phase images due to the presence of functioning hepatocytes and the presence of biliary canaliculi. Accurate characterization of FNH has been reported as high as 88% [74, 75]. Unnecessary biopsies,

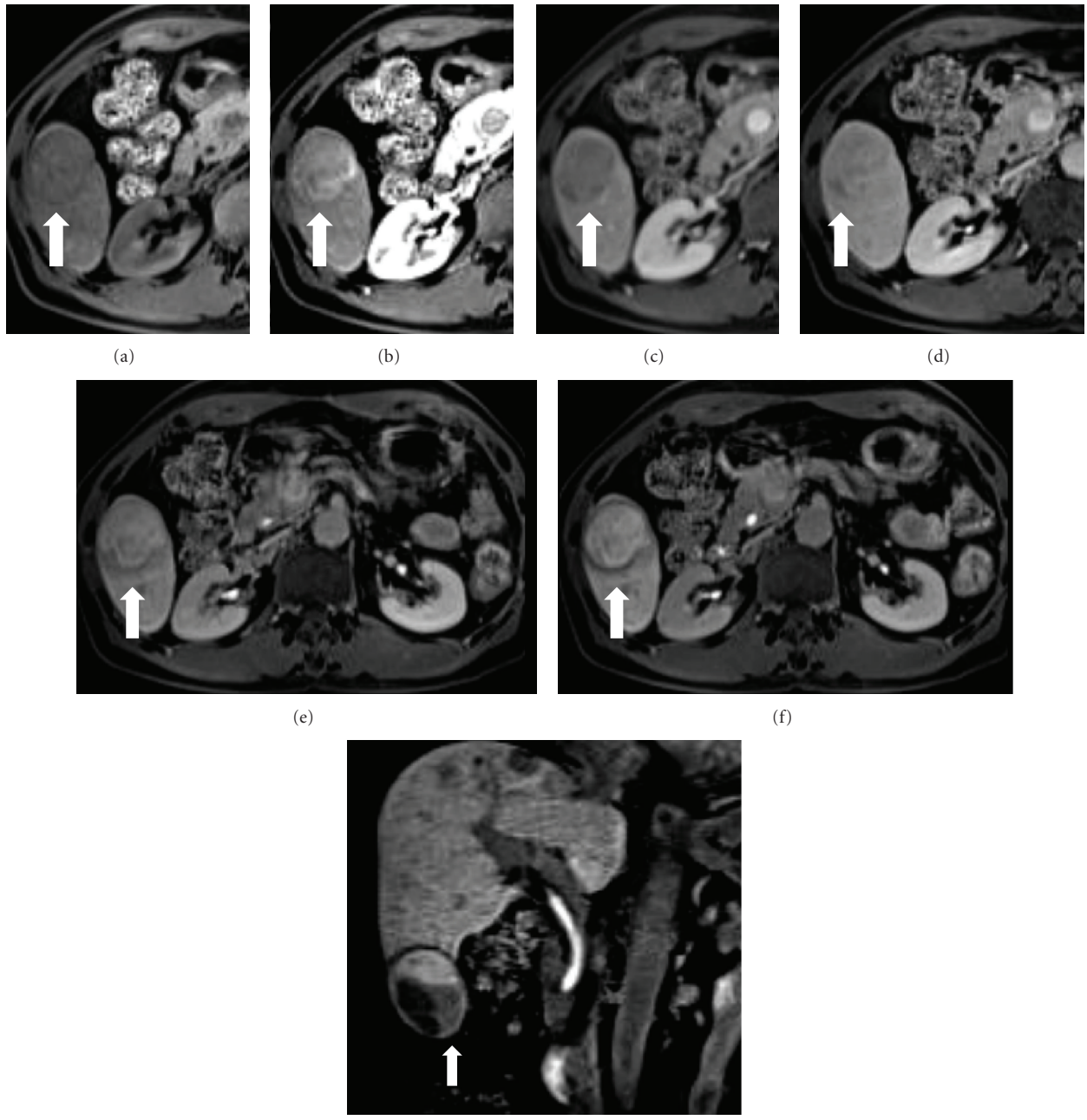



Figure 3: (a–d) Gadoxetate acid-enhanced MRI in the precontrast, arterial, venous, and equilibrium phases of Hepatitis B virus carrier showing a nodule in segment 6 of the liver with early arterial enhancement and late-phase washout compatible with HCC. (e), (f) Gadoxetate acid-enhanced MRI in the hepatobiliary phase 10–20 minutes after injection, showing progressively hyperintense portions of the nodule, implying lesional uptake, in a heterogeneous pattern. Note the hypointense pseudocapsule. Final surgical histopathology showed moderately differentiated Edmondson-Steiner grade II HCC. (g) Coronal view.

operations or close monitoring with 3–6 monthly MR or ultrasound imaging can be avoided.

Figures 4(a)–4(f) demonstrate typical FNH features on gadoxetate acid-enhanced MRI.

*4.4. Differentiating HCC from Liver Adenoma.* Hepatic adenoma is a rare, benign liver tumor that predominantly affects women who take oral contraceptive pills. Like FNH, adenomas are typically hypervascular during the arterial phase but there is no central scar. In the hepatobiliary phase, it is thought that adenomas do not typically accumulate gadoxetate acid due to absence of functioning biliary elements unlike FNH. However, a few cases with hyperintense appearance in the hepatobiliary phase have been reported [76–78]. Currently, there is little published data to confirm the predominant pattern for adenomas, and larger studies with histopathological confirmation are needed.

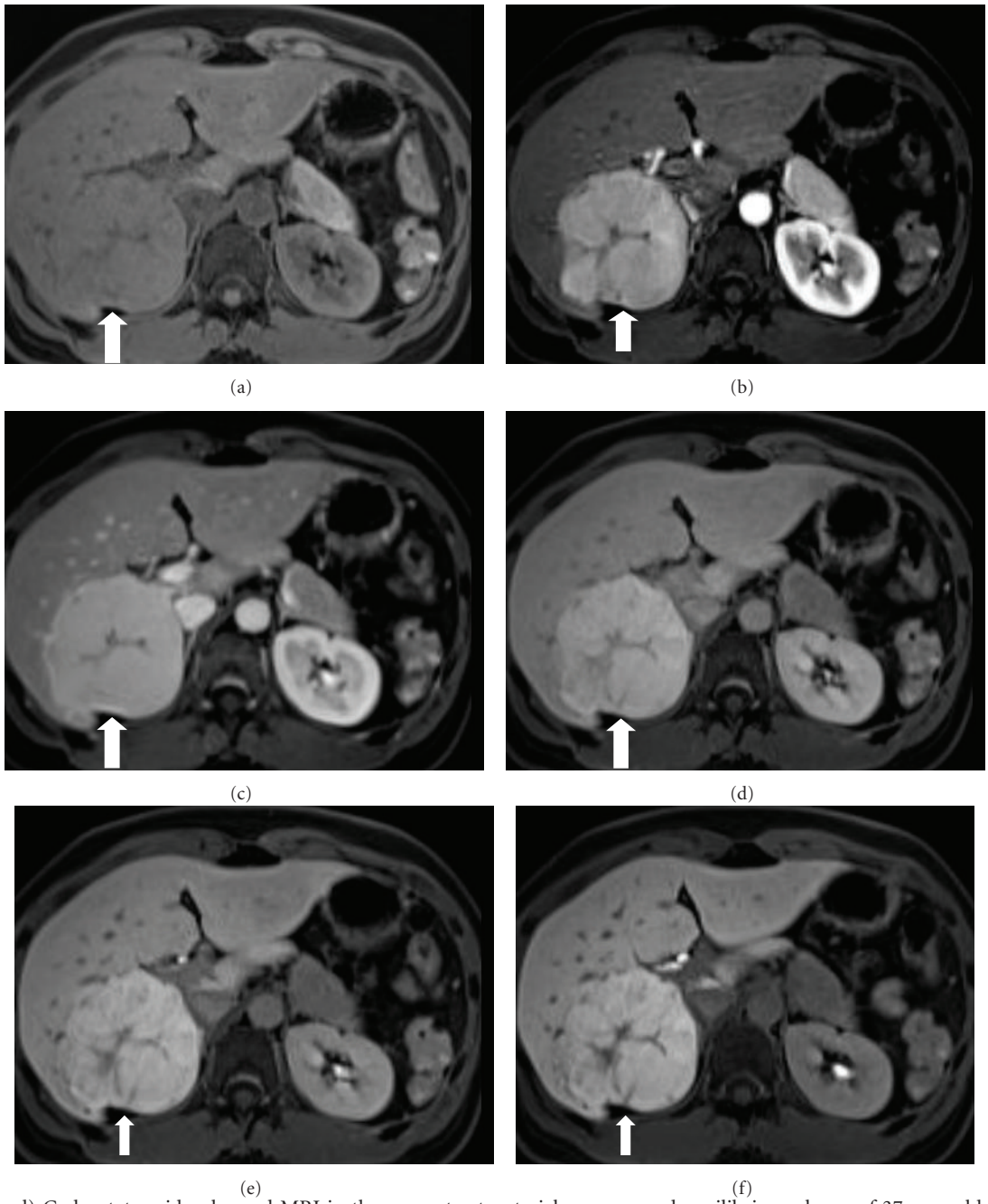



Figure 4: (a–d) Gadoxetate acid-enhanced MRI in the precontrast, arterial, venous, and equilibrium phases of 37-year-old female non-Hepatitis B or C virus carrier showing a large mass in the right lobe of the liver with early arterial enhancement and persistent late-phase enhancement with a small central hypointense scar. (e, f) Gadoxetate acid-enhanced MRI in the hepatobiliary phase 10–20 minutes after injection showing progressively hyperintense enhancement, in a homogeneous pattern apart from the hypointense small central scar. The MRI findings are typical for focal nodular hyperplasia.

## 5. Gadoxetate Acid: Sensitivity, Specificity, and Accuracy in HCC Detection in Comparison with Other Types of Contrast Agents or Imaging Techniques

Earlier studies comparing the diagnostic performance of gadoxetate acid-enhanced MRI against unenhanced MRI [75, 79, 80] and biphasic spiral CT [81, 82] showed clear superiority of gadoxetate acid-enhanced MRI over the other two in the detection and characterization of focal liver lesions, with as high as 10% increase in sensitivity [75, 79, 80] as compared to the unenhanced scan and 20% increase in sensitivity and 9% increase in specificity when compared to biphasic CT [81, 82]. This increase in diagnostic performance is notably significant for lesions smaller than 1 cm. At present, multidetector CT (MDCT) has surpassed spiral CT as the imaging of choice for the evaluation of focal liver lesion.

*5.1. Evaluation against MDCT.* In 2009, Kim et al. [59] reported his results on the diagnostic performance of gadoxetic acid-enhanced MRI and MDCT on the detection of HCC. His study population comprised of 83 HCCs (75 moderately-differentiated HCCs, 5 well-differentiated HCCs, 3 poorly-differentiated HCCs) with a mean size of 2.9 cm. Forty-eight percent of this population had Child-Pugh A cirrhosis; the rest had chronic hepatitis. The group found that although there is a trend for gadoxetate acid-enhanced MRI to have better performance in the detection of HCC, especially for those smaller or equal to 1 cm in size, there is otherwise no statistical significance in the performance of the two. The sensitivity was 91.6–94% in the gadoxetate group versus 82.2%–92.8% in the MDCT group. It is important to keep in mind that this study comprised mostly larger-sized tumors that are moderately-differentiated on the background of good liver function.

In the same year, another Korean group [83] published a statistically superior diagnostic accuracy result of HCC detection with gadoxetate acid-enhanced MRI when compared to MDCT. Here, 81 HCCs with a mean size of 1.5 cm were analysed by 2 observers. The group reported 91.4% sensitivity in the gadoxetate group versus 71.6% sensitivity in the MDCT group, with 24.7% higher percentage of HCC detection in smaller lesions (<1.5 cm). No nodules were missed at MRI but 4/81 nodules that were seen on MDCT were not verifiable on gadoxetate acid-enhanced MRI. It is important to note that more than 50% of the population had cirrhosis but not all had histological confirmation.

Finally, in 2010, Martino et al. [84] also found that gadoxetate acid-enhanced MRI yielded superior diagnostic performance in HCC detection in the 87 HCCs (mean size 1.8 cm) on the background of liver cirrhosis, in both the diagnostic accuracy and sensitivity, when compared with those analysed by MDCT. Diagnostic accuracy was 88% and 74% and average sensitivity was 85% and 69% for the gadoxetate group and the MDCT group, respectively. This increased performance is clear for lesions smaller than 1.5 cm as well. However, it must be noted that only 61% of the population had histological diagnosis.

### 5.2. Evaluation against Other Contrast Agents

*5.2.1. Comparing Gadoxetate Acid-Enhanced MRI and Gadobenate Dimeglumine-Enhanced MRI in the Detection and Characterization of HCC.* Although prior study showed that both gadoxetate acid and gadobenate dimeglumine can achieve similar enhancement in normal liver, this finding is different in the cirrhotic liver. Filippone [85] found, in his multicenter trial comprising of 70/295 patients with cirrhotic livers, that use of gadoxetate acid resulted in better liver enhancement in the overall (57.24% versus 32.77%) and in the cirrhotic subgroup (57.00% versus 26.85%) population than when gadobenate dimeglumine is used. The enhancement pattern of liver parenchyma for the cirrhotics on gadoxetate acid-enhanced MRI, however, was comparable to the enhancement ability achieved in the overall population using gadoxetate acid (57.00% versus 57.24%).

Based on these above findings, one would think that this means definite improvement in HCC detection in gadoxetate acid-enhanced MRI compared to gadobenate dimeglumine-enhanced MRI in the detection of HCCs in the cirrhotic subgroup because of presumed increase in liver-to-lesion contrast. However, Park et al. [86]—who, to the authors' best knowledge, is the only group that compared the diagnostic performance of gadoxetate acid- and gadobenate dimeglumine-enhanced MRI for the detection of hepatocellular carcinoma—reported similar diagnostic performance of gadoxetic acid- and gadobenate-enhanced MRI. It is important to note here that the study population is small (18 patients with 22 HCCs), with a relatively large-sized HCCs (mean size of 2.9 cm) and in patients with good liver function. Overall, the authors still advocate the use of gadoxetate acid due to the other additional benefits of earlier enhancement and shorter total examination time.

*5.2.2. Comparing Gadoxetate Acid-Enhanced MRI and SPIO-Enhanced MRI in the Detection and Characterization of HCC.* SPIO has been used and proven effective in the detection of malignant focal liver lesions, both HCC and metastases [87, 88], with a sensitivity range of 68%–97% [89, 90].

Kim et al. [91] reported significantly improved sensitivity (90.7% versus 84.7%) in the detection of 118 histologically confirmed HCCs by gadoxetate acid-enhanced MRI when compared with SPIO-enhanced study. The authors noticed that the improved sensitivity is most pronounced for lesions greater than 1.5 cm in size and that lesion characterization with certainty remains an issue with gadoxetate acid-enhanced MRI, despite its superior detection rate.

Lee et al. [92] reported similar diagnostic performance between gadoxetate acid- and ferucarbotran-enhanced MRI on a 3.0-T unit in a population of 38 histologically proven HCCs. However, it should be noted that the majority of the HCCs in the study were of relatively larger size (mean size of tumors is 2.8 cm), and 34/38 HCCs were moderately differentiated HCCs.

Okada et al. [93] set out to compare the diagnostic performance between the two types of contrast-enhanced MRI in characterizing enhancement patterns of well-differentiated HCC and dysplastic nodules. They can have similar MRI features, making accurate radiological diagnosis difficult. His study population of HCCs was different from the study by Lee. In this prospective study analyzing 37 histologically proven HCC in 36 patients: 22/37 were well-differentiated HCCs with a mean size of 14 mm (sizes ranging from 6 to 28 mm; 15/37 were moderate to poorly-differentiated HCCs (as compared to the study by Lee JY where 35/38 were moderately-differentiated HCCs) with sizes ranging from 13–46 mm; 4 were dysplastic nodules with a mean of 16 mm (sizes ranging from 13 to 22 mm). Okada found gadoxetate acid-enhanced MRI to be more sensitive than ferucarbotran-enhanced MRI in the accurate evaluation of the enhancement patterns of his study population. However, one must note that 74% of patients in the study were Child-Pugh class A; Child-Pugh class C were excluded from the study.

## 6. Accepted Gadoxetate Acid-Enhanced MR Protocol

The current suggested protocol for gadoxetate acid-enhanced MR imaging of the liver comprises two main parts, as laid out

below [69, 76]. In order to reduce the time the patient spends in the MRI room, the longer T2-weighted and diffusion-weighted sequences can be performed after the dynamic post-contrast phase, rather than prior to the injection of contrast as in conventional MRI protocols, without significant alteration of the lesional signal characteristics. The total scan time is slightly longer than conventional MR but the difference is minimized by this rearrangement of the sequences.

(1) Precontrast sequences (similar to that of conventional MR imaging) includes the following.

   (a) Coronal single shot, fast spin echo T2-weighted sequences.

   (b) T1-weighted in/opposed phase. This combination sequence allows comparison of the varying signal intensities of the same lesion, further defining its true nature. This sequence is most helpful in the interpretation of fat-containing tissues or lesions, for example, in the determination of hepatic steatosis. Fatty lesions demonstrate "signal drop"—where fat, which is bright during the 'in' phase, appears correspondingly darker in the "opposed" phase.

   (c) T1-precontrast sequence. This forms the baseline signal to which post-contrast images are compared to.

(2) Administration of gadoxetate acid, either as a standard dose of 10 mls or 0.025 mmol/kg body weight of gadoxetate acid, given as an intravenous bolus at 1.5–2 ml/sec, flushed immediately with 20 mL saline.

(3) Post-contrast sequences are then obtained in the following manner.

   (a) Dynamic imaging.

      (i) T1-weighted dynamic images are to be obtained immediately post-contrast administration. This includes the arterial, porto-venous, and equilibrium phase up to 5 minutes post-contrast images. These images evaluate a lesion's perfusion and washout characteristics.

   (b) Axial T2-weighted and diffusion-weighted sequences.

   (c) Hepatobiliary phase.

      (i) T1-weighted hepatobiliary phase in both axial and coronal views. These images are usually acquired at 10–20 minutes post contrast administration. This hepatobiliary phase utilizes the unique properties of gadoxetate acid, as discussed earlier, to yield additional valuable information for lesion characterization.

## 7. Area of Future Studies

Most HCCs arise in the background of cirrhosis. Most of these early small nodules (<2 cm) in the background of early liver cirrhosis have been shown to appear hypointense relative to the surrounding liver parenchyma on the hepatocyte-specific phase of gadoxetate acid-enhanced MRI [60, 61, 94–98], although the signal enhancement of cirrhotic liver parenchyma is not as strong as that of normal liver [69, 80]. However, challenges remain in three categories of patients: (1) those that have small lesions in the background of early liver cirrhosis—distinguishing the small HCCs from other premalignant nodules is difficult radiologically; (2) those with renal impairment—can gadoxetate acid be safely used in this group of patients?; (3) those with advanced or decompensated liver cirrhosis—suboptimal or no enhanced liver-to-lesion contrast can be achieved.

Cruite et al. [65] discussed the reasons behind the 3 unique diagnostic challenges faced in the diagnoses of HCCs in patients with advanced or decompensated cirrhosis. Firstly, there is expected impairment of contrast agent uptake due either to the reduced number of functional or the presence of dysfunctional hepatocytes. Secondly, there may be delayed or decreased biliary excretion from the impaired contrast uptake. Correspondingly, enhancement of the liver parenchyma, and the liver-to-lesion conspicuity, is decreased. In addition, there may also be pooling of contrast agent in the blood because of the significant reduction in the hepatic, and possibly renal, elimination as patients with advanced liver disease often have renal impairment as well, making gadoxetate acid behave like an ECF agent. Further studies are required to confirm the role of gadoxetate acid-enhanced MRI in the diagnosis of liver lesions in these groups of patients.

## 8. Summary

Gadoxetate acid-enhanced MRI of the liver has certain advantages over other imaging modalities in the detection and characterization of HCC in the high-risk liver. With increasing experience and application globally, it may potentially be established as the diagnostic imaging modality of choice in this setting.

## Disclosure

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*Review Article*

# Targeted Therapy in Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is one of the commonest cancers worldwide, as well as a common cause of cancer-related death. HCC frequently occurs in the setting of a diseased cirrhotic liver and many patients present at an advanced stage of disease. Together with a poor functional status, this often precludes the use of systemic therapy, especially conventional cytotoxic drugs. Moreover, HCC is known to be a relatively chemo-refractory tumor. There have been many targeted drugs that have shown potential in the treatment of HCC. Many clinical trials have been carried out with many more in progress. They include trials evaluating a single targeted therapy alone, two or more targeted therapy in tandem or a combination of targeted therapy and conventional chemotherapy. In this article, we seek to review some of the more important trials examining the use of targeted therapy in HCC and to look into what the future holds in terms of targeted treatment of HCC.

## 1. Introduction

Liver cancer is the sixth most common cancer worldwide, accounting for 5.7% of new cancer cases, and the third most common cause of cancer-related death [1]. The majority of cases and deaths occur in developing countries. Of the primary liver tumors in adults, hepatocellular carcinoma (HCC) is the commonest [2].

HCC frequently occurs in the setting of a diseased cirrhotic liver. It has well-defined risk factors, the most common being infections with hepatitis B virus (HBV) and hepatitis C virus (HCV). Chronic excessive alcohol consumption, environmental toxins, for example, aflatoxin B and nonalcoholic steatohepatitis (NASH), make up the rest of the main causes. The etiological factors vary by geographical locations [3]. In Africa and East Asian countries including Taiwan, China, and Korea, HBV is the main cause whereas in the West and in Japan, HCV is the main risk factor, together with other causes of cirrhosis including alcohol [3, 4].

The asymptomatic nature of a HBV and HCV carrier state, the insidious presentation of early HCC, and screening programs that are not properly defined or adhered to results in the majority of patients with HCC presenting at an intermediate or advanced state. Potentially curative strategies such as resection and transplantation as well as loco-regional therapies such as radiofrequency ablation and transarterial chemoembolization are often not possible at these stages.

Systemic treatment with chemotherapy is not routinely employed in the treatment of advanced HCC for a variety of reasons. As HCC usually occurs in the context of a diseased cirrhotic liver, poor hepatic reserves often preclude or limit systemic chemotherapy. Also, HCC is known to be a relatively chemorefractory tumor, in part due to overexpression of drug-resistant genes including *MDR1* [5]. Trials involving chemotherapeutic agents were carried out in diverse populations, limiting their application across the board to the entire cohort of HCC patients.

Several studies of chemotherapeutic agents have shown them to have limited activity in HCC [6–8]. Various clinical trials investigating the role of single-agent chemotherapy on the other hand have previously reported response rates from 0% to 20%. Anthracyclines, for example, doxorubicin have shown a response rate of up to 20% [9–12]; their usage, though, has been limited by elevated toxicity.

A randomized phase III study by Yeo et al. [13] reported a response rate of 21% using PIAF (cisplatin, doxorubicin, interferon, and fluorouracil) in 91 of 94 assessable patients with unresectable HCC with a median overall survival (OS) of 8.7 months. Lombardi and colleagues demonstrated a response rate of 24% with pegylated liposomal doxorubicin

and gemcitabine in patients with advanced HCC [14]. In this study, one patient went on to undergo liver transplantation and another underwent surgical resection. About half of the patients were Child-Pugh B.

Although chemotherapy in advanced HCC has been shown in various trials to have relatively significant response rates, its usage is limited by toxicities, especially in patients with poor hepatic reserves. Moreover, the phase III trial using PIAF did not show survival benefit over single agent doxorubicin alone.

The poor prognosis of patients with advanced or metastatic HCC, with a median survival of a few months [15], coupled with suboptimal chemotherapy efficacy and inability of patients with poor liver function to tolerate chemotherapy, has resulted in a need for alternative treatment strategies.

## 2. Molecular Pathogenesis of HCC

Two main mechanisms are thought to predominate in the pathogenesis of HCC. The first being cirrhosis after tissue damage resultant from either HBV, HCV infections or toxins such as aflatoxin B and from metabolic causes including obesity and NASH [16, 17]. The second is that of oncogene or tumor suppressor gene mutations [18–23]. Both are associated with abnormalities in cell signaling pathways. Targeting various levels in the signaling cascade may help in both the chemoprevention and the treatment of HCC.

Various signaling pathways have been implicated in HCC, including VEGFR, EGFR, ERK/MAPK, and mTOR, among others [17, 24].

## 3. Vascular Endothelial Growth Factor Receptor (VEGFR) Pathway

HCC is a vascular tumor and is dependent on angiogenesis for growth. Important growth factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), angiopoietins, and fibroblast growth factors. These induce angiogenic signaling via various pathways, including the activation of the RAF/ERK (extracellular regulated kinase)/MAPK (mitogen-activated protein kinase), mammalian target of rapamycin (mTOR), and WNT-signaling transduction pathways.

Adult hepatocytes are able to upregulate the production of the growth factors listed above following liver damage or injury. This up-regulation is usually transient but poses a problem when it becomes dysregulated in a chronically injured liver, leading to sustained growth signaling [25].

Vascular endothelial growth factor (VEGF) is a primary mediator of angiogenesis in HCC [26, 27]. The upregulation of VEGF and increased expression of VEGFR have been demonstrated in both HCC cell lines and serum of HCC patients [28–32].

The disruption of the VEGFR pathway and targeting growth factors that drive the angiogenic process can thus interrupt effective angiogenesis and have clinical effect in the treatment of HCC. Antiangiogenic drugs such as sorafenib and bevacizumab target different points along the VEGFR pathway.

## 4. Sorafenib

Sorafenib (Nexavar, Bayer HealthCare Pharmaceuticals-Onyx Pharmaceuticals) is an oral multikinase inhibitor. It has potent effects against VEGFR-2, VEGFR-3, and PDGFR and also targets kinases of wild-type B-Raf, mutant V559EB-Raf, and C-Raf [25]. Its main action is thought to be that of competitively inhibiting ATP binding to the catalytic domains of the various kinases [33].

Preclinical experiments in mouse xenograft model of human hepatocellular carcinoma showed that sorafenib had antiproliferative activity and that it reduced tumor angiogenesis and tumor cell signaling as well as increased tumor cell apoptosis [34].

A phase II study by Abou-Alfa et al. [35] (see also Table 1) of 137 patients with advanced HCC showed that high pretreatment levels of pERK (phosphorylated extracellular regulated kinase) correlated with a longer time to progression (TTP) following treatment with sorafenib. This suggests that tumors containing higher levels of pERK are more sensitive/responsive to sorafenib and that the Raf/ERK/MEK pathway has an important role in HCC. Significantly, it has also identified pERK as a potential biomarker with predictive significance in HCC.

In this study, 34% of patients achieved stable disease (SD) for at least 16 weeks and 8% achieved partial response (PR) or minor response (MR). The median OS was 9.2 months. Compared to historical controls, the results appear favorable. For example, single-arm studies evaluating combination therapy (cisplatin, interferon, doxorubicin and fluorouracil (PIAF) or doxorubicin plus cisplatin) in HCC patients [36, 37] demonstrated median overall survival (OS) of 8.9 and 7.3 months and SD rates of 28% and 16%, respectively.

Important grade 3/4 adverse events observed included hand-foot skin (HFS) reaction, diarrhea, and fatigue, but they were infrequently dose-limiting. No clinically relevant pharmacokinetic differences between Child-Pugh (CP) Class A and Class B patients were noted, and it is unlikely that any dose adjustment is required when administering sorafenib to these 2 groups of patients.

Of note, 72% of patients were classified as CP Class A and 28% as CP Class B. 17% were HBV positive and 48% were HCV positive.

Two subsequent pivotal studies then led to the approval of sorafenib for the treatment of advanced HCC in the USA and Europe [38, 39].

The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) [38] trial by Llovet et al. was concluded early after the second interim analysis showed that advanced HCC patients treated with sorafenib had a significant survival benefit over placebo-treated controls.

This was a multicenter, double-blinded, and placebo-controlled phase 3 trial of 602 patients with advanced HCC with no previous systemic therapy randomized to either 400 mg of sorafenib twice daily or matching placebo. Treatment was continued until the occurrence of both radiologic progression as defined by RECIST [40] and symptomatic progression as defined by the Functional Assessment of Cancer Therapy-Hepatobiliary Symptom Index 8 (FHSI8)

Table 1

| Agent | Study | Phase | Comparator arm | No. of patients | Response rate | TTP (median months) | OS (median months) | AEs |
|---|---|---|---|---|---|---|---|---|
| Sorafenib | Abou-Alfa et al. [35] | II | — | 137 | 34% SD<br>8% PR/MR | — | 9.2 | HFS, diarrhea, fatigue |
| | SHARP trial Llovet et al. [38] | III | Vs placebo | 602 | 2% PR<br>No CR | 5.5 versus 2.8 | 10.7 versus 7.9 | HFS (21%), diarrhea (39%) |
| | Cheng et al. [39] | III | Vs placebo | 271 | — | 2.8 versus 1.4 | 6.5 versus 4.2 | HFS (45%), diarrhea (26%), rash (20%), fatigue (20%) |
| Sorafenib + TACE | START trial Chung et al. [41] | II | — | 50 (evaluable) | 36% CR<br>60% PR/SD | — | — | — |
| Sorafenib + doxorubicin | Abou-Alfa et al. [42] | II | Vs doxorubicin | 96 | — | 6.4 versus 2.8 | 13.7 versus 6.5 | Same both arms |
| Bevacizumab | Siegel et al. [43] | II | — | 46 | 13% PR | | 53% (1 yr)<br>28% (2 yr)<br>23% (3 yr) | Hypertens ion (15%), thrombos is (6%) |
| Bevacizumab + gemcitabine + oxaliplatin | Zhu et al. [44] | II | — | 30 (evaluable) | 20% RR<br>27% SD | — | 9.6 | — |
| Bevacizumab + capecitabine + oxaliplatin | Sun et al. [45] | II | — | 30 (evaluable) | 13% PR<br>77% SD | 4.5 | 10.3 | — |
| Bevacizumab + capecitabine | Hsu et al. [46] | II | — | 45 | 9% RR<br>52% CR/PR/SD | 2.7 (PFS) | 5.9 | HFS 9%<br>BGIT 9% |
| Bevacizumab + erlotinib | Thomas et al. [47] | II | — | 40 | — | 9 (PFS) | 15.6 | BGIT 13%, fatigue 20%, hypertens ion 15% |
| Sunitinib | Zhu et al. [48] | II | — | 34 | 50% SD | 4.1 | — | — |
| | Faivre et al. [49] | II | — | 37 | 2% PR<br>35% SD | 3.7 (PFS) | 8 | Significant 4 deaths, trial stopped |
| ABT-69 | Toh et al. [50] | II | — | 44 (34 evaluable) | 8.7% (23 CP A pts) | 3.7 | 9.8 | Mostly mild mod |
| Erlotinib | Philip et al. [51] | II | — | 38 | 9% PR | 32% (6 months PFS) | 13 | — |
| | Thomas et al. [52] | II | — | 40 | — | 28% (6 months PFS) | 3.3 | — |

RR: overall response rate, MR: minor response, PR: partial response, SD: stable disease, CR: complete response, PFS: progression-free survival, TTP: time to progression, OS: overall survival, AEs: adverse events, HFS: hand-foot syndrome, BGIT: bleeding gastrointestinal tract, CP A: Child Pugh A.

questionnaire or the occurrence of either unacceptable adverse events or deaths.

The results were encouraging, with a median OS of 10.7 months in the sorafenib group versus 7.9 months in the placebo-treated group (hazard ratio in the sorafenib group, 0.69; 95% confidence interval (CI), 0.55 to 0.87; $P < .001$). Although there was no significant difference between the two groups in the median time to symptomatic progression (4.1 months versus 4.9 months, respectively, $P = .77$), the median time to radiologic progression was almost doubled, 5.5 months in the sorafenib group versus 2.8 months in the placebo group ($P < .001$). 7 patients (2%) in the sorafenib group and 2 (1%) in the placebo group had a PR, no patient had a complete response (CR).

Similar to the phase II trial by Abou-Alfa et al. [35], HFS, diarrhea, and weight loss were the most common side effects in the sorafenib group. Adverse effects reported for patients receiving sorafenib were predominantly grade 1 or 2 in severity and mainly gastrointestinal, dermatologic, or constitutional in nature. In particular, diarrhea, hand-foot skin reactions (HFS), weight loss, alopecia, and anorexia were significantly more common in the sorafenib group compared to the group receiving placebo. Grade 3 adverse effects included diarrhea (8% in sorafenib group versus 2% in placebo group, $P < .001$) and HFS (8% versus <1%, $P < .001$). Except for grade 3 hypophosphatemia (11% versus 2%, $P < .001$), grade 3 or 4 laboratory abnormalities occurred at similar frequencies in both groups. The most common adverse events leading to sorafenib discontinuation were gastrointestinal events (6%), fatigue (5%), and liver dysfunction (5%). The rate of discontinuation of study drug due to adverse events, however, was similar in both groups (38% versus 37%).

This was the first phase III study of a systemic therapy to have shown a survival advantage in patients with advanced HCC. In this group of patients with advanced HCC, the median OS and time to radiologic progression were nearly 3 months longer for patients treated with sorafenib than those given placebo.

This group of patients was carefully selected, with the majority having eastern cooperative oncology group (ECOG) performance status of 0 or 1 and the remainder ECOG 2 status. They were CP Class A. 56% of the patients had HCV.

A second similar study was conducted in Asia with 271 patients with advanced (unresectable or metastatic) HCC [39]. None had prior systemic therapy, and all had CP Class A. This trial had no predefined primary endpoint, and the objective was to assess the efficacy and safety of sorafenib in Asia-Pacific patients with advanced HCC.

Median OS was 6.5 months (95% CI 5.56–7.56) in patients treated with sorafenib compared to 4.2 months (95% CI 3.75–5.46) in the placebo group, hazard ratio 0.68 (95% CI 0.50–0.93, $P = .014$). Median time to progression (TTP) was 2.8 months in the sorafenib group and 1.4 months in the placebo group. There was no significant difference in the time to symptomatic progression (TTSP) between the two groups.

Like in the previous studies, sorafenib was generally well tolerated with manageable side effects. The most common drug-related adverse events in the sorafenib group were HFS (67 out of 149 patients (45%)), diarrhea (38 of 149 (25.5%)), alopecia (37 of 149 (24.8%)), fatigue (30 of 149 (20.1%)), rash or desquamation (30 of 149 (20.1%)), hypertension (28 of 149 (18.8%)), and anorexia (19 of 149 (12.8%)). These were predominantly grade 1 or 2 adverse events.

In comparison, overall incidence of HFS was 21% and diarrhea 39% in the SHARP study. In this Asian study, treatment discontinuation due to adverse events was similar in both groups (19.5% versus 13.3%). Dose reductions due to adverse events were required in 30.9% (46 of 149 patients) of patients in the sorafenib group compared to 2.7% (2 of 75) in the placebo group. Most common reasons for dose reductions in the sorafenib group were HFS (11.4%) and diarrhea (7.4%).

Although the absolute survival was greater in the SHARP trial for both study groups, the hazard ratios (HRs) for survival (i.e., reduction in the risk of death associated with sorafenib treatment) was comparable between the two studies (0.68 in the study by Cheng et al. [39] and 0.69 in the SHARP trial [38]). This suggests that there is comparable efficacy for sorafenib in both studies and that there are differences in the patient population in the two studies.

Indeed, at baseline, more patients had extrahepatic spread, greater number of hepatic tumor lesions, poorer ECOG status and higher alpha-fetoprotein (AFP) levels in the study by Cheng et al. than in the SHARP trial. It may well be than the patients enrolled in the former study had more advanced disease than those in the latter, accounting for the difference in the absolute survival for both sorafenib and placebo groups across the two studies.

However, other significant differences exist between the two studies. As previously stated, etiological factors for HCC in the Asia-Pacific region differ from other regions. For example, 73% of the patients in the study by Cheng et al. had baseline HBV infection and 8.4% had baseline HCV infection, compared with 12% and 30% for HBV and HCV, respectively, in the SHARP trial. There has been some evidence that patients with HBV-associated HCC may have worse prognosis that those with HCV-related HCC [53] and others which suggests sorafenib may be less efficacious in HBV patients [54].

A subset analysis of their patients with HBV infection showed that those treated with sorafenib had longer OS and TTP than those given placebo, and another study showed that the safety profile of sorafenib in HBV patients was similar to the overall study population [55], leading the authors to conclude that sorafenib is just as efficacious in HBV patients.

Subgroup analysis of patients with HCV in the SHARP study showed similar safety profile in the 178 patients with HCV compared to the overall population [56]. Adverse events were mostly predictable and manageable. OS and TTP in this subset of patients were similar to those of the overall study population. These findings support the efficacy and safety results reported in the SHARP trial in patients with HCC and demonstrate a consistent clinical benefit regardless of HCV status.

Although sorafenib is approved in the USA for the treatment of all unresectable advanced HCC based on the trials above, the results need to be interpreted with caution. In both trials, patients recruited were CP Class A and had relatively good performance status (ECOG 2 or less). These patients were chosen as it was felt liver function impairment associated with CP Class B or C may potentially confound the results of the study. Hence, the effect of sorafenib in patients with poor liver function or decompensated liver disease is still unclear.

The study by Abou-Alfa et al. [35] suggests no difference in the tolerability of sorafenib in patients with CP Class A or B disease. Updated data from this trial suggests a similar pharmacokinetic and toxicity profile for CP Class A and B patients [57]. 28 out of 137 patients had blood samples analyzed for pharmacokinetics (21 CP A and 7 CP B patients).

AUC (0–8) and Cmax were comparable, as were incidence rates for all adverse events and serious adverse events. Elevated bilirubin in this analysis may be related to sorafenib inhibition of UGT1A1 activity. As expected, CP B patients did worse than CP A patients, with more frequent worsening of their liver cirrhosis. It was unclear, though, if this was drug related or due to underlying disease progression. More data is needed to confirm the safety and efficacy of sorafenib in CP B patients.

Pinter et al. [58] also reported a retrospective series evaluating sorafenib in 59 patients, 40% of whom had CP Class B disease and 17% CP Class C disease. The median survival times for these patients with CP Class A, B, and C disease were 8.3, 4.3, and 1.5 months, respectively, leading the authors to conclude that there was no benefit from systemic targeted therapy in patients with very advanced HCC. A phase I and pharmacokinetic study suggested that sorafenib doses should be titrated against the bilirubin levels (an indication of degree of liver dysfunction) and patients with severe liver impairment may not even be able to tolerate attenuated doses [59].

Further studies to evaluate and confirm the benefits and safety of sorafenib in HCC patients with poorer liver function are required. Also the role of sorafenib as an adjuvant therapy after resection or locoregional therapy needs to be studied, as well as the efficacy of combining sorafenib with either chemotherapy or other targeted therapies.

START, a phase II study of the combination of transcatheter arterial chemoembolization (TACE) with sorafenib in Asian patients with unresectable HCC is still ongoing [41]. The second interim analysis of 50 patients evaluable for efficacy showed that 20 (40%) did not require more than 2 TACE procedures. And of these, 18 achieved a CR while 2 had progressive disease. The remainder 30 had PR or SD. Grade 3 adverse events (AEs) occurred in 38 patients (60%), most common of which was hand-foot syndrome. There was 1 grade 4 AE (AST elevation). All AEs improved with sorafenib dose modification, and no patient discontinued due to AE. Preliminary data hence shows that the combination of TACE and sorafenib is safe and tolerable, and further results are awaited.

A phase II trial evaluating the safety and efficacy of doxorubicin plus sorafenib compared to doxorubicin alone in patients with advanced HCC, and CPA disease was conducted by Abou-Alfa and colleagues [42]. In this study, patients were randomly assigned to receive 60 mg/m$^2$ of doxorubicin intravenously every 21 days plus 400 mg of either sorafenib or placebo orally twice a day. Ninety-six patients were accrued and following complete accrual, an unplanned early analysis for efficacy was performed and the trial was halted. The median time to progression was 6.4 months in the doxorubicin-sorafenib group and 2.8 months in the doxorubicin-placebo group. PFS was 6.0 months, and 2.7 months and median OS was 13.7 months and 6.5 months in these 2 groups, respectively. Toxicity profiles were similar to those for single agents.

Synergism between sorafenib and doxorubicin is postulated to be the reason behind the improved TTP, OS, and PFS in the group on combined therapy. An ongoing phase III study in advanced HCC patients comparing sorafenib with and without doxorubicin is underway [60]. This combination is as yet not indicated for routine clinical use.

Yau and Chan conducted a phase II trial of sorafenib with capecitabine and oxaliplatin (SECOX) in 51 patients with locally advanced or metastatic hepatocellular carcinoma [61]. In this single-arm, multicentre study, the SECOX regime demonstrates significant clinical activity and good tolerability in this group of patients.

Eighty-four percent of patients were chronic HBV carriers, and 98% had CP A cirrhosis. The best response rate (RR) was 14%, and 61% achieved SD, with median TTP being 7.1 months and OS 10.2 months. Toxicities were mainly grade 1 or 2, with hand-foot syndrome (73%), diarrhea (69%), and neutropenia (63%) being the most commonly encountered.

Notwithstanding the above studies, sorafenib as single agent remains the only drug so far that has shown overall survival benefit over placebo in a multicentre, double-blind, placebo-controlled randomized phase III trial in patients with advanced HCC [38, 39].

## 5. Bevacizumab

Bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA, USA) is a recombinant humanized monoclonal antibody directed against VEGF [62]. Bevacizumab is also used in the treatment of other malignancies including colon, breast, and kidney cancer. It has been studied both as a single agent, as well as in combination with chemotherapeutic or targeted agents, for example, erlotinib, in the treatment of patients with advanced HCC.

A phase II study of 46 patients using bevacizumab alone in unresectable HCC by Siegel et al. [43] reported a 13% partial response (PR). The 6-month progression-free survival (PFS) was 65%. Overall survival (OS) at 1, 2, and 3 years was 53%, 28%, and 23%, respectively. Grade 3 to 4 adverse events included hypertension (15%) and thrombosis (6%, including 4% with arterial thrombosis). Grade 3 or higher hemorrhage occurred in 11% of patients, including one fatal variceal bleed.

Bevacizumab was also evaluated in various combinations with chemotherapy including gemcitabine and oxaliplatin [44], capecitabine and oxaliplatin [45] and capecitabine [46].

Zhu et al. showed that combining bevacizumab with gemcitabine and oxaliplatin resulted in a 20% overall response rate in evaluable patients and stable disease in 27%. The median OS was 9.6 months, and median PFS was 5.3 months [44].

A phase II trial performed to evaluate the combination of bevacizumab with capecitabine and oxaliplatin reported a median OS of 10.3 months and a median time to progression (TTP) of 4.5 months. 13.3% (4 out of 30 evaluable patients) had PR and 76.6% (23 patients) had SD [45].

Bevacizumab in combination with capecitabine was evaluated in a study by Hsu et al. [46]. Overall response rate was 9% and 52% of patients achieved CR, PR, or SD.

A trial of anti-EGFR therapy (Erlotinib) with bevacizumab is reported below.

## 6. Sunitinib

Sunitinib (Sutent; Pfizer Labs, New York, NY, USA) is another oral tyrosine kinase inhibitor that blocks several receptors, including VEGFR1, 2 and 3, PDGFR-$\beta$, c-kit, and FLT3 and RET kinase. Most antiangiogenic effects of sunitinib are shown in preclinical studies to be mediated via VEGFR and PDGFR-$\beta$ [63–65]. Sunitinib is being used in the treatment of renal cell carcinoma and gastrointestinal stroma tumor.

In a phase II trial of sunitinib, Zhu et al. [48] showed that that 17 out of 34 patients had SD for at least 12 weeks and 1 had PR. Median progression-free survival (PFS) was 3.9 months and time to progression (TTP) was 4.1 months in this study, in which sunitinib was administered at a dose of 37.5 mg/day.

In a second phase II study of 37 patients with unresectable HCC, sunitinib (for four weeks out of every six) at 50 mg/day was used. 1 patient achieved PR and 35% had SD. Median PFS was 3.7 months and median OS, 8 months. Significant toxicities, however, were observed, including four deaths. This trial was discontinued early due to low response rate and failure to meet the primary end point [49].

A phase III trial comparing sorafenib with sunitinib was terminated early as a result of a higher incidence of serious adverse events in the sunitinib arm compared to the sorafenib arm and the fact that sunitinib did not meet the criteria to demonstrate that it was either superior or noninferior to sorafenib in the survival of patients with advanced hepatocellular cancer.

## 7. ABT-869

ABT-869 (Linifanib) is an oral tyrosine kinase inhibitor with potent activity against both VEGFR and PDGFR [66]. A phase II open-label, multicenter study of ABT-869 was carried out in 44 patients with unresectable or metastatic HCC [50]. ABT-869 at a dose of 0.25 mg/kg was administered daily to CP A patients and every other day to CP B patients until progressive disease or intolerable toxicity. Of the 34 patients available for analysis, 28 were CP A and 6 CP B. Estimated response rate was 8.7% for 23 CP A patients. Median TTP and PFS for all 34 patients were 112 days, and median OS was 295 days. Most AEs were mild/moderate and reversible with interruption/dose reductions or the discontinuation of ABT-869. ABT-869 appears to benefit HCC patients with an acceptable safety profile. A randomized phase III study in CP A patients with advanced HCC comparing ABT-869 with sorafenib is ongoing [67].

## 8. Brivanib

Brivanib (BMS-582664) is a dual inhibitor of VEGFR and fibroblast growth factor receptor signaling pathways. It has shown tumor inhibitory effects in mouse HCC xenograft models. Raoul et al. [68] conducted a phase II study of brivanib in pts with advanced or metastatic HCC who had no prior systemic therapy (Cohort A) or 1 prior regimen of an angiogenesis inhibitor (Cohort B). 96 patients were enrolled, 55 in Cohort A and 41 (including 38 who failed sorafenib) in Cohort B. In Cohort A, median OS was 10 months and median TTP was 2.8 months. Brivanib appears to have activity as both first-line and second-line post-sorafenib systemic treatment in HCC.

There are ongoing phase III trials assessing brivanib in both first-line setting in comparison with sorafenib as well as in sorafenib-refractory setting in comparison with best supportive care in patients with advanced HCC, and results are awaited [17].

## 9. EGFR and Anti-EGF/EGFR Therapies

EGFR is overexpressed in 40–70% of HCCs [69], and its activation is involved in HCC pathogenesis [70, 71]. EGF is thought to have an important role in tumor angiogenesis, primarily via the activation of the Raf/MEK/ERK and mTOR pathways. The receptor may be targeted via antibodies that block it extracellularly, for example, cetuximab and panitumumab. Intracellular targeting of the EGFR tyrosine kinase with tyrosine kinase inhibitor such as gefitinib and erlotinib are already in use in the treatment of lung and pancreatic tumors [72, 73].

Erlotinib and gefitinib are among some of the tyrosine kinase inhibitors that have shown activity in HCC cell lines and animal models of HCC [74–79].

In a phase II study by Philip et al. [51] of 38 patients with unresectable HCC using single-agent erlotinib, 3 (9%) achieved PR, 12 (32%) were progression-free at 6 months, and the median OS was 13 months. Thomas et al. [52] studied erlotinib alone in 40 patients with CP class A or B advanced HCC. Four months-PFS was 43% and 6 months-PFS was 28%. There was no CR or PR and median OS was 13.3 weeks.

Combining erlotinib and bevacizumab in a phase II study involving 40 HCC patients, Thomas et al. [47] reported a median PFS of 9 months and an impressive median OS of 15.6 months. 12.5% of the patients had CP Class B disease, and 27.5% had received prior therapy. Side effects included gastrointestinal bleeding (12.5%), fatigue (20%), hypertension (15%). After the initiation of screening for and treating any esophageal varices before being eligible for the study, there were no further episodes of gastrointestinal bleeding.

An ongoing phase 3 placebo-controlled double-blinded SEARCH (Sorafenib and Erlotinib, a Randomized Trial Protocol for the Treatment of Patients with HCC) trial is being conducted in patients with advanced HCC and CP Class A liver cirrhosis to determine if the OS seen with sorafenib in advanced HCC can be improved by the addition of erlotinib, resulting in combined inhibition of EGF, VEGF, and the RAS/RAF/MEK signaling pathways [80].

Gefitinib (Iressa, Astrazeneca Pharmaceuticals LP, Wilmington DE, USA) has shown activity in preclinical studies in HCC cell lines and animal models, but these results have not been matched in clinical studies. In the study by O'Dwyer et al. [81], single-agent gefitinib showed low activity, with 1 out of 31 patients achieving PR and 7 having SD. Median PFS was 2.8 months, and median OS was 6.5 months.

Cetuximab (IMC-C225 Erbitux; ImClone LLC, New York, NY and Bristol-Myers Squibb, Princeton, NJ, USA) is a recombinant chimeric monoclonal immunoglobulin 1

antibody targeting the extracellular domain of the EGFR. Similar to gefitinib, however, it has not shown evidence of significant tumor response in HCC. A small study of 30 patients with unresectable or metastatic HCC showed no CRs or PRs, with just 5 patients achieving SD and a median PFS of 1.4 months [82]. Another phase II study by Gruenwald et al. 2007 [83] of single-agent cetuximab in 32 patients showed only limited activity for the drug with a median TTP of 2 months.

Because of the multilevel receptor cross-stimulation and redundant signaling pathways, it is postulated that just blocking one of these pathways alone may result in others acting as salvage or escape mechanisms for tumor cells. There has been evidence that blocking multiple signaling pathways with a combination of targeted agents may achieve synergistic antitumor effect [84–88]. Most of the anti-EGFR studies being carried out now are thus in combination with cytotoxics or with other targeted agents.

## 10. mTOR Pathway

Several downstream proteins are activated by the EGF and insulin growth factor (IGF) signaling pathways, including phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), and mTOR (mammalian target of rapamycin). expression of both IGF and IGF receptor is upregulated in HCC and human cirrhotic liver [89]. Rapamycin is a natural antibiotic which is a potent inhibitor of mTOR [90]. Three analogues of rapamycin have recently been developed and have been shown to have superior pharmacokinetic and biologic properties.

Sirolimus (Rapamycin) is an mTOR inhibitor with immunosuppressive properties and has been used in the posttransplantation setting. A small pilot study by Rizell and colleagues showed that 6 out of 21 patients had either SD or PR [91].

Temsirolimus is a soluble ester analogue, and everolimus is an orally bioavailable rapamycin derivative. Early clinical trials have shown these agents to have antineoplastic activity, and they are currently being tested in various open clinical trials in the treatment of colorectal, endometrial, and refractory solid tumors [92–94].

There are currently several ongoing phase I and II trials studying temsirolimus and everolimus in patients with advanced HCC, either as a single agent or in combination with another targeted therapy, for example, sorafenib or cytotoxics, for example, pegylated doxorubicin.

Both rapamycin and everolimus have been shown in xenografts and mouse models to have activity against HCC, either singly or in combination for, example, with sorafenib [95, 96].

Data so far suggests that mTOR inhibitors including the rapamycin analogues are promising agents, and several ongoing trials are exploring this.

## 11. Conclusion

HCC is a complex disease with multiple signaling pathways involved in its pathogenesis. It has proven to be a difficult disease to treat especially in advanced stages. Inhibition of specific growth factor receptors and their various signaling pathways via targeted therapy appears to be a promising approach for the treatment of HCC. More work is required to fully clarify its molecular pathogenesis and to identify other key targets for intervention.

The use of combination therapy, either with multiple targeted agents or targeted therapy in combination with conventional chemotherapy, may be a more effective way of treating advanced HCC. Combination therapy can target multiple receptors and signaling pathways. Many of these combinations have been shown in preclinical studies to have synergistic effect and may block proposed resistance pathways [97]. Also, fewer overlapping drug toxicities may result when blockade at different pathways via combination therapy is used.

Studies are also underway evaluating vertical as well as horizontal pathway blockade [24]. In vertical blockade, different points along the same pathway are targeted. For example, the use of bevacizumab (VEGF antibody) together with sorafenib (multikinase inhibitor with activity against VEGFR). This may potentially block feedback loops and lead to more complete blockade. In horizontal blockade, however, different signaling pathways are targeted with different drugs, such as the tandem usage of bevacizumab with erlotinib (an EGFR tyrosine kinase inhibitor). Trials combining chemotherapy and other targeted agents with sorafenib are also underway.

Sorafenib was a major breakthrough as an effective targeted treatment in a selected population of patients with advanced HCC. There is an interest in its being used in an adjuvant or neoadjuvant setting in patients undergoing locoregional therapies and even as a chemopreventive in cirrhotic patients.

Other new pathways and molecular targets being investigated include resistance and apoptosis pathways. Also, identifying both predictive and prognostic biomarkers in patients with HCC will be the next step in helping to better tailor HCC treatment.

Much work remains to be done to identify new molecular targets, assess the role of targeted therapy in the adjuvant, neoadjuvant, and metastatic setting, determine the various combinations of treatment, either tandem targeted agents or with conventional cytotoxics, and evaluate the role of sequential versus concurrent therapy.

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*Review Article*

# Liver Cancer Stem Cells

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Hepatocellular carcinoma is the most common primary malignancy of the liver in adults. It is also the fifth most common solid cancer worldwide and the third leading cause of cancer-related death. Recent research supports that liver cancer is a disease of adult stem cells. From the models of experimental hepatocarcinogenesis, there may be at least three distinct cell lineages with progenitor properties susceptible to neoplastic transformation. Identification of specific cell surface markers for each of the liver cell types, production of corresponding monoclonal antibodies and cell sorting techniques have together revolutionized the characteristics of normal stem cells. In hepatocarcinogenesis, multiple signaling transduction pathways, important for stem cell proliferation and differentiations, are deregulated. Strategies are being developed to identify and characterize the liver cancer stem cells. Targeting liver cancer stem cells may bring hope to curing hepatocellular carcinoma.

## 1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver in adults. It is also the fifth most common solid cancer worldwide and the third leading cause of cancer related death [1, 2]. Moreover, HCC incidence and death rate are rising in the United States and demonstrate the highest annual percent increase of the top 15 cancers by incidence [3]. The worldwide incidence of HCC varies according to the prevalence of hepatitis B (HBV) and hepatitis C (HCV) infection and the age-standardized incidence rates vary from 4.9 per 100,000 population in North America to 80 per 100,000 population in China [4]. It is worth noting that chronic HCV infection is the leading cause of HCC in Europe, Japan, and the United States whereas HBV infection is the leading cause in the majority of Asian and African countries [2].

Recent research supports that cancer is a disease of adult stem cells (SC). Adult stem cells are the only cells that persist in the tissue for a sufficient length of time to acquire the requisite number of genetic changes for neoplastic development. In contrast to intestinal mucosa and epidermis where a steady flux of cells occurs from the stem cell zone to the terminally differentiated cells that are imminently to be lost, liver normally exhibits a very low level of cell turnover. However, when abnormal hepatocyte loss occurs, such as after partial hepatectomy (PH) or toxic injury, the liver demonstrates an enormous regenerative capacity. The clonality of HCC is now well established based upon the studies examining viral integration sites of HBV in tumor samples [5], as well as on the determination of restriction fragment length polymorphisms of X-linked genes in tumor cells [6]. However, the cell type that has given rise to HCC has not been universally accepted. From the models of experimental hepatocarcinogenesis, there may be at least three distinct cell lineages with progenitor properties susceptible to neoplastic transformation [7].

## 2. The Stem Cell Origin of Liver Cancer

*2.1. Hepatocytes Have "Stem Cell" Properties.* Hepatocytes in normal adult liver have a lifespan of over a year. However, in response to parenchymal cell loss, the hepatocytes restore the liver mass by self-replication. In rodents, the liver can restore its original volume after two-thirds partial hepatectomy (PH) in approximately 10 days [8, 9]. Serial transplantation experiments have shown that hepatocyte can divide at least 69 times, demonstrating the clonogenic potential of hepatocytes—one of the crucial properties of an SC [10]. In HCV infected liver, the hepatocyte proliferation

rate increases with increasing cellular damage [11]. Many models of liver cancer utilize a brief exposure to a genotoxic carcinogen at a time when the liver is in a proliferative state, either during the period after a PH or necrogenic insult [12]. Hepatocytes have been found to be directly involved in carcinogenesis of HCC in 2-acetylaminflourene and DEN-treated rats where hepatocytes were labeled with $\beta$-galactosidase [13]. Hepatocytes in proliferation appear to be the origin of cancer.

*2.2. Oval/Liver Progenitor Cells as Targets for Malignant Transformation.* When hepatocyte and/or cholangiocytes are damaged or inhibited in their proliferation, a potential SC compartment located within the smallest branches of the intrahepatic biliary tree, the ductules, and canals of Hering gets activated [14]. The "oval cells" in rodent or "the liver progenitor cells" in human liver involve a population of cells that are bipotential and capable of differentiating into hepatocytes or cholangiocytes. The oval/progenitor cells are labeled by over 30 surface markers including biliary-type cytokeratin (CK), CK7, CK19, oval cell markers OV6 and OV1, neuroendocrine marker chromogranin A, neural cell adhesion molecule and parathyroid hormone-related peptide, and connexin 43. The origin of HCC from hepatic progenitor cells (HPC) is is often suggested from the fact that tumors contain an admixture of mature cells and cells phenotypically similar to HPCs [15, 16]. Oval/HPC proliferations and activations are observed after severe liver parenchyma injury, viral hepatitis, alcoholic hepatitis, and nonalcoholic fatty liver disease. HPC/oval cell activation accompanies many instances of liver damage, irrespective of etiology, suggesting such cells are carcinogen targets during hepatocarcinogenesis. Oval cells from p53-null mice formed HCC when transplanted into athymic nude mice [17]. A probable origin from oval cells is suggested by the fact that if oval cell expansion is blocked in the CDE diet mouse modeling by targeting c-Kit with imatinib mesylate, the HCC formation is reduced [18]. Furthermore, the gene expression profile from a selected group of HCC is consistent with the profile of HPCs.

*2.3. Bone Marrow-Derived Stem Cells.* Petersen et al. demonstrated that hepatocytes could be derived from circulating bone marrow cells [19]. Hematopoietic Stem Cells (HSC) from wild-type mice were able to repopulate the liver of FAH-deficient ($fah^{-/-}$) mice [20]. In the setting of sex-mismatched bone marrow transplantation, bone marrow-derived hepatocyte are found in the recipient liver with a large variation in their frequency ranging from less than 1% to >40%. However, in a chimerical mouse model with genetically labeled bone marrow, there was no malignant transformation of the bone marrow-derived liver SC during hepatocarcinogenesis induced by chemical carcinogen [20]. These results suggest that bone marrow-derived liver SC may not be targets for malignant transformation in HCC.

*2.4. Isolation of Liver Cancer Stem Cells.* In the last decade, identification of specific cell surface markers for each of the liver cell type, production of corresponding monoclonal antibodies, and cell sorting techniques have together revolutionized the characteristics of normal stem cells. It has been show that cancer SCs in HCC can be identified by several cell surface antigen CD133, CD90, CD44, OV6, and epithelial cell adhesive molecule (EpCAM), or by selecting the side population (SP) cells in Hoechst dye-staining [21–25]. Table 1 shows markers that are associated with liver cancer SC. The surface markers enrich HCC cells with greater tumorigenicity in immunodeficient mice, higher colon-forming efficiency, and proliferation ability in vitro. In addition, most of the markers are found to be expressed in only a minute proportion of HCC cells, and the expression of the markers correlate with poor prognosis and tumor recurrence. However, it remains to be seen how much overlap there is between these various markers, or whether there is a "one-fits-all" marker for cancer SCs in HCC. Most of the markers which are used for isolating cancer SCs from primary tumor samples were established and adapted from established cancer cell lines. It is not clear whether the cancer SCs that are derived from established cancer cell lines and cultured in vitro reflect the SCs from primary tumor in the gene expression of these surface marker. It remains a challenge to isolate enough clonally derived cancer SCs from primary tumor without in vitro propagation for lineage tracking and differentiation experiments, identification of deregulated signaling pathways that lead to the malignant transformation of normal adult SC to cancer SCs.

*2.5. Pathways Important for Stem Cell Function Are Deregulated in Hepatocarcinogenesis.* From HCC animal model and gene array analysis, a growing body of research suggests that many signaling pathways known to be involved in SC maintenance, self-renewal, and pluripotency, are altered in HCC. This alteration may result in the malignant transformation of liver SC [26]. These observations support the hypothesis that molecular changes in HCC originate in cancer SC [27]. Moreover, these pathways could serve as prognostic markers and targets for therapeutic interventions [27].

## 3. WNT/$\beta$-Catenin

Disrupted Wnt signaling is observed in approximately one-third of all HCC which underscores its importance in carcinogenesis [28]. The Wnt pathway has a fundamental role in embryogenesis with signaling effects on proliferation and apoptosis in developing cells [29]. Wnt pathway activation is essential for maintenance of SC compartment and regulates cellular differentiation [30]. The "canonical Wnt pathway" describes a cascade of events beginning with the translocation of $\beta$-catenin from the cell membrane into nucleus, where $\beta$-catenin then acts as a coactivator of the TCF/LEF family of transcription factors, these in turn regulate specific target genes including c-myc, cyclin D1, and survivin [31]. The signaling cascade is normally initiated when Wnt ligand binds to Frizzled (FZD), a transmembrane receptor [32]. FZD then signals to $\beta$-catenin to escape its association with E-cadherin. The cytoplasmic elements of the activated Wnt pathway prevent $\beta$-catenin from being phosphorylated by a

Table 1: Markers that have aided in the identification of stem cells.

| Markers |
|---|
| Cluster of differentiation (CD)133+ |
| CD44+ |
| CD45− |
| $CD90^+$ |
| CD34 |
| OV6 |
| Side population (SP) |
| Epithelial cell adhesion molecule (EpCAM) |
| OC.2, OC.3, OC.4, OC.5, OC.10 |
| BDS7 |
| Thy-1 |
| c-kit |
| ABCG2/BCRP1(breast cancer resistance protein) |
| Connexin 43 |
| Tumor rejection antigen 1-81 (TRA-1-81) |
| TRA-1-60 |
| Sry-box containing gene 2 (SOX2) |
| Surface antigen stage-specific embryonic antigen 3 (SSEA-3) |
| CK7, CK19, CK14 |
| $\alpha$-fetoprotein (AFP) |
| $\gamma$-glutamyltranspeptidase |
| Placental form of glutathione-S-transferase |
| Flt-3 ligand |
| DMBT1(deleted in malignant brain tumor 1) |
| Neural cell adhesion molecule 1(NCAM)/CD56 |
| Chromogranin A |
| Parathyroid hormone related peptide (PTHrP) |

degradation complex made up of a serine-threonine kinase, GSK3B, protein scaffolds, AXIN, and adenomatous polyposis coli (APC) [29, 31, 32]. Mutations of proteins that may allow $\beta$-catenin accumulation in the nucleus to promote transcription of its target genes are found in many cancers [33]. Mutation of $\beta$-catenin, described in HCC, is located in exon 3 of the CTNNB1 gene, which is the phosphorylation site for GSK3B, AXIN1, and AXIN2 mutation. Activation of Wnt signaling has also been demonstrated in different prospectively isolated SC [34]. 20 to 40% of human HCC bear abnormal cytoplasmic and nuclear accumulation of $\beta$-catenin by immunohistochemical staining [35]. Markers for elevating expression of Wnt include CD $133^+$ and $EpCAM^+$ [36]. The knockdown of the expression of EpCAM, a Wnt/beta-catenin signaling target, in liver cancer SC resulted in decreased proliferation, colony formation, migration, and drug resistance [36]. RNA interference machinery- (RNAi-) mediated knockdown of $\beta$-catenin resulted in the inhibition of lung cancer SCs [34].

## 4. Transformation Growth Factor-Beta (TGF-$\beta$)

A wide range of secreted factors regulate SC proliferation and fate. TGF-$\beta$ shows remarkable functional conservation between species and between tissues that self-renew through asymmetric divisions or populational asymmetry. TGF-$\beta$ signaling is important for embryonic hepatocyte proliferation, as well as in the formation of gastrointestinal cancer [37–39]. Tang et al. demonstrated that lack of responsiveness to TGF-$\beta$ pathway in liver SC led to carcinogenesis [40]. Subsequently, it has been shown that targeting this pathway using indirect modulation of IL6/STAT3 appeared to be effective in eradication of cancer SC [26, 40].

## 5. Hedgehog

The Hedgehog signaling pathway consists of a complex suite of molecules which regulate cell differentiation, regeneration, and stem cell biology. The pathway plays important roles in the development and homeostasis of the gut tissue [41]. Studies have identified a possible role for this pathway in HCC with expression of Sonic, the predominant ligand of the Hedgehog pathway in liver, that is present in up to 60% of human HCC samples [42, 43]. The Hedgehog pathway is deregulated in hepatocarcinogenesis [42]. Genes involved in the Hedgehog pathway are highly expressed in tumorigenic $CD133^+$ liver cancer SC [21]. Suppression of Hedgehog pathway not only decreased HCC cell proliferation but also chemosensitized HCC cells to 5-fluorouracil and to the induction of cell apoptosis [44].

## 6. Target CSCs in the Treatment of HCC

Cancer SCs are predicted to mediate tumor recurrence after chemo- and radiation-therapy due to the relative inability of these modalities to effectively target cancer SCs. Eradicating Cancer SCs brings the hope for cure. Interesting results have been demonstrated in inhibiting breast cancer SC by targeting TGF-$\beta$ and Notch pathways [45]. Similarities between normal and malignant SC, at the levels of cell-surface proteins, molecular pathways, cell cycle quiescence, and microRNA signaling present challenges in developing cancer SC-specific therapeutics. Treatment against cancer SCs should be developed targeting known stem cell regulatory pathways that are deregulated in cancer SCs compared to normal SC, as well as through unbiased high-throughput siRNA or small molecule screening. Both experimental approaches require identification and characterization of the putative liver cancer SC in order to target liver cancer SC specifically to decrease the toxicities. The current strategies of identifying cancer SCs are based on the expression of extracellular markers, the growth of cancer SCs in tumor sphere assays under nondifferentiating conditions, dye exclusion due to the overexpression of drug efflux pumps in cancer SCs, and greater tumorigenicity in immunodeficient mice compared cancer cells that are not cancer stem cells. Despite the amount of literature on liver cancer SCs, it is still not clear as to what constitutes a universal liver cancer SC-specific profile. Given the fact that the diverse etiology for hepatocarcinogenesis and multiple types of progenitor cells are involved in malignant transformation, it is unlikely that a universal liver cancer SC-specific profile will be used for therapeutics development. Ultimately, targeting liver cancer

SCs in treating HCC will be in the context of personalized medicine.

## 7. Concluding Remark

Current research supports that HCC derived from malignant transformation of HPC. There may be at least three distinct cell lineages with progenitor cell properties susceptible to neoplastic transformation: hepatocyte, oval/hepatic progenitor cells, and bone marrow-derived stem cells. Multiple signaling transduction pathways important for stem cell proliferation and differentiations are found deregulated during hepatocarcinogenesis. Strategies are being developed to identify and characterize the liver cancer SCs. Targeting liver cancer SCs may bring hope in curing HCC.

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*Review Article*

# Improving Outcomes with Surgical Resection and Other Ablative Therapies in HCC

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With rising incidence and emergence of effective treatment options, the management of hepatocellular carcinoma (HCC) is a complex multidisciplinary process. There is still little consensus and uniformity about clinicopathological staging systems. Resection and liver transplantation have been the cornerstone of curative surgical treatments with recent emergence of ablative techniques. Improvements in diagnostics, surgical techniques, and postoperative care have lead to dramatically improved results over the years. The most appropriate treatment plan has to be individualised and depends on a variety of patient and tumour-related factors. Very small HCCs discovered on surveillance have the best outcomes. Patients with advanced cirrhosis and tumours within Milan criteria should be offered transplantation. Resection is best for small solitary tumours with preserved liver function. Ablative techniques are suitable for low volume tumours in patients unfit for either resection or transplantation. The role of downstaging and bridging therapy is not clearly established.

## 1. Introduction

Hepatocellular carcinoma (HCC) is the fifth commonest cancer in the world in men and is the third highest contributor towards any cancer-related mortality [1]. Although the highest number of cases relates to the Far East, Middle-East, and Africa, the last decades have seen nearly a doubling of the incidence of HCC in the western world, particularly in the United States with the trend still on the rise [2]. The vast majority of HCCs occur on a background of pre-existing liver disease, and more recently, Hepatitis C (HCV) and nonalcoholic steatohepatitis (NASH) have emerged as the leading causes of cirrhosis and thereby, HCC.

Unfortunately, late presentation is all too common, and a recent analysis of the SEER (Surveillance, Epidemiology and End Result) database revealed that just about 16% of patients were suitable for some kind of surgical therapy in the form of resection, transplantation, or ablation [3]. However, surgical and ablative modalities offer the only possibility of long-term cure. Surgical treatment options depend not only on the extent of the cancer but also on the status of the liver and the general condition of the patient. In theory, the best outcomes should be obtained in patients with well-compensated liver disease without severe portal hypertension, who are generally in good health and have a small tumour burden. Hence surveillance programmes have been established, particularly in high-risk geographical areas, for the early detection of HCCs to facilitate curative treatment and improved outcomes [4]. This paper discusses the improving outcomes associated with surgical management of HCC.

## 2. Staging of HCC

Clinical management of HCC is a multidisciplinary process involving hepatologists, surgeons, oncologists, and radiologists. Staging is an integral part of the decision-making process so that treatment can be individualised. Since the vast majority of HCCs occur on a background of liver disease with or without cirrhosis, it is clear that prognosis does not depend exclusively on tumour-related factors but also on liver function, general health, and other comorbidities of the patient and response to various medical treatments depending on the aetiology [5]. Staging of HCC is difficult, and a wide variety of systems have been in existence for

years. They include those that deal exclusively with tumour staging pre- and postoperatively, pathological staging of the resected tumour, general staging for liver disease, and those that were initially developed to predict factors determining outcome of liver disease with or without HCC. However, only three of them have been validated in patient cohorts [6]. The detailed description and analysis of these are beyond the scope of this paper. The current consensus is that no single staging system is universally applicable and there is significant heterogeneity in patient groups even within the same stage, particularly since the aetiology and prognosis of liver disease are multifold [7]. Tumour size alone is an inconsistent determining factor, yet transplant criteria are based predominantly on size. Histological characteristics which can potentially prognosticate outcome cannot unfortunately be determined preoperatively. Some uniformity in staging is essential, and the various diagnostic tools used to stage and assess HCC pretreatment need to be standardised.

The BCLC (Barcelona Clinic Liver Cancer) staging, which has been recently updated, attempts to match staging with both prognosis and treatment options, thereby developing an evidence-based algorithm for the surgical and medical management of HCC [8]. This has not gained universal acceptance and is probably popular mainly in the European countries. Other geographical study groups have also published consensus recommendations. The Asian Pacific Association for the Study of Liver (APASL) convened an international working party to develop consensus recommendations for the diagnosis, surveillance, and management of HCC. A treatment algorithm was proposed, which, again, takes into account resectability and size of the HCC and the general condition of the patient [9]. Finally, the National Comprehensive Cancer Network (NCCN) has published and updated clinical practice guidelines for hepatobiliary oncology with a treatment algorithm for the diagnosis and management of HCC which, similar to the APASL, is based on resectability, status of liver disease, and general condition [10]. Unlike the BCLC, neither specifically makes an attempt to formally classify HCC into stages. It should, however, be noted that both the APASL and the NCCN are consensus guidelines derived from evidence-base and large panels of international experts rather than a single-centre approach. Individual aspects of these algorithms are discussed further in the paper.

## 3. Surgical Modalities for the Management of HCC

*3.1. Liver Transplantation.* Liver transplantation (LT) has been used to treat HCC with cirrhosis for nearly three decades. It is the only surgical treatment which simultaneously addresses the liver condition and, essentially, cures two related problems. Early results of LT for HCC were disappointing. In absence of specific inclusion criteria, many patients with HCC were transplanted for advanced disease resulting in an overall poor survival [11–13]. For LT to be universally acceptable as a treatment option for HCC, it not only had to demonstrate better results than other treatment options but also to achieve at least 50% survival at 5 years to justify use of scarce donor organs. Therefore, it was necessary that certain criteria are used to preselect patients suitable for transplantation. Increasing tumour size and bulk, vascular invasion, extrahepatic nodal disease, and worse tumour histology were long known to be indicators of poor prognosis with other treatment modalities. Prognosis after transplantation for HCC was also noted to be better in early stage disease. It was only in 1996 that Mazzaferro et al. in a prospective study clearly defined inclusion criteria (single tumour <5 cm or 1–3 tumours, none >3 cm) which showed a significant survival benefit [14]. Since then, the so-called "Milan criteria" have gained universal acceptance, and the results have been replicated in other studies [15, 16]. These have long been adopted by UNOS (United network for organ sharing) as the optimal criteria for LT and in the TNM staging. After the introduction of MELD score for organ allocation, bonus "points" were awarded to early stage (T1 and T2) HCCs in an attempt not to disadvantage patients with low-grade tumours and good synthetic liver function. However, this led to an overcorrection and a significant increase in the number of patients transplanted for HCCs at the expense of other indications. It was noted that the dropout rate for T1 tumours in the pre-MELD era was under 10%, which is less than the overall waiting list mortality. This has thus led to elimination of the score upgrading for T1 lesions and a lesser upgrade for T2 lesions [17, 18]. This has not necessarily had an adverse impact on survival, and there has been a significant increase in the number of transplants performed for early HCC in cirrhosis [19].

*3.1.1. Results of Liver Transplantation for HCC.* The original Milan study reported 4-year and recurrence-free survival rates of 75% and 83%, respectively, and their 10-year overall survival is over 70% in transplants performed for HCC within Milan criteria [20]. Similar results have been achieved in other centres, and a 5-year survival of well over 70% has been reported in patients undergoing LT for HCC within Milan criteria [15, 16].

It has to be argued, however, that these are data from single centres and may not accurately reflect the entire picture. Any comparison between differing treatment modalities has to take into account an intention-to-treat analysis which, in case of LT, is tempered by waiting times and waiting list dropout and mortality which vary between 20% and 30% [4]. It has been shown that mortality from the time of listing for LT increases significantly with increasing waiting times [21]. Pooled registry data incorporating a very large number of patients have clearly shown that the long-term survival figures do not necessarily replicate data from the best single centres. An analysis of 4482 patients within the UNOS Organ Procurement Transplant Network data demonstrated that overall intention-to-treat 5-year survival after LT for HCC was 61% even for those favourable group of patients within Milan criteria [22]. This figure went up to 65% when only patients who underwent LT were taken into account. Table 1 summarises outcomes after LT for HCC in major series.

Over the last decade, there has been a vigorous debate over expansion of the Milan criteria. Proponents have demonstrated outcomes comparable to those with Milan

Table 1: Results of liver transplantation for HCC.

| Author | Year | Number of patients | Inclusion criteria if any | 3-year survival (%) | 5-year survival (%) |
|---|---|---|---|---|---|
| Iwatsuki et al. [11] | 1991 | 105 | None | 47 | |
| Bismuth et al. [12] | 1993 | 60 | None | 47 | |
| Ringe et al. [13] | 1991 | 61 | None | | 15.2 |
| Mazzaferro et al. [14] | 1996 | 48 | Milan criteria | | 74 (4-year) |
| Jonas et al. [15] | 2001 | 120 | Milan | | 71 |
| Figueras et al. [16] | 2001 | 307 | Milan | | 63 |
| Yao et al. [23] | 2001 | 70 | USCF | | 75[a] |
| Onaca et al. [24] | 2007 | 1206 | Milan | | 62 |
| Duffy et al. [25] | 2007 | 467 | Milan<br>UCSF | | 79<br>64[b] |
| Pelletier et al. [22] | 2009 | 2898 | Milan | | 65[c] |
| Cescon et al. [29] | 2010 | 283 | Milan | | 75 |

UCSF: University of California San Francisco criteria (single tumour <6.5 cm, 2-3 tumours, none >4.5 cm and total tumour dimensions up to 8 cm).
[a]Survival for all patients within UCSF criteria.
[b]Survival for patients beyond Milan but within UCSF criteria.
[c]Intention-to-treat survival: 61%.

Table 2: Results of liver transplantation for HCC beyond Milan criteria, based on preoperative imaging. (From national/large regional studies.)

| Author | Year | Number of patients | 5-year survival (%) | Notes |
|---|---|---|---|---|
| Decaens et al. [26] | 2006 | 44<br>145 | 45.6<br>34.7 | Beyond Milan, within UCSF<br>Beyond UCSF |
| Duffy et al. [25] | 2007 | 185<br>109 | 64<br>41 | Beyond Milan, within UCSF<br>Beyond UCSF |
| Pelletier et al. [22] | 2009 | 346 | 38<br>32 | Beyond Milan<br>Intention-to-treat survival |

criteria and argue that maintaining the restriction of criteria would exclude patients that would otherwise do well after transplantation despite a larger tumour burden [23–25]. Others equally insist that original criteria are strictly adhered to in view of the inconsistent results achieved after transplanting patients with larger tumours, specifically arguing that potential beneficiaries of expansion of criteria have significantly worse outcomes [26]. The UNOS data demonstrated that the intention-to-treat 5-year survival for patients listed LT for HCC beyond Milan criteria was only 32% and 38% for those patients that actually underwent LT [22]. Table 2 summarises results of these studies. Retrospective designs of most studies and the impossibility of prospective randomised controlled comparative studies between these groups make direct comparisons unreliable. Also, there is no definite consensus in terms of how further should these criteria be expanded. Finally, ready acceptance to expand the criteria is tempered by the two critical issues facing the transplantation community: burgeoning waiting times and increasing dropout rates and mortality due to tumour progression and complications of underlying liver disease. Hence, currently, Milan criteria still remain valid in most transplant units.

*3.1.2. Factors Determining Outcome after LT for HCC.* There is clear evidence that postoperative histology correlates with disease recurrence and survival. Even in the group of patients within Milan criteria, vascular invasion and tumour undifferentiation carry worse prognosis [15, 27]. Others have demonstrated that variables, such as higher total tumour burden, higher preoperative alpha-fetoprotein, and presence of tumour necrosis, predict significantly worse outcomes [28, 29]. It has been discussed that survival of patients beyond Milan but within UCSF criteria is worse thereby suggesting that tumour size may indeed be a surrogate marker of adverse histological features such as vascular invasion, the one criterion consistently shown to predict worse survival.

*3.1.3. Living Donor Liver Transplantation (LDLT) for HCC.* Dropout rate for HCC is related both to waiting list mortality in patients with advanced liver disease per se and to tumour progression beyond Milan criteria despite preserved liver function. LDLT could potentially benefit such patients who would otherwise be rendered nontransplantable. It could also cater for the 10–20% patients with HCC beyond Milan but within UCSF criteria without having an impact

on the availability and distribution of organs across the program. Patient survival and disease-free survival after LDLT for HCC are comparable to cadaveric transplantation. As with other series, tumour size, histological grade, vascular permeation, preoperative serum alpha-fetoprotein, and preoperative MELD score correlated with survival and disease recurrence. Survival was worse in patients beyond Milan criteria [30, 31]. In another study, LDLT had poorer outcome compared to cadaveric transplantation in patients with large HCCs [32]. Although it was not statistically significant, the 2-year patient survival was 60%. Long-term outcomes were not reported.

The ethical issues with LDLT and, in particular, the potential dangers to a healthy adult have been long debated. There is small but significant risk mortality to the donor. Significant morbidity occurs in about 20% of donors, and up to 50% experience various minor complications [33]. Postoperative biliary and vascular complications are higher in the recipient. The projected patient and graft survival rates are potentially lower in view of these complications and LDLT being used for more advanced disease. HCV-associated cirrhosis, which is frequently associated with HCC, carries a worse prognosis, and there is evidence that recurrence is more severe after LDLT [34]. There is a danger that if LDLT is advocated for tumours beyond Milan criteria, there would be a pressure on the patient to find a suitable living donor and on the donor to fulfil an obligation for a potentially nonbeneficial cause. Altruistic donation, too, could come under close scrutiny if used for such indications. However, HCC represents a good indication for LDLT. The majority of patients listed for LT do not have advanced liver disease and would have a much better prognosis than patients transplanted for end-stage liver disease.

Families involved in LDLT need to be given clear advice, and their wishes need to be taken into consideration. Since LDLT does not primarily tap into cadaveric organ pool, even a slightly low survival should be considered acceptable since the outcome would be significantly better than other treatment modalities. However, in the event of graft failure in a patient transplanted for HCC exceeding current criteria, it would be highly contentious to turn to retransplantation with a cadaveric organ, and this issue has to be clearly discussed with the family. Thus LDLT has an important role to fill in LT for HCC.

*3.2. Surgical Resection.* Surgical resection for HCC was the only modality for curative treatment before the routine use of LT and has several practical advantages over it. Firstly, there are no restrictions on tumour size and numbers as long as resection can be safely performed. Secondly, resections can be performed in any nontransplant setup that has an adequate radiological and medical backup. Finally, it does not rely on a donor pool, and there are no waiting times for treatment. However, there are distinct disadvantages. Resection does not address and cure the background liver disease, thereby retaining a fertile background for recurrence. Secondly, it compromises an already damaged liver by removing vital functioning liver mass and is reliant on a well functioning liver with adequate reserves. Finally, in the event of liver decompensation and failure, emergency liver transplantation as a rescue treatment may not be available, particularly if the Milan criteria in the resected specimen have been exceeded or if poor prognostic features are evident on histology.

*3.2.1. Results for Liver Resection for HCC.* The key factor that determines outcomes is patient selection. As mentioned before, although tumour bulk need not necessarily present restriction, liver function and extent of the background liver disease do. Just as early results with LT for HCC were disappointing, so were results with resection, and the best 5-year survival rates in the 1980s were about 32% [35]. These figures were significantly improved upon in the later decades with large Eastern studies demonstrating a 5-year survival of nearly 50% in the latter part of the series which compared favourably with 36% seen in the earlier cohort [36]. Interestingly, it was also shown that significantly more patients in the latter group were found to have HCCs at an earlier stage, and many were detected at a subclinical stage. This was clearly a result of emerging surveillance programmes. Recently, median survival rates of 75 months and 5-year survival rates of 64% to 70% have been reported which compare favourably with results with LT [37, 38]. Latest series from the far east have demonstrated a very high 5-year survival rate of 79–81% in patients with early HCC up to 5 cm although the majority of patients in this series had favourable background factors [39, 40]. However, even in expert centres, results are significantly worse for larger HCCs, especially those exceeding Milan criteria [41]. Once again, it has to be acknowledged that these are data from high-volume centres in a select group of patients and may not reflect the overall picture. Despite these excellent results, recurrence rates at 5 years, even after curative resections, remain disappointingly high at nearly 80% with early recurrence observed in nearly a third of patients [37, 42]. Rates of early and cancer-related deaths are relatively high at 8–10%, particularly for extended resections [43]. Outcomes are particularly poor in resection performed for advanced HCC with multinodular or microvascular involvement [44]. Table 3 summarises results seen with resection for HCCs and clearly demonstrates significant improvement in survival figures over the last 10 years.

*3.2.2. Factors Determining Outcome after Resection for HCC.* With background liver disease remaining untreated, postoperative morbidity and noncancer mortality are related to the extent of liver dysfunction, presence of significant portal hypertension, and intraoperative factors such as blood loss. An attempt must be made to spare as much liver parenchyma as possible.

Specific tumour-related factors have been analysed by many authors in an attempt to prognosticate outcome and also to streamline patient selection. Multiple tumours, vascular invasion, preoperative serum alpha-fetoprotein levels, and tumour size are independent predictors of outcome [37]. Similar factors along with extent of mitoses were demonstrated to significantly determine outcome in a multicentre study [45]. This study also demonstrated a high

Table 3: Improving results of liver resection for HCC.

| Author | Year | Number of patients | Inclusion criteria if any | 3-year survival (%) | 5-year survival (%) |
|---|---|---|---|---|---|
| Iwatsuki and Starzl [35] | 1988 | 55 | None | | 25 |
| Poon et al. [36] | 2001 | 136[a]<br>241[b] | None | 47<br>62 | 36<br>49 |
| Shi et al. [46] | 2007 | 169 | Solitary HCC[c] | 79 | 61 |
| Ishii et al. [38] | 2008 | 162 | Milan | 89 | 70 |
| Yamakado et al. [40] | 2008 | 62 | Milan | 93 | 81 |
| Canter et al. [41] | 2010 | 94 | Exceeding Milan | 66 | |
| Huang et al. [63] | 2010 | 115 | Milan | 92 | 76 |
| Hung et al. [39] | 2011 | 229 | Milan | | 79.3 |

[a]Resections performed between 1989 and 1994.
[b]Resections performed between 1994 and 1999.
[c]Majority within Milan criteria.

1-year mortality of 22%, the majority of them dying of cancer recurrence or liver failure. In solitary HCCs, where parenchymal sparing is not necessarily a problem, a wide surgical resection margin of 2 cm is associated with lower rates of recurrence and better outcomes [46]. There is also some recent evidence that patients undergoing resection for small HCCs associated with cirrhosis due to HBV have better long-term survival than those with HCV [47]. This is relevant whilst interpreting and comparing data from differing geographical areas since it is evident that the majority of patients in the far east have cirrhosis related to HBV infection whereas the commonest aetiology in the western world is HCV. Large multifocal HCCs with vascular involvement should be considered as contraindications for major liver resections as should association of three or more of the other risk factors [37, 44]. Thus, although there are no current restrictions on the upper limit of size of HCC suitable for resection, it is clear from these data that best results are, once again, obtained in solitary or small HCCs confirming to Milan criteria.

*3.2.3. Preoperative Portal Vein Embolisation (PVE) for Major Resections for HCC.* Portal vein embolisation is a well-established method to increase the volume and function of the future liver remnant (FLR) prior to major liver resection for any pathology. The number of patients that undergo hypertrophy after PVE and the extent of that hypertrophy is less in livers with chronic liver disease compared to that seen in normal livers [48]. A large meta-analysis has confirmed the safety and efficacy of PVE with low morbidity and ability to perform major resections with very low mortality [49]. Another study has demonstrated better immediate outcomes in liver resections performed for HCC with PVE than without [50]. Unlike normal livers, the FLR necessary for cirrhotic livers is purported to be up to 40% even in presence of preserved liver function [51]. Recently, PVE has also been used in combination with transarterial chemoembolisation (TACE) to demonstrate better hypertrophy, postoperative outcomes, and recurrence-free survival compared to PVE alone, although no prospective randomised trials exist [52]. Thus, on the current evidence, PVE is safe and efficacious and should be regularly used to enable major curative resections for HCC.

*3.2.4. Resection or Transplantation for HCC?*

With comparable results achievable with either LT or resection in select patient groups, there has been a vigorous debate in terms of the best possible curative option for HCC. The pros and cons of both modalities have already been outlined in this paper. It is clear that best results are achieved in small HCCs, typically within Milan criteria, with excellent liver function and no associated comorbidities. More recently, comparable results were demonstrated between heterogeneous groups of patients undergoing LT or resection for HCCs beyond Milan criteria although the median followup was only 34 months and significantly more patients in the LT group had established cirrhosis [41]. Outcomes have to be based on an intention-to-treat basis, taking into account waiting times, dropouts, and waiting-list mortality. It would be impossible to perform a prospective randomised trial to establish the best modality of treatment. Although LT addresses the issue of liver disease, recurrence for certain conditions such as the viral hepatides is common. These patients also have to be on life-long immunosuppression which is unnecessary after a liver resection.

A recent consensus conference concluded that LT is the preferred method for patients with cirrhosis and HCC meeting Milan criteria while resection with wide margins is the treatment of choice for selected patients with cirrhosis that have well-preserved liver function, with no portal hypertension without a size restriction [53]. The Barcelona group have also proposed an algorithm based on their staging system and suggest that resection should be used for very early single HCCs (<2 cm) with normal liver function and no portal hypertension whereas all other patients within Milan criteria and suitable for curative treatment should be considered for LT [8]. The APASL guidelines recommend liver resection as a first-line curative treatment of solitary or multifocal HCC confined to the liver, which are anatomically

Table 4: Results for RFA for HCC.

| Author | Year | Number of patients | Inclusion criteria if any | 3-year survival (%) | 5-year survival (%) |
|---|---|---|---|---|---|
| Chen et al. [58] | 2006 | 71 | Solitary <5 cm | 71 | 68[a] |
| Livraghi et al. [59] | 2008 | 218 | Solitary <2 cm | 76 | 55[b] |
| N'Kontchou et al. [60] | 2009 | 222 | Up to 3 HCC <5 cm | | 40[c] |
| Peng et al. [62] | 2010 | 224 | Solitary <5 cm | | 60 |
| Huang et al. [63] | 2010 | 115 | Milan | 70 | 55 |

[a]4-year survival.
[b]Survival increased to 69% for "operable" patients.
[c]Survival increased to 76% for "operable" patients.

resectable and where there is satisfactory liver function reserve. LT should preferably be used for HCCs within Milan criteria in patients with more advanced liver disease (Child Pugh B or C) if medically fit [9]. The NCCN guidelines are similar but more ambiguous about the optimal size of HCC best suited for resection. LT is reserved for patients within Milan criteria and more advanced liver disease and potentially for those that are "unresectable" due to unfavourable tumour location or inadequate liver reserve [10]. This reflects the increasing use of resection as the first line of management for early HCC and may, in part, be also due to the fact that UNOS criteria specify that patients eligible for LT should not be considered for resection. Thus, although there are certain differences in all these guidelines, it is clear that use of surgical resection as the first treatment for small HCCs in a well-preserved liver is increasingly prevalent. This is clearly helped by the fact that although long-term results after LT have remained relatively static over the last 10 years, those with resection have significantly improved.

*3.3. Ablative Techniques for HCC.* Ablative techniques have an established role in the management of HCC. Radiofrequency ablation (RFA) is the most commonly used ablative technique for HCC. Other modalities include percutaneous ethanol injection (PEI) and microwave ablation (MWA). RFA is a minimally invasive procedure that can be performed percutaneously or operatively using both an open and a laparoscopic approach, with relatively low major complication rates. It can also be performed in patients who would be unsuitable for surgery (either LT or resection) due to associated comorbidity. It, however, is the only potentially curative technique that does not permit histological analysis of the tumour, and hence tumour-based prognostic criteria for best outcomes cannot be readily determined. In terms of safety and efficacy, a large meta-analysis in 2001 demonstrated an overall mortality of 0.5% and a complication rate of 8.9% [54]. More recent studies have demonstrated further lowering of mortality (0.1%) and complication rates [55]. The commonest complications are liver abscesses, biliomas, haemorrhage, and so forth. Although both RFA and PEI are effective techniques, studies have demonstrated that necrotic effect of RFA is more predictable for larger tumour sizes and that RFA is superior in terms of local tumour progression and disease-free survival [56].

*3.3.1. Results of RFA for HCC.* RFA is best used for tumours less than 3 cm after which the incidence of local recurrence increases. Vascular proximity leads to a heat-sink effect minimising the efficacy of the burn and thereby promoting higher recurrence rates. Significantly better results seem to be obtained when the procedure is performed operatively rather than percutaneously [57]. A randomised trial reported comparable outcomes between RFA and surgical resection for solitary small HCCs <5 cm with 4-year survival rates between 64 and 68% [58]. Another more recent study demonstrated sustained complete response rate for RFA for very small HCCs to be over 97% with a 5-year survival of 69% in tumours that would be considered operable [59]. This was improved upon in another series reporting a 5-year survival rate of 76% for patients considered operable disease by BCLC criteria [60]. A large retrospective study demonstrated that in Child Pugh A cirrhotics, RFA and resection offered equivalent benefits for tumours less than 3 cm while resection provided better survival when the HCC was larger than 3 cm but still within Milan criteria [61]. A Chinese study demonstrated 5- and 7-year survival of 60% and 55% with RFA as the primary treatment for HCCs within Milan criteria [62]. The latest randomised controlled trial comparing RFA and resection for HCCs within Milan criteria demonstrated that overall survival and recurrence-free survival were significantly better with curative resection rather than RFA [63]. In this study, the overall 5-year survival rates were 55% with RFA and 76% with resection, both comparing favourably with LT. Most of these series enrolled patients with Child Pugh score A and tumours either within Milan criteria or small solitary tumours <5 cm. Table 4 summarises results of RFA for HCCs.

These data would suggest that RFA is probably as effective as both resection and LT for small HCCs in early cirrhotic patients with preserved liver function. However, more prospective randomised trials with much larger number of patients would be necessary to demonstrate the superior treatment modality. Recent trials have demonstrated slight inferiority of RFA over resection for small HCCs. The BCLC algorithm recommends RFA as the primary treatment for single small HCCs in patients that are high risk for operative management due to associated comorbidity [8]. Similar approach is advocated by both APASL and the NCCN which recommend RFA as an equivalent alternative for

any HCC considered suitable for resection, namely, solitary HCC <3 cm in a patient with Child Pugh A cirrhosis. This approach may yet change as more data on randomised trials between RFA and resection becomes available.

More recently, other ablative techniques such as MWA and high-intensity focussed ultrasound (HIFU) have been used in an attempt to overcome some of the limitations of RFA. These and others such as electroporation need to be further evaluated in clinical trials [64].

*3.3.2. RFA as a Bridge or a Holding Therapy to Transplantation.* Longer waiting times for LT and rising dropout rates prompted the evaluation of RFA and TACE as holding techniques for patients who would otherwise progress beyond Milan criteria and also for downstaging patients with HCCs already beyond Milan criteria to make them eligible for LT [65]. Such early feasibility studies indicated that some tumours could be successfully downstaged. However, it is doubtful whether downstaging larger tumours with RFA or TACE alters prognosis or biological behaviour of the tumour. A study which applied this practice demonstrated overall 5-year survival less than 50% [66]. In fact, nearly half of all patients "dropped out," and the survival on an intention-to-treat basis was less than 25%. It is assumed that nonresponders are a self-selecting group of patients that manifest unfavourable tumour biology. Much better outcomes were demonstrated recently with a dropout rate of 30% and an intention-to-treat 4-year survival of 69% [67].

The role of RFA and TACE as holding therapy for patients satisfying organ allocation criteria is equally contentious. It could be employed to minimise dropout rates, a natural occurrence on waiting lists. However, it does not confer additional benefits or improve survival after successful LT [68]. Once again, large randomised trials are necessary to conclusively demonstrate benefit but are probably not feasible.

## 4. Conclusions

HCC is a common but complex multifactorial condition with poor outcomes worldwide. Few patients ever come to curative surgical therapy. The role of surgical techniques has gradually expanded over the years with significant improvement in outcomes with liver resection whilst those with LT have remained static. Outcome after any curative treatment for HCC is related not only to the stage of the tumour but also to tumour biology, background liver disease, and associated comorbidities.

Staging algorithms such as those proposed by the BCLC, APASL, and the NCCN provide useful, evidence-based guidance towards decision-making. Treatment should be individualised, preferably in high-volume centres of expertise with facilities for both liver resection and liver transplantation.

For small solitary HCCs <2-3 cm and normal liver function, LT, resection and RFA seem to confer comparable benefit although recent trials confirm superiority of resection compared to RFA. Milan criteria continue to be utilised by most transplant programs, and although there seems to be a case for modest increase, the results have not been replicated across national programs. LT should be the preferred approach for patients with larger tumours within Milan criteria especially with advanced liver dysfunction. Resection should be preferred either for very small HCCs or for those that have exceeded Milan criteria but still have excellent liver function and no portal hypertension. RFA should be the preferred method of ablation and should be utilised for small HCCs not otherwise fit for surgical management.

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*Review Article*

# Assessment of Stromal Invasion for Correct Histological Diagnosis of Early Hepatocellular Carcinoma

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Stromal invasion (invasive growth of tumor tissue into portal tracts and fibrous septa) is now recognized as the most important finding in the diagnosis of the well-differentiated type of early hepatocellular carcinomas (HCCs). In differentiating stromal invasion from pseudoinvasion (benign hepatic tissue in fibrous stroma), the following 5 items are useful: (1) macroscopic or panoramic views of the histological specimen, (2) the amount of fibrous components of stroma, (3) destruction of the structure of portal tracts, (4) loss of reticulin fibers around cancer cells, and (5) cytokeratin 7 immunostaining for ductular proliferation. Knowledge of stromal invasion is also useful for a better understanding of the vasculature (hypovascular HCCs) and histological features (fatty change) of early HCCs. Invasion of preexisting arteries and portal veins causes hypo-vascularity of HCCs. Further, hypovascularity causes fatty change as a hypoxic change of cancer tissues.

## 1. Introduction

Recently, international consensus for the histological diagnosis of hepatocellular carcinoma, especially of well-differentiated type of early stage (early HCC), was published by the International Consensus Group for Hepatocellular Neoplasia (ICGHN) [1]. This was an epoch-making event for the early diagnosis and early treatment of hepatocellular carcinomas (HCCs). In this consensus paper, stromal invasion (invasive growth of tumor tissue into portal tracts and fibrous septa) was recognized as the most important finding for the diagnosis of early HCCs. Unfortunately, however, this finding is not commonly known except among a small number of liver pathology experts. To present the correct histological diagnosis of early HCCs, histological features of stromal invasion are herein explained, with details shown in many figures. It is also described how stromal invasion is closely related to characteristic image findings and histological features of early HCCs.

## 2. History of Studies of Stromal Invasion of HCCs

Stromal invasion, formerly called interstitial invasion of HCC, is defined as invasive growth of tumor tissue into fibrous septa, portal tracts, and/or blood vessels [2–7]. Stromal invasion by other tumors of other organs is a commonly recognized concept, and has long been important evidence for the definitive diagnosis of malignant tumor [8, 9]. However, stromal invasion of HCC has not been generally known until quite recently. This finding was first reported as a "streak pattern" in the fibrous septa of cirrhosis around an HCC nodule by Kondo Y. et al. [2]. Kondo F. et al. then reported that this finding was frequently found within preexisting portal tracts as well as fibrous septa [3], emphasizing that this finding was very useful for the diagnosis of well-differentiated HCCs. The invasion pattern was classified into 3 types—crossing type, longitudinal type, and irregular type. It was also reported that stromal invasion could be detected even by macroscopic view and by panoramic view of a histological specimen. At that time this finding was called "interstitial invasion" instead of "stromal invasion." Tomizawa et al. reported that the growth activity of well-differentiated HCC was rather suppressed with the stromal invasion [4]. Nakano et al. divided stromal invasion into three types: (1) stromal invasion into fibrotic tissue and/or portal tracts, (2) blood vessel wall invasion of portal veins or hepatic veins, and (3) tumor thrombus [5]. Miyao et al. described that HCC tissue in the state of stromal invasion

was unaccompanied by reticulin frameworks and type IV collagen [6].

In 1995, an International Working Party (IWP) of the World Congress of Gastroenterology published a consensus nomenclature and diagnostic criteria for nodular hepatocellular lesions [10]. In this article, stromal invasion was listed as a criterion for the histological diagnosis of well- and moderately differentiated HCC. Even after publication of this article, however, this finding was still not well known especially among pathologists in Western countries, possibly because related articles regarding stromal invasion were written by Japanese pathologists. This fact caused serious differences in criteria for the diagnosis of early HCCs between Eastern and Western pathologists.

In order to solve this serious problem, an International Consensus Group for Hepatocellular Neoplasia (ICGHN) was convened in April 2002 in Kurume, Japan. This group met several times and discussed histological criteria for the diagnosis of early HCCs subsequently, up to July 2007 [1]. In these meetings, the findings of stromal invasion were discussed in detail. Finally, all the participants including Western pathologists generously accepted the importance and usefulness of this finding. Park et al. reported that ductular reaction confirmed by cytokeratin 7 (CK7) is helpful in defining early stromal invasion, small hepatocellular carcinomas, and dysplastic nodules (DNs) [7]. This was the first article of stromal invasion written by a non-Japanese pathologist. All authors of this article were members of ICGHN. The authors consisted of 1 Korean, 4 Western, and 4 Japanese pathologists.

In 2009, ICGHN published the consensus paper [1], which described that stromal invasion was the most helpful in differentiating early HCC from high-grade DNs. However, this finding was not sufficiently disseminated even after publication of the consensus paper. To achieve progress in the early diagnosis of many HCC patients in the world, this finding must be explained in detail.

## 3. How to Evaluate Stromal Invasion Correctly: Macroscopic and Histological Assessment of Stromal Invasion

Stromal invasion is invasive growth of tumor tissue into stroma (fibrous septa, portal tracts, and/or blood vessels). It is histologically classified into 3 types—crossing type, longitudinal type, and irregular type (Figures 1(A), 1(B), and 1(C) [4].

In the crossing type, HCC invades across fibrous septa of tumor nodules (Figure 1(A)). In the longitudinal type, tumor cells grow longitudinally within fibrous septa (Figure 1(B)). In the irregular type, portal areas are irregularly invaded by tumor cells (Figure 1(C)). The crossing type is usually observed in moderately or poorly differentiated HCCs whereas the longitudinal and irregular types are usually found in well-differentiated HCCs, although also at times in moderately or poorly differentiated HCCs. In the evaluation of stromal invasion, comparison of cancer areas with noncancerous areas is very useful (Figure 1(D)), and we have to differentiate "pseudo-invasion" from true stromal invasion. Pseudo-invasion means benign non-cancerous tissue in the fibrous stroma (Figure 1(E)), and this does resemble stromal invasion.

For the differentiation, the following factors are very useful.

(1) Macroscopic and/or panoramic (low-magnification) views of the nodule.

(2) Amount of fibrous components of the stroma.

(3) Continuity to vascular invasion and destruction of the structure of portal tracts.

(4) Loss of reticulin fibers around tumor cells.

(5) Cytokeratin 7 immunostaining.

Stromal invasion can be identified even by a macroscopic and/or panoramic view of histological specimens. As is seen in Figure 1(F) (macroscopic view of HCC), in the non-cancerous area without invasion (area of (a)), the fibrous septa are clearly visible. However, in the area of tumor spread (area of (b)), the septa are indistinct. Similarly, in a panoramic view of a histological specimen of HCC (Figure 1(G)), distinct fibrous septa (area of (a)) and indistinct fibrous septa (area of (b)) can be clearly identified. In these indistinct septa, tumor invasion was then detected by microscope (Figures 1(B) and 1(C)). The amount of the fibrous component is quite different between the invasive and noninvasive areas, an important point for the differentiation from pseudo-invasion. The amount of the fibrous component was decreased as a result of the tumor invasion, and this decrease caused the indistinctness of the fibrous septa. Pseudo-invasion is usually caused by fibrosis around benign non-cancerous liver tissue. Therefore, it does not show reduction in the fibrous component. When stromal invasion is very mild and fibrous components are minimally reduced, histological and macroscopic assessment of stromal invasion is difficult. However, stromal invasion is severe enough, histological and macroscopic assessment is easy (Figures 1(F) and 1(G)). Even in cases of HCCs with minimal invasion and DNs, proportion of fibrous stroma or portal tracts are reduced to some extent as described later. Therefore, macroscopic view is helpful for recognizing eHCC and DN. The continuity to vascular invasion and destruction of the structure of portal tracts are also important findings (Figure 1(H)). The former is a decisive finding of malignancy. Although it is not a common finding, it can be detected in some early HCCs. Tumor tissue first invades into fibrous septa, then into vascular walls, and finally into vascular lumina. The connection among endothelial cells was most certainly destroyed by the mechanical force exerted by tumor growth. Portal vein invasion in Figure 1(H) is in vascular space. It means tumor cells are disseminated in circulation. However, tumor cell dissemination does not directly cause metastasis. Before forming metastatic foci, tumor cells have to survive within circulation, have to reach to remote areas, have to invade vascular walls from inside to outside, and have to proliferate outside the blood vessels. Interpretation of tumor cells in the subendothelial space

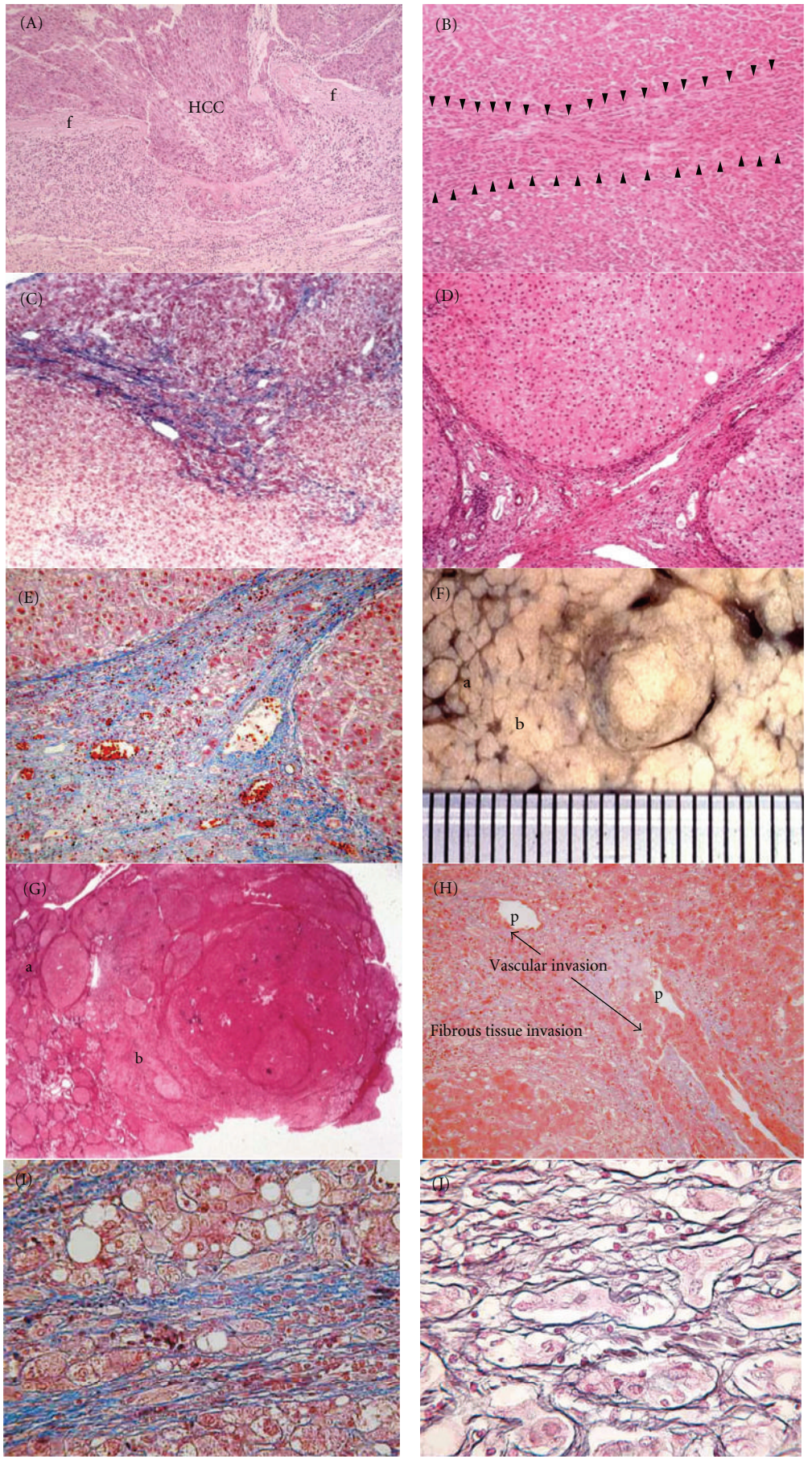


Figure 1: Continued.

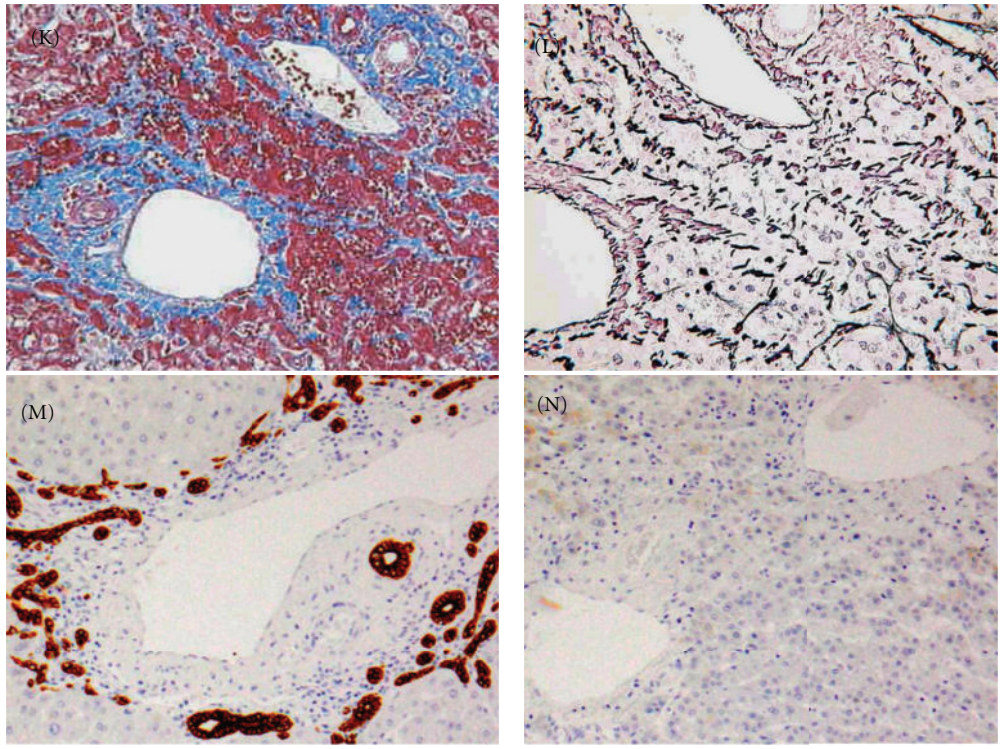


Figure 1: Various features of stromal invasion of hepatocellular carcinoma (HCC) and pseudo-invasion (A) Crossing type. Cancer tissue (HCC) invades across fibrous septa (f) of tumor nodule. (B) Longitudinal type. Tumor cells grow longitudinally within fibrous septa (arrowheads). (C) Irregular type. Portal areas are irregularly invaded by tumor cells (Masson trichrome stain). (D) A non-cancerous area without invasion, and a portal area and fibrous septa are clearly seen. (E) Pseudo-invasion. Benign non-cancerous cells are found in the fibrous stroma (Masson trichrome stain). (F) Macroscopic view of stromal invasion. In the non-cancerous area without invasion (area of (a)), fibrous septa are clearly seen. In the area of tumor spread (area of (b)), septa are indistinct. (G) A panoramic view of stromal invasion. In the same way as in (F), the non-cancerous area without invasion (area of (a)) shows distinct fibrous septa. The area of tumor spread (area of (b)) shows indistinct septa because stromal invasion of longitudinal type and irregular type ((B), (C)) reduced the amount of fibrous component. (H) Continuity of fibrous invasion and vascular invasion. The arrows show portal vein (p) invasion. Vascular invasion is continuous to stromal invasion of fibrous tissue of the portal "tract" and fibrous septum (Masson trichrome stain). (I) Masson trichrome staining of pseudoinvasion. (J) Silver staining of the same specimen as (I). Liver cells are clearly surrounded by reticulin fibers. (K) Masson trichrome staining of true invasion. (L) Silver staining of the same specimen as (K). Carcinoma cells are not surrounded by reticulin fibers. (M) (N) Cytokeratin (CK) 7 immunostaining in a non-cancerous area (M) and cancerous area (N). (M) Ductular reaction, confirmed by CK 7 staining, is clearly seen in a non-cancerous, non-invasive area. (N) Ductular reaction is not found in the invasive area. (N) Adapted from Y. Kondo et al. [2], F. Kondo et al. [3], and from F. Kondo [11].

is controversial. It can be true sub-endothelial invasion. However, it can be interpreted as blood space invasion after re-covering with endothelial cells. Endothelial cells can easily cover intravascular foreign substance. Destruction of the portal tract structure is more frequently found in stromal invasion while this feature is not seen in pseudo-invasion (Figure 1(E)).

Loss of reticulin fibers around the tumor cells is another useful finding [7]. Figures 1(I) and 1(J) show Masson trichrome staining and silver staining of pseudo-invasion. And Figures 1(K) and 1(L) show those of true invasion, respectively. Magnification of Figures 1(J) and 1(L) is a little higher than that of Figures 1(I) and 1(K). The liver parenchyma is clearly surrounded by reticulin fibers in the pseudo-invasion (Figure 1(J)). By contrast, the liver tissue of the true invasion lacks such surrounding reticulin fibers (Figure 1(L)). Tumor cells are embedded in the septal fibers without being clothed by reticulin fibers.

As described above, Park et al. reported that CK7 immunostaining is useful for identifying stromal invasion [7]. Ductular reaction confirmed by CK7 staining is frequently found in non-cancerous hepatocellular nodular lesions (Figure 1(M)) while it is less frequently found in HCCs with true stromal invasion (Figure 1(N)). Ductules around the fibrous septa are non-cancerous components. They must have been invaded by well-differentiated HCC cells around the fibrous septa or by HCC cells from the fibrous septa.

For the correct assessment of true stromal invasion, these silver and CK7 stainings are useful. Masson trichrome stain, Azan-Mallory stain, and Victoria blue stain are also useful for clarifying the fibrous components.

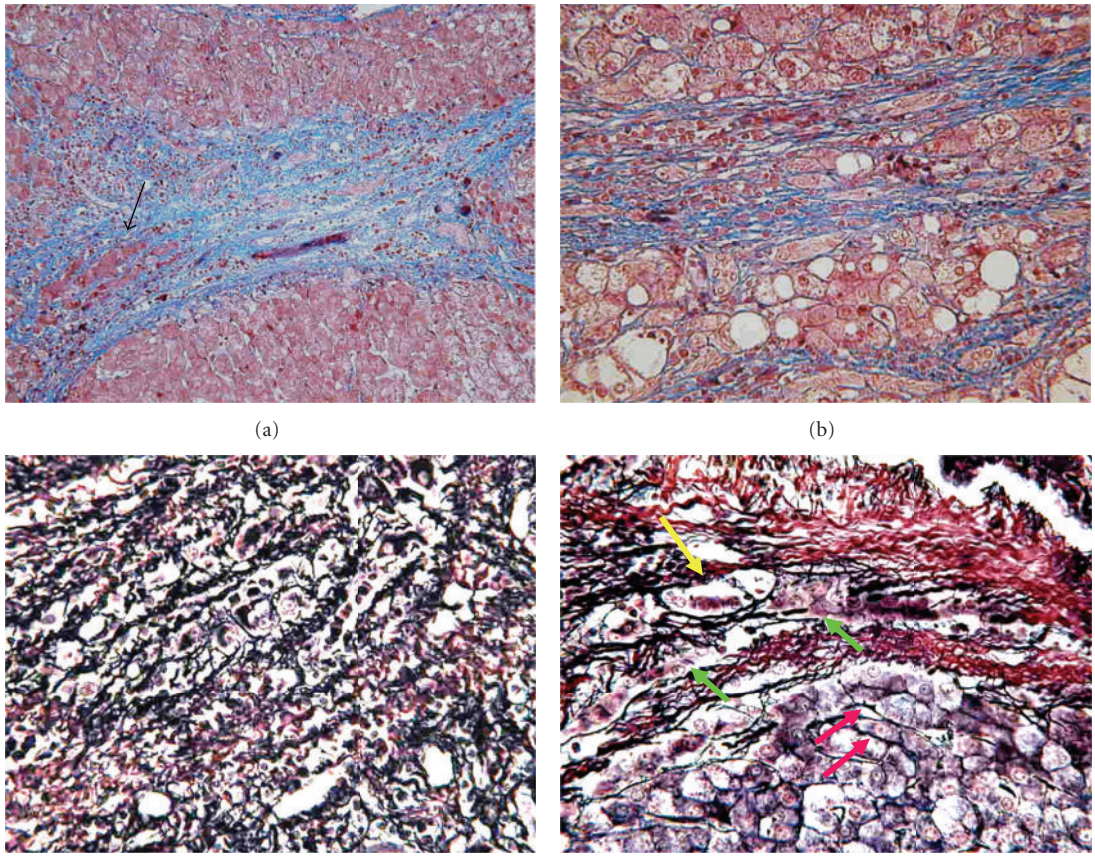

Figure 2: Histological features which make the assessment of stromal invasion difficult (a) True stromal invasion of very mild grade. The fibrous septum is almost intact except for a small area (arrow). (b) Pseudo-invasion consisting of very thin fibrous bundles within and around thick liver cell cords. This pattern was formed by dissection of liver parenchyma by very thin fibrous tissue. (c) A specimen of very poorly performed silver stain. (d) Silver stain of HCC tissue within and around a fibrous septum. Reticulin fibers circumscribing cancer tissue are seen even in the area of true invasion (yellow arrow). However, noncircumscribed tumor cells are also seen in the same fibrous septum (green arrows). This area is a "battle front" of invasion. Red arrows show ordinary tumor tissue with reticulin fibers surrounding the fibrous tissue.

Next, some histological features that make the assessment of stromal invasion difficult must be shown (Figure 2).

Figure 2(a) shows true stromal invasion of a very mild grade. The fibrous septum is almost intact except for a small area (arrow). By contrast, Figure 2(b) shows pseudo-invasion consisting of very thin fibrous bundles within and around thick liver cell cords. This pattern was not formed by the reduction of fibrous component but rather by dissection of liver parenchyma by very thin fibrous tissue. Observing these two figures, pathologists may doubt the concept of stromal invasion. In such cases, however, silver stain is very useful. Reticulin fibers are lost in the case of true invasion but not in the case of pseudo-invasion. In cases like Figure 2(a), I recommend pathologists to search for more severely invaded portal tracts that can easily be assessed as true invasion. Even very well-differentiated HCCs sometimes include severely invaded portal tracts as well as minimally invaded portal tracts. Figure 2(c) shows a specimen of very poorly performed silver staining. Such poorly stained specimen makes the diagnosis difficult.

Figure 2(d) shows that reticulin fibers sometimes circumscribe cancer tissue even in the area of true invasion (yellow arrow). However, noncircumscribed cells are usually seen in the same fibrous septum (green arrows). This area is a "battle front" of invasion. By contrast, red arrows show ordinary tumor tissue with reticulin fibers outside the fibrous tissue. In fact, reticulin fibers are sometimes observed within and around true invasive areas. After the invasive process is over, the cancer cells form ordinary cancer areas. In such phase of tumor growth, reticulin fibers must be formed again.

## 4. Influence of Stromal Invasion on Images and Histological Features of Early HCCs

Stromal invasion is closely related to the images and histological features of early HCCs. Figure 3 shows the relationship between cancer development, vascularity, histological feature (fatty change), and stromal invasion. Although there exists no direct evidence in a strict meaning, the possibility or

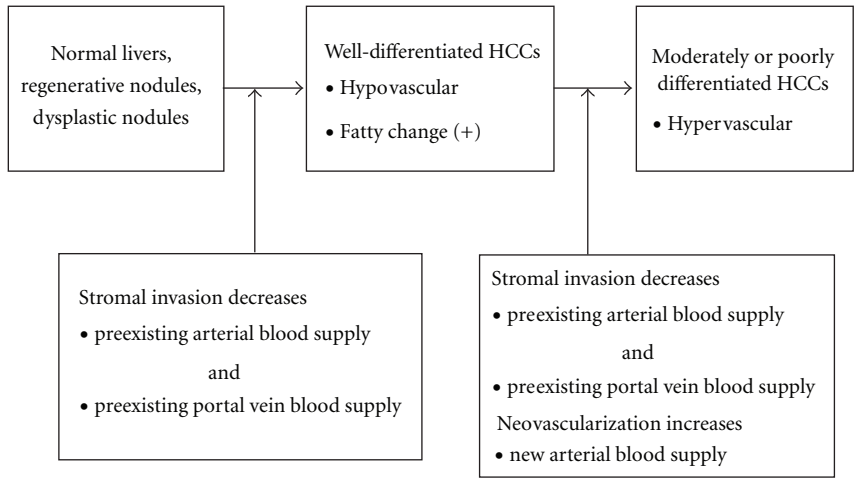


Figure 3: Relationship between cancer development, vascularity, histological feature (fatty change), and stromal invasion.

hypothesis shown in Figure 3 well explains the formation mechanism of vascularities and fatty change of HCC. At least, previous studies [12–18] can be good indirect evidence for the description in Figure 3. Well-differentiated HCCs emerge from non-cancerous liver tissues (normal liver, regenerative nodules, and DNs), and then they progress into moderately or poorly differentiated HCCs. Vascularity (usually evaluated by contrast medium-enhanced images) changes during this process. Well-differentiated HCCs are usually hypo-vascular lesions [12–17]. This hypo-vascularity means a decrease in pre-existing arterial and portal venous blood supply caused by stromal invasion. During the process in which a well-differentiated HCC progresses into a moderately or poorly differentiated HCC, vascularity usually changes to become hypervascular [12–17]. This vascular change is caused by proliferation of abnormal arteries (neovascularization) [1, 17].

As a matter of fact, abnormal arteries are found within DNs [1, 17]. However, the increase of arteries is not sufficient to cause hyper-vascularity. DNs sometimes show hypo-vascularity without stromal invasion [17]. This hypo-vascularity is attributed to a relative decrease of density of pre-existing portal tracts. Because the parenchymal component increases within the DN nodule, the density of pre-existing portal tracts decreases. After DNs transforms into early HCCs, the density may decrease more severely by stromal invasion. This process must have caused hypo-vascularity of early HCCs.

This hypo-vascularity can also explain the formation mechanism of fatty change, a well-known feature of early HCCs (Figure 3) [18]. Although fatty change may be attributed to metabolic change of tumor cells with tumor development independent of hypoxic change, hypo-vascularity may cause fatty change as a hypoxic change.

As mentioned above, knowledge of stromal invasion is very useful to understanding the vascularity and histological features of early HCCs.

## 5. Limitations of Assessment of Stromal Invasion

Finally, limitations of the assessment of stromal invasion have to be described. Stromal invasion cannot always be assessed histologically, and it is very rarely assessed in the examination of thin-needle biopsy specimens [11]. Biopsy specimens are simply too small to allow examination of stromal invasion. For this reason, very well differentiated HCCs lacking typical features of ordinary well-differentiated HCCs are not diagnosed by biopsy [11]. As histological criteria for the biopsy diagnosis of well-differentiated HCCs, (1) nuclear crowding (hypercellularity), (2) hyperstainability of cytoplasm (basophilia or eosinophilia), and (3) microacinar formation have been used til now [19]. These criteria have been proved to be useful because ordinary well-differentiated HCCs have considerable parenchymal atypia. However, some very well-differentiated HCCs are not diagnosed by biopsy and are definitively diagnosed after examination of stromal invasion in resected specimens.

To make progress in the early diagnosis of HCCs, we have to develop new parenchymal tumor markers that can be used for biopsy diagnosis. Some attempts have been made recently to utilize immunohistochemical markers for the diagnosis of well-differentiated HCCs [20–25]. Heat shock protein 70 (HSP70) [20, 21], glypican 3 (GPC3) [20, 22, 23], and glutamine synthetase (GS) [20, 24, 25] have been used independently or in combination. At present, these markers are used in a complementary manner to morphological criteria. Newer markers have also been tried [26, 27]. We are hopeful that excellent markers with high sensitivity and high specificity are developed in the future.

## 6. Conclusions

(1) Stromal invasion is a very important finding for the histological diagnosis of early HCCs.

(2) For the correct assessment of stromal invasion, the following 5 items are useful: (1) macroscopic or panoramic views of the histological specimen, (2) amount of fibrous components of the stroma, (3) destruction of the structure of portal tracts, (4) loss of reticulin fibers around cancer cells, and (5) CK 7 immunostaining for ductular proliferation.

(3) Knowledge of stromal invasion is very useful to understand the formation mechanism of images (vascularity) and histological features (fatty change) of early HCCs.

(4) Stromal invasion cannot be assessed in thin-needle biopsy specimens.

(5) New parenchymal tumor markers usable for biopsy diagnosis need to be developed.

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*Review Article*

# The Role of Antiviral Therapy for HBV-Related Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a highly prevalent and lethal cancer worldwide; despite the curative treatment for HCC, the rate of tumor recurrence after hepatectomy remains high. Tumor recurrence can occur early (<2 years) or late (>2 years) as metastases or de novo tumors. Several tumor factors were associated with HCC recurrence; high hepatitis B virus (HBV) load is the major risk factor for late recurrence of HCC after resection. Preoperative antiviral therapy improves liver function, and postoperative reduce HCC recurrence. In this paper, we focus on antiviral treatment to improve the liver function, prevent recurrence, and lengthen the overall survival for HBV-related HCC.

## 1. Introduction

Hepatocellular carcinoma (HCC) is one of the major health problems worldwide, ranking as the third leading cause of cancer-related mortality in the world, and the second in China [1]. The annual incidence of HCC in hepatitis B cirrhotic patients can run as high as 3–5%, and one-third will develop HCC in their lifetime [2]. For patients with hepatitis B virus-related HCC (HBV-related HCC), early-stage tumors and preserved hepatic function, liver resection, and liver transplantation offer the best therapeutic choice. The palliative treatment modalities include transarterial chemoembolization (TACE) and targeted systemic chemotherapy with sorafenib. Unfortunately, despite the continuing efforts for the curative treatment HCC with surgical resection, the rate of tumor recurrence after hepatectomy remains high (>70% at 5 years), which still limits survival of the patients [3]. Several factors are reported to be associated with an increased risk of HCC recurrence after surgical resection, including tumor characteristics such as multiplicity, size, and portal invasion, AFP level, PIVKA-II level, and hepatic functional parameters such as albumin level, PT, and Child-Pugh class [4, 5]. Recently, accumulating evidence has shown that a high serum hepatitis B viral (HBV) DNA level is another risk factor for de novo HCC development in HBV carriers irrespective of hepatitis activity [6, 7]. Additionally, some investigators have shown the viral replicative status of subjects as a predictor of postoperative recurrence of HCC [8, 9]. Therefore, it was very significant and interesting to investigate of the molecular mechanism of the direct carcinogenic effect of HBV, and it may help us to clarify additional therapeutic targets for HCC prevention. However, in previous studies, the relation between HBV load and the recurrence of HCC after resection may be confounded by other major risk factors for recurrence, such as macroscopic vascular invasion or noncurative resection. In this paper we review the incidence of HBV-related HCC and its impact on the prevention of recurrence with antivirus therapy.

## 2. The Incidence and Surveillance of HBV-Related HCC

Individuals with chronic hepatitis B (CHB) infection have a risk of developing HCC, that is, 100-fold greater than the persons who are not infected [10]. Most carriers of CHB, including Asians, Africans, and a proportion of persons in Mediterranean countries, acquire the infection at birth or within the first 1 to 2 years after birth [11]. Once chronic

infection is established, complete eradication of the virus is still not possible, and these patients are facing the risk of HCC development [10]. Previous longitudinal studies have shown that genotype B patients have an earlier and more frequent hepatitis B e antigen (HBeAg) seroconversion than genotype C patients, [12, 13] indicating that genotype C patients may have more severe liver disease than genotype B patients. In addition, genotype C HBV was associated with increased viral load, and associations of HBV genotype and viral load with HCC risk were additive. This suggests that viral load and genotype determination may be important factors to consider regarding screening program for the detection of HCC and treatment indication.

In patients with CHB, screening for HCC is necessary even after clearance of serum hepatitis B surface antigen (HBsAg) and HBV DNA and remission of hepatitis, especially in those with a high antihepatitis B core antibody (anti-HBc) titer [14, 15] because the oncogenic potential due to occult HBV infection or the integration of HBV DNA is considered to continue [16]. The earlier the seroconversion of HBeAg, the better the clinical outcome of HBV carriers. A single randomized study from China comparing surveillance and nonsurveillance in HBV patients using periodic serum AFP and abdominal ultrasound at 6-month intervals demonstrated the benefit of surveillance in terms of reduced mortality [17]. With AFP assays and the development of modern imaging systems, such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), more and more hepatitis B-related HCCs can be detected and diagnosed and hepatectomy early. However, the prognosis of HCC remains unsatisfactory, even after curative resection, yet with recurrence of HBV-related HCC is extremely high [18], which is also the main cause of death, in addition to concomitant hepatic decompensation. It has shown that with the successful implementation of HCC surveillance and curative treatment, more patients could avoid the risk of early recurrence and thus survive longer.

## 3. The Mechanisms of HBV-Related HCC Recurrence

It is well known that there are two distinct types of HCC recurrence: tumors grown from dissemination of the primary tumor and de novo tumors arising from the "field effect" in diseased liver [19, 20]. That is, the latter is clonally independent from the primary tumor. However, the mechanism for recurrent carcinogenesis associated with HBV in the remaining liver in patients who have undergone curative resection remains unclear. Over the past years, studies have suggested that high viral load is via direct and indirect ways which are thought to be involved for recurrence [21]. It is possible that sustained viremia and subsequent active viral replication may contribute to the carcinogenic process. Active replication of HBV may initiate malignant transformation through a direct carcinogenic mechanism by increasing the probability of viral DNA insertion in or near proto-oncogenes, tumor-suppressor genes, or regulatory elements of cellular DNA [22, 23]. The integration of viral DNA may increase the production of transactivator protein hepatitis B X antigen, which may promote the neoplasia of hepatocytes, as well as, bind to the p53 tumor-suppressor gene and disrupt its functions [24, 25]. Indirectly, continuing HBV replication can also induce chronic liver fibrosis and inflammation and mediate alteration in transforming growth factor-beta1 (TGF-$\beta$1) and alpha-M production, thereby leading to carcinogenesis [26, 27].

Imamura proposed a convenient framework to clinically differentiate each type of recurrence as "early" or "late" recurrence based on a cutoff of 2 years after surgery [28]. This framework has made it possible to assess risk factors for each type of recurrence [29]. For one thing, early recurrence, which appears within 2 years after surgery, is associated with tumor-related factors including the presence of vascular invasion and additional tumor sites besides the primary lesion (satellite lesion), which is consistent with the notion that this type of recurrence is tumor dissemination as a consequence of malignant characteristic of the primary tumor. For another, late recurrence, which appears more than 2 years after surgery, is considered to be associated with the severity of hepatic inflammation and liver damage closely linked to the "field effect." Early intrahepatic recurrence has poorer prognosis than late intrahepatic recurrence. Discrimination of these types of recurrence is clinically important because the biological basis producing each recurrence is different, and the following therapeutic intervention should be considered accordingly [30]. Recently, Kim et al. reported that persistent viremia is associated with disease-free survival after 12 months of surgery, suggesting its association with late recurrence [31]. And Wu et al. also evaluated clinical variables together with HBV-related factors including viral load, genotype, and recurrent mutations, for their prognostic implication with respect to early and late recurrence in 193 HBV-related HCC patients [9]. During the median followup of 5 years, 134 patients (69%) had HCC recurrence [19]. It was found that tumor-related factors: microvascular invasion, positive cut margin, and high serum AFP level were associated with the risk of early recurrence, whereas liver inflammation/damage-related factors: histological inflammation and ICG-15 retention rate were independently associated with the risk of late recurrence [9]. Interestingly, the high HBV viral load was found to be associated with the risk of late, but not early recurrence, probably because the high HBV DNA level is the most functional measure reflecting the exposure to the direct carcinogenic effect of HBV.

## 4. The Necessity of Antiviral Treatment on HBV-Related HCC

As above mentioned, for patients with CHB, serum HBV DNA levels have emerged as the key risk factor for the development of HCC. This may argue for an earlier antiviral intervention, before the development of cirrhosis, to prevent HCC development, and even more, as adjuvant therapy after the resection HCC for the patients with a high HBV DNA level to prevent late recurrence. But only a few recent studies have evaluated HBV replication status as a predictor of HCC recurrence [8, 32], and the interpretation of their results was

complicated by the use of antiviral therapy. Notably, several studies found a significant association between high HBV load and increased risk of HCC and liver cirrhosis [6, 33]. Elevations in serum HBV DNA level are not only a major risk factor for HCC recurrence, but also the risk factor most amenable to modification.

Several large cohort studies from China, Taiwan, and Senegal reported that high serum HBV DNA levels at the time of enrollment were associated with an increased risk of cirrhosis and HCC. Therefore, it was suggested that serum HBV DNA level, and not only liver disease activity, might be used as an indication for antiviral therapy. In a large prospective study of 3653 HBV carriers in Taiwan, Chen and colleagues [6] reported that 164 had HCC after a mean follow-up of 11.4 years. The incidence of HCC correlated with serum HBV DNA level at entry in a dose-response relationship. The authors concluded that high serum HBV DNA levels ($>10^4$ copies/mL) were a strong predictor of HCC independent of HBeAg, ALT, and the presence of cirrhosis. Moreover, a subanalysis showed that spontaneous decline of viremia levels from levels higher than $10^5$copies/mL to levels below $10^4$ copies/mL was associated with a reduced risk of HCC development by comparison with patients who maintained high viremia levels. Thus, the authors emphasize that effective control of HBV replication with antiviral therapy may lower the risk of HCC.

*4.1. The Impact of Antiviral Therapy on HBV Load for HBV-Related HCC.* Antiviral treatment may render patients with HBV-related HCC better able to tolerate HCC treatments and may improve prognosis. However, the efficacy of antiviral therapy on HBV viral status and underlying liver function in patients is still unclear. Many questions remain to be answered in terms of clinical management of CHB to improve the prevention of HCC late recurrence: (1) can the correlations between high viral load and HCC recurrence risk be generalized to all HBV carriers whatever their HBeAg status, alanine aminotransferase (ALT) levels, and stage of CHB? and (2) the major clinical question is whether antiviral therapy can prevent HCC late recurrence. Lin conducted a study in order to evaluate the effectiveness of IFN-$\alpha$ with 16 HBV patients after medical ablation therapy for primary tumors [34]. They found that HCC recurred in four of four (100%) untreated patients and in four of 12 (33.3%) IFN-$\alpha$ treated patients ($P = .0384$). They concluded that IFN-$\alpha$ therapy may reduce HCC recurrence after medical ablation for primary HCC although the sample size was too small to reach a firm conclusion. The Asian Cirrhosis Lamivudine multicenter randomized controlled trial (RCT) study showed that lamivudine can reduce disease progression in HBV-related cirrhosis, including an approximately 50% decrease in HCC incidence. Such efficacy was achieved despite the emergence of drug resistance in approximately 50% of cases. In a small study, Hung has reported 72 patients who underwent HCC resection and found that patients with viral load of more than 2000 IU/mL had a significantly higher risk of HCC recurrence after resection [8], with viral load being the most important correctable risk factor for HCC recurrence (odds ratio 22.3, 95% CI 3.3–151, $P = .001$). However, only 10 patients were treated with lamivudine, and none of these patients had HCC recurrence compared to those without antiviral therapy, but this finding could be due to the small sample size. Recently, a nonrandomized comparative study for postoperative antiviral treatment was conducted on patients who underwent curative hepatectomy for advanced HCC [35]. Patients in the treatment group ($n = 43$) received lamivudine with or without adefovir dipivoxil, while the control group ($n = 36$) received no antiviral treatment. The treatment group had a significantly higher HBeAg seroconversion rate (57.2% versus 5.6%; $P < .05$). And HBV DNA suppression rates at 12 and 24 months were 87.2% and 98.0%, respectively, in the treatment group, compared with 2.8% and 3.6%, respectively, in the control group ($P < .05$). The data of this study has shown the efficacy of postoperative antiviral therapy in suppressing viral replication. Thus, to improve the liver function, antiviral therapy should be initiated in patients with detectable serum HBV DNA level after resection. Further RCTs with larger numbers of patients and longer follow-up periods are urgently necessary to clarify whether the efficacy of antiviral therapy on HBV load for HBV-related HCCs' patients who underwent hepatectomy.

*4.2. The Impact of Antiviral Therapy on Perioperative Liver Function for HBV-Related HCC.* Recent reports found that an effective preoperative anti-HBV therapy could contribute to improve liver function. Thia reported the incidence of postoperative HBV and exacerbation of chronic hepatitis B (ECHB) [36], that transient elevation of serum ALT in the first week after resection occurred in 92% of cases and resolved by the second week. The peak serum ALT was 222.0 IU/L and declined by week 2 after resection. The serum activities of AST and ALT were significantly higher in the patients with a high viral load than in those with a low viral load ($P = .0005$ and $P = .0089$, resp.) [37]. Notably, the AST and ALT activities were significantly higher in the patients with a high viral load, and the percentage of patients with moderately or severe active hepatitis was significantly higher in the patients with a high viral load. A previous study indicated that reoperative prealbumin was $223.7 \pm 56.0$ mg/L versus $226.1 \pm 60.5$ mg/L ($P = .859$), albumin/ globulin ratio was $1.4 \pm 0.2$ versus $1.3 \pm 0.2$ ($P = .129$), and $\gamma$-globulin on protein electrophoresis was $20.0 \pm 4.3$ versus $20.6 \pm 4.4$, in the treatment and the control groups respectively ($P = .540$) [35]. There were no significant differences between the two groups, and at the sixth postoperative month of followup, prealbumin was $201.3 \pm 52.4$ mg/L versus $224.3 \pm 85.8$ mg/L ($P = .148$), and albumin/globulin ratio was $1.3 \pm 0.3$ versus $1.2 \pm 0.3$ ($P = .114$). By analysis, there was no correlation between prealbumin and logarithmic difference in HBV DNA level ($P = .688$), and between albumin/globulin ratio and logarithmic difference in HBV DNA level ($P = .130$). However, the treatment group had a significantly greater increase in residual liver volume per unit surface area following hepatectomy ($78.0 \pm 40.1$ $cm^3/m^2$ versus $35.8 \pm 56.0$ $cm^3/m^2$) at the sixth postoperative month. these results indicated that remnant liver functions in the nucleotide analog group were maintained better than those

in the control group. Remnant liver function is an important factor in selecting further treatment for HCC recurrence and is a prognostic factor for the survival rate. Therefore, patients treated by nucleotide analogs have more aggressive therapies for HCC recurrence, resulting in improving the cumulative survival rate.

*4.3. The Impact of Antiviral Therapy on Postoperative Recurrences for HBV-Related HCC.* As we all known, prolonged suppression of HBV replication with nucleoside or nucleotide analogs may reduce the risk of HBV-related HCC development [38]. It aslo may prevent postsugery HCC recurrence. In a cohort study design, Kim et al. [31] have reported patients on antiviral therapy at the time of liver resection. 157 patients were included, among them 89 were non-viremic and 68 were viremic. the 5-year cumulative recurrence rate was 73% for viremic group compared to the non-viremic group by 55% ($P = .043$). However, in the previous study [35] we found there was no significant difference in recurrence rate after surgery in the two groups (76.7% versus 91.7%; $P = .077$), after a median follow-up of 12 months. The median time to recurrence in the treatment and control groups were 7.0 and 6.0 months, respectively ($P = .072$). Indeed, Kuzuya et al. [39] study has also reported that the cumulative recurrence rates of HCC after initial and curative treatment for HCC did not decrease by the administration of nucleotide analog. Consequently, to confirm the efficacy of nucleotide analogs against the recurrence of HCC, further studies with a larger number of patients and longer follow-up period are needed to address this question.

*4.4. The Antiviral Therapy on the Overall Survial for HBV-Related HCC.* Up till now, there have been very few studies that have documented whether antiviral therapy is beneficial to the survival after treatment for HCC. In theory, modulation in liver function may not only affect survival directly but also indirectly by influencing the patient's tolerance to various treatments for recurrence. Miao reported in a meta-analysis study that [40], postoperative antiviral therapy as a whole has been shown to reduce HCC recurrence at year 1, 2, 3, and 5. Several small sample size of RCT and NRCTs have evaluated the efficacy and outcome of antiviral therapies in patients with HBV-related HCC after curative treatment, however, clinically meaningful differences are less. In the Kuzuya et al. study [39], no significant differences regarding the recurrence rates of HCC was found ($P = .622$). the cumulative HCC recurrence rates at 1, 2, and 3 years in the lamivudine group were 13.5%, 35.1%, and 35.1%, respectively, while those in the control group were 13.4%, 39.2% and 53.2%, respectively. All 16 patients in the lamivudine group still alive during their follow-up period, but six of 33 patients died in the control group. There were no significant differences with regard to survival rate between the two groups; however, the survival rates in the lamivudine group tended to be higher than those in the control group ($P = .063$).

In the RCT of Liaw et al. study, continuous treatment with lamivudine has been shown to delay clinical progression in patients with CHB and advanced fibrosis or cirrhosis by significantly reducing the incidence of hepatic decompensation and the risk of HCC [38]. HCC occurred in 3.9% in the lamivudine group and 7.4% in the placebo group (hazard ratio, 0.49; $P = .047$). The previous study also found that after a median follow-up of 12 months, 41 patients of the treatment group and 36 patients of the control group had died [35]. The 1- and 2-year overall survival rates were 41.9% and 7.0%, respectively, for the treatment group, and 33.3% and 0%, respectively, for the control group. ($P = .0094$) [35]. The 1- and 2-year disease-free survival rates were 23.3% and 2.3%, respectively, for the treatment group, and 8.3% and 0%, respectively, for the control group. ($P = .072$). The date did not show a significant effect of postoperative antiviral therapy on HCC recurrence, but it showed a significant benefit in overall survival. Although nucleoside analogs did not reduce short-term recurrence rate or progression of disease, they promoted postoperative viral clearance, increased residual liver volume, and enhanced hepatocyte regeneration in HCC patients associated with active hepatitis B, which significantly enhanced the tolerance to subsequent therapy. As a result, the overall survival was improved for those patients with postoperative antiviral therapy. We putative that if compared with other adjuvant therapies, antiviral therapy may serve as a cost-effective and favorable alternative to improve the prognosis of patients, and long-term prospective studies of antiviral therapy in chronic HBV carriers may aslo be required.

## 5. Character of Antiviral Drugs

*5.1. Interferon.* The first treatment that had some success against CHB was interferon alpha (IFN-$\alpha$). IFN-$\alpha$ has both antiviral and antiproliferative properties. Meta-analyses have shown that IFN-a has a beneficial effect on HBeAg loss and sustained reduction in serum HBV DNA levels [41, 42]. The antiproliferative effects of IFN include retardation of G1/S phase transition and inhibition of cell proliferation without apoptosis [43], and also induction of antiproliferative signaling through the JAK/STAT pathway [44]. However, it is not clear whether it has potential effect on HCC prevention. Only one RCT and several case-control or cohort studies have shown its benefits for preventing HCC, particularly in cirrhotic patients who responded to therapy. In patients with decompensated cirrhosis, standard or pegylated INF-$\alpha$ is usually contraindicated or causes profound intolerance, but it is still one of the choices for the operative candidates.

*5.2. Nucleos(t)ide Analogs.* During the last decade, the rise of oral nucleos(t)ide analogs has changed the treatment landscape for CHB. Long-term lamivudine treatment can prevent complications of HBV-related liver disease as long as viral suppresion is maintained [38]. It is considered to slow the progression of severe liver disease to cirrhosis as well as to HCC [38, 45]. However, the overwhelming majority of patients relapsed after treatment cessation. It could form (as will other nucleosides with even lower rates of resistance) the backbone of maintenance combination therapies. The major disadvantage of lamivudine treatment is the high rate

of resistance observed in both HBeAg and anti-HBe-positive HCC patients. The resistance usually emerges after the first 6 months with cumulative rates of 15–25% by 12 months and 60–65% by 4 years of therapy [46].

Adefovir dipivoxil and entecavir have been shown to be safe and effective for the treatment of patients with CHB that does not respond to lamivudine [47, 48]. It is effective against both wild-type and lamivudine-resistant HBV strains [46]. In the pivotal anti-HBe positive adefovir study [49], 185 patients were randomised to placebo or adefovir 10 mg daily for 48 weeks. At 48 weeks, the adefovir-treated group had significant improvement when compared with placebo improvement in liver histology (64% versus 33%), reductions in HBV DNA (3.91 versus 1.35 log copies/mL), normalisation of ALT (72% versus 29%), an undetectable HBV DNA (<400 copies/mL), and HBeAg seroconversion (12% versus 6%). Data from a recent study of 125 patients undergoing long-term adefovir treatment indicated that 0% of patients had resistance in year 1, 11% in year 3, and 28% in year 5. Interestingly, all patients who developed adefovir resistance were not receiving lamivudine and adefovir combination therapy, but adefovir monotherapy [50]. Moreover, based on in vitro studies and limited clinical data, lamivudine has been shown to be effective in patients with adefovir-resistant HBV [51, 52]. For these reasons above, we deduce that lamivudine and adefovir combination therapy may be better than adefovir monotherapy. Because of the suboptimal profile of both lamivudine and adefovir monotherapy for patients with HBV-decompensated cirrhosis, a first-line combined indefinite use of lamivudine and adefovir is recommended in several guidelines, despite the lack of data on efficacy and safety for such a strategy [53]. Tenofovir is the latest antiviral medicine and has similar safety profile as adefovir in the phase III trials.

## 6. Future Perspectives

The goal of antiviral therapy for CHB is to prevent the development of cirrhosis and HCC. To date, several guidelines for the treatment of CHB patients are presented. However, there are no uniform guidelines globally for the usage of antivirals in the treatment CHB, let alone antivirals on HBV-related HCC at present. Currently the definite indications for the treatment of CHB are serum HBV DNA levels greater than $10^5$ copies/mL and ALT levels more than $2 \times$ ULN [54, 55]. According to the American Association for the Study of Liver Diseases and Asian Pacific Association for the Study of the Liver guidelines, biopsy-confirmed liver disease is a key requisite for initiating treatment in patients older than 40 years of age with serum ALT levels between 1 and $2 \times$ ULN. If cirrhosis is present, an HBV DNA level greater than $10^5$ copies/mL is the sole criterion for treatment. Treatment end points, including reduction of HBV DNA levels to less than $10^5$ copies/mL, ALT normalization, HBeAg loss, HBsAg loss, and improvement in liver histology, are used to determine treatment success. These guidelines may apply to patients who acquire the HBV infection during adolescence or adulthood but are less suitable for most HBV carriers, who are infected in early life. In light of the reports, the liver-related mortality and complications were greater in patients with ALT levels between 0.5 and $1 \times$ ULN than in those with ALT levels less than $0.5 \times$ ULN [56, 57], and the revision of the ULN for patients with CHB is recommended by some guidelines [11, 55, 58]. Therefore, HBeAg seroconversion may not be an adequate end point for these patients; the ideal treatment end points are permanent suppression of HBV DNA to levels undetectable by polymerase chain reaction and reduction of ALT levels to less than $0.5 \times$ ULN. In the current treatment guidelines, antiviral treatments should be started among cirrhotic patients despite lower HBV DNA levels [59]. Treatment is based on HBV replication status and stage of liver disease, modulated by the age of the patient, HBeAg status, and patient preference.

However, results of experimental studies suggest that early treatment intervention is necessary to prevent liver cell damage and decrease viral genome integration. Another important finding from recent studies is that viral genome integration persists despite antiviral induced viral suppression and cccDNA clearance. This was shown to be associated with the expansion of cellular clones not expressing viral antigens. Therefore, screening of HCC remains mandatory even in patients with sustained viral suppression induced by antiviral therapy to detect HCC for which curative treatments can be proposed. Late recurrence mostly corresponds to de novo carcinogenesis associated with HBV viremia as well as the "field effect" in HBV-related HCC. This may support prioritized use of anti-HBV treatment as adjuvant therapy after the resection or ablation of HCC for the patients with a high HBV DNA level to prevent late recurrence, given that the incidence rate of recurrence is higher than that of the initial HCC development [60]. Furthermore, investigation of the molecular mechanism of the direct carcinogenic effect of HBV may help clarify additional therapeutic targets in terms of HCC prevention. Currently, available evidence, mostly obtained from PCR-based assays with limited scale, has identified a handful of the genomic integrations potentially affecting the function of genes, for example, cyclin A and telomerase reverse transcriptase, in a sporadic manner [61, 62].

Recently, emerging genomics technology like high-throughput sequencing [63, 64] may provide a more comprehensive view of the critical recurrent oncogenic integration events. Combination of the new sequencing assay with chromatin immunoprecipitation (ChIP-Seq) [65], may help to identify oncogenic transactivation by HBV proteins to obtain complementary information of the direct carcinogenic effect caused by HBV. Although an antineoplasm effect is not expected by nucleoside analogues, the incidence rate of HCC would decrease due to a cessation of hepatitis. Future RCTs with larger sample size, longer followup, and regular HBV DNA monitoring will be needed to substantiate the beneficial effects of antiviral therapies which where performed in the light of the recently updated HBV treatment guidelines, on the prognosis of HCC and HCC recurrence. Of course, they are focusing on the need to lower the threshold of commencing antiviral treatment based on HBV-related HCC.

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*Review Article*

# Non-Invasive Radiofrequency-Induced Targeted Hyperthermia for the Treatment of Hepatocellular Carcinoma

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Targeted biological therapies for hepatocellular cancer have shown minimal improvements in median survival. Multiple pathways to oncogenesis leading to rapid development of resistance to such therapies is a concern. Non-invasive radiofrequency field-induced targeted hyperthermia using nanoparticles is a radical departure from conventional modalities. In this paper we underscore the need for innovative strategies for the treatment of hepatocellular cancer, describe the central paradigm of targeted hyperthermia using non-invasive electromagnetic energy, review the process of characterization and modification of nanoparticles for the task, and summarize data from cell-based and animal-based models of hepatocellular cancer treated with non-invasive RF energy. Finally, future strategies and challenges in bringing this modality from bench to clinic are discussed.

## 1. Introduction

Hepatocellular cancer (HCC) presents a global challenge. It is the sixth most common cancer and the third most common cause of cancer-related deaths worldwide [1]. The incidence of HCC is on the rise. It is estimated that approximately 1 million new cases of HCC are diagnosed each year [2]. Chronic infection with hepatitis B and hepatitis C virus coupled with other risk factors such as diabetes, obesity, smoking, and heavy alcohol consumption contribute to this rising incidence [3]. Growing burden of disease presents a significant problem, as majority of patients diagnosed with HCC cannot be treated with curative intent [4]. This is because of delay in diagnosis and concomitant hepatic dysfunction. Worldwide, the median survival of patients with advanced HCC who remain untreated is less than 4 months [5].

Surgical resection and transplantation yield 5-year survivals ranging from 35% to over 70% [4, 6–10]. These therapies are suited for few candidates that have limited local disease and fit into a strict clinical criteria. For other patients with HCC, treatment options include intratumoral injection of absolute ethanol or acetic acid, invasive thermal destruction using microwave or radiofrequency needles and transarterial chemoembolization (TACE) using drug-eluting beads. Considered together, local-regional therapies have lead to a modest increase in median survival [11].

While targeted biological therapies such as monoclonal antibodies have been successful in treating other cancers, HCC remains a challenge. Recently Sorafenib, a multikinase inhibitor, has shown an improvement in median survival of 2.3–2.8 months compared to placebo in clinical trials [12, 13]. Futility of biological therapies is because of multiple pathways to oncogenesis in HCC and rapid development of resistance to these agents. Non-invasive electromagnetic field-induced targeted hyperthermia for the treatment of HCC is a radical departure from traditional therapies and holds immense potential.

Electromagnetic energy in the form of near-infrared (NIR) photothermal energy, inductively coupled magnetic field or radiofrequency field, has been employed to deliver non-invasive targeted hyperthermia to malignant cells [14–17]. The rationale for such therapies is based on the observation that metal nanoparticles targeted to tumor cells generate heat when exposed to electromagnetic energy

causing them to undergo heat-stress-triggered apoptosis while sparing normal tissues. The use of non-invasive NIR energy to produce photothermal toxicity is limited by its low tissue penetrance and hence inability to treat deeper lesions as in HCC [18]. Use of inductively coupled magnetic fields to heat charged magnetic dextran-coated metal nanoparticles such as iron oxide ($Fe_3O_4$) has also been demonstrated. However, thermal enhancement is limited by the magnetic field strength applicable to abdominal tumors (<4.5 kA/m, 100 kHz) and by difficulty in targeting magnetic nanoparticles to malignant cells [16, 17]. In contrast, non-invasive radiofrequency field-induced heating of metal nanoparticles offers several advantages over others in the treatment of HCC, as detailed later. The purpose of this paper is to summarize current strategies for delivering non-invasive radiofrequency field-mediated hyperthermia to malignant cells and its application to HCC.

## 2. Radio Waves in the Treatment of Cancer

Radio waves are low-frequency electromagnetic waves that have low tissue-specific absorption rate (SAR) and, therefore, excellent whole body tissue penetration. Radio waves are considered safe with several studies reporting no harmful effects in humans exposed to RF field for several hours [19, 20]. Because of their excellent safety profile, radio waves have been widely utilized in medicine including communication devices, diagnostic imaging, and ablation therapies.

Radiofrequency ablation (RFA) has particularly been effective for local regional control of HCC in patients not amenable to surgical resection or awaiting transplantation. This technique requires high RF energy transfer from an electrode placed within the tumor percutaneously or intraoperatively under image guidance. Energy dissipated through the RF electrode causes coagulative necrosis and thermal destruction of the tumor [21]. In contrast to RFA, nanoparticle targeted hyperthermia is a non-invasive approach to deliver hyperthermia at a cellular level without harming surrounding normal tissue (Figure 1).

## 3. Kanzius RF Generator

Non-invasive radiofrequency-based hyperthermia, unlike radiofrequency ablation, requires an external radiofrequency field generator (Kanzius RF generator) [14, 22, 23]. This is a variable power (0–2 KW) 13.56 MHz RF field generator (Therm Med LLC, Erie, Pennsylvania). The RF generator is connected to a high Q coupling system with a Tx head (focused end-fired antenna circuit) and reciprocal Rx head (as a return for the generator) mounted on a swivel bracket allowing the RF field to be oriented in either a horizontal or vertical direction (Figure 2). The distance between the two heads is adjustable. The coaxial end-fire circuit in the Tx head produces an electronic focused RF field up to 15 cm in diameter. The electromagnetic field strength between the Tx and Rx head is established and calibrated in a Faraday-shielded room to exclude any interference from external RF sources. The field is measured using a Hewlett Packard Spectrum Analyzer (model 8566B, Agilent, Santa Clara, CA), an isotropic field monitor, and a probe (models FM2004 and FP2000, Amplifier Research Inc., Souderton, PA). Utilizing an output power of 600 W, maximum electric field strength (Ep) of 12.4 kV/m is measured at a distance 2.5 cm from the Tx head.

## 4. Radiofrequency-Induced Heating of Nanoparticles

We have demonstrated heating of several nanoparticles in the RF field including gold nanoparticles (AuNP), gold silica nanoshells, single-walled carbon nanotubes (SWNT), and water-soluble derivatives of C60 fullerenes [14, 22–27]. A treatment strategy based on molecular targeting of gold and carbon nanoparticles has several advantages: they are simple and inexpensive to synthesize; they are easily characterized due to their signature optical absorptions; their surface chemistry readily permits manipulation of charge and shape and attaching cancer cell-targeting molecules, including antibodies, peptides, or pharmacologic agents, is easily achieved. A detailed discussion on the methods utilized to characterize and synthesize such nanoparticles is beyond the scope of this paper and is described elsewhere.

Heating of AuNPs in RF field is concentration and size dependent as shown in Figure 3. AuNPs with small diameters (5 nm) heat better than larger particles. In our previous papers we have explained the increased heating of smaller particles on the basis of increased ohmic dissipation with increased resistivity of smaller particles [28]. The exact physical basis of heat generation by nanoparticles is not entirely clear and is an area of active investigation.

Similar to AuNPs, single-walled carbon nanotubes (SWNT) functionalized with a biocompatible nonionic polymer (Kentera) demonstrate a linear rise in temperature after RF activation [26]. The heating rate also increases linearly with RF generator output power. However, the heating rate of SWNT suspensions increases nonlinearly with increasing concentrations (Figure 4).

## 5. Targeting Strategies

In order to deliver targeted hyperthermia to cancer cells it is crucial that the nanoparticles are modified to specifically enhance uptake by tumor cells. In our studies, we have conjugated monoclonal antibodies (raised against tumor-specific targets) to nanoparticles. Two approaches are described here using chimeric anti-epidermal growth factor receptor (EGFR) antibody (or C225) conjugation to AuNPs as a prototypical example.

*Noncovalent Conjugation.* Colloidal suspensions of spherical AuNPs are stabilized during synthesis using citrate as a stabilizing agent to prevent aggregation. For the purposes of conjugation the AuNPs are concentrated to remove citrate. These are then resuspended in a buffer solution whose pH matches the isoelectric point of the monoclonal antibody (pH = 8.5 for C225). The monoclonal antibody is then slowly added to AuNP colloidal suspension in a (w/w) ratio of 20 : 50 and gently mixed. Surface modification is confirmed

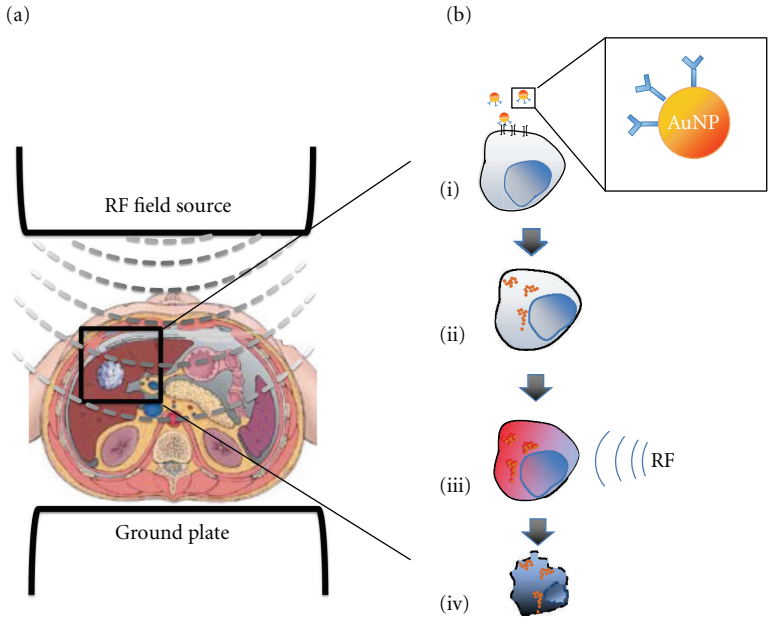



Figure 1: Principle of the non-invasive RF based treatment of HCC. A. RF field source is used to generate a uniform low frequency electromagnetic field that penetrates tissues and reaches the tumor. B. Nanoparticles that can be thermally activated are conjugated to monoclonal antibodies against known targets expressed on HCC (i), internalized specifically by cancer cells after systemic administration (ii), and upon RF activation release heat (iii) causing targeted cancer cell death.

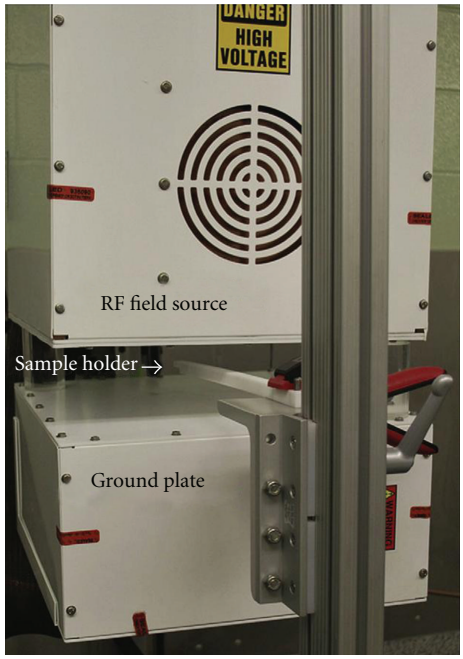



Figure 2: Kanzius RF generator: RF field source transmission antenna (Tx head) and ground plate (Reciprocal Rx head) are separated by 10 cm air-gap. Samples are placed 2.5 cm from the Tx head on the Teflon holder.

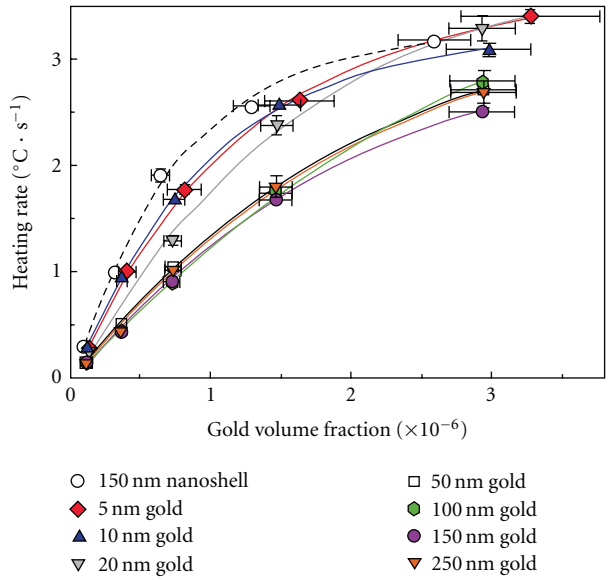



Figure 3: Size-dependent heating of gold nanoparticles in non-invasive RF field. 150 nm gold nanoshells (a shell thickness of 10–15 nm) demonstrate heating rates similar to 5 nm gold nanoparticles. *Reproduced with permission from Nano Research, vol. 2, no. 5, pp. 400-405, 2009.*

by <10 nm red shift in UV-Vis peak absorption spectra of modified AuNPs. While easy to perform, NonCovalent conjugation is nondirectional. Moreover, other proteins in biological samples can replace surface-bound antibodies.

*Thiol-Based Covalent Linkage.* Near covalent bonds can be formed on the surface of AuNP when monoclonal antibodies are attached to linker with a thiol functional group. Thiol-based conjugation is stronger and more stable than NonCovalent electrostatic interaction and hence preferred. Directional conjugation also presents Fab portion of the

antibody to the tumor antigens maximizing receptor-ligand interaction. We have employed methods described by Kumar et al. with slight modifications [29].

## 6. *In Vitro* Thermal Cytotoxicity of RF-Induced Hyperthermia

We have demonstrated the effect of RF treatment on various heptaocellular cancer cell lines using different nanoparticles. Hep3B and HepG2 cells treated with kentera modified SWNT were exposed to an 800 W RF field [26]. Significant thermal cytotoxicity was demonstrated with 2 minutes of RF exposure in a concentration-dependent manner. Higher concentrations (500 mg/L) produced 100% thermal cytotoxicity in comparison to untreated controls (11%) and cells treated with kentera solution only (35%), $P$ value < .01.

In separate experiments, Hep3B cells were exposed to naked 5 nm AuNPs at 1, 10, or 67 $\mu$M for 24 hours [27]. The gold containingmedium was aspirated and replaced by fresh medium. Cells were then exposed to RF treatment for 1, 2, and 5 minutes. The resulting thermal cytotoxicity is summarized in Table 1. This RF-induced gold nanoparticle-based thermal cytotoxicity was concentration dependent (data not shown).

These experiments indicate that non-invasive RF field-based hyperthermia using untargeted nanoparticles is highly effective in treating HCC cell lines. In separate experiments, a more targeted approach was implemented. Panc-1 cells treated with C225-conjugated AuNP and exposed to RF field in RF showed higher thermal cytotoxicity than cells treated with naked gold nanoparticles and exposed to RF field (data in press). Using a similar approach for HCC presents challenges. Unlike pancreatic cancer, expression of EGFR on HCC cell lines is moderate at best. A systematic investigation to identify better and more specific molecular targets on HCC is currently underway.

## 7. Tumor Response to RF-Induced Hyperthermia in Animal Models

In order to demonstrate that SWNT localized to VX2 tumor can be remotely activated by RF field to produce thermal cytotoxicity, adult New Zealand white rabbits bearing orthotopic VX2 tumors ranging in size from 1.0 cm to 1.3 cm in greatest dimension underwent a direct intratumoral injection of water-soluble SWNTs or control solutions [26]. Rabbits were treated with or without RF for 2 minutes. Two days after RF treatment, all animals were sacrificed. Histopathology sections from tumors injected with SWNTs revealed complete thermal necrosis of the tumor tissue with a surrounding 2 mm to 5 mm zone of thermal injury to the liver. There was no evidence of nonspecific injury to other organs and tissues. Tumors that had been injected with SWNTs but not treated with RF also were completely viable, as were tumors that had not been injected with SWNTs or control solutions and had been treated with RF alone (data not shown).

As a next step and to develop an entirely non-invasive treatment modality, our goal was to inject antibody-conjugated nanoparticles systemically and allow them to concentrate specifically in the tumor tissue. To investigate that further and as a proof of principle, we used an ectopic murine model of EGFR expressing Panc-1 tumors. This is because of ease of availability and extensive characterization of chimeric C225. C225 was directionally conjugated to 10nm AuNPs. The conjugates when systemically injected concentrated specifically to the tumor site unlike nontargeted AuNPs. Weekly cycles of injection of nanoconjugates followed by RF treatment for 10 minutes halted the growth of tumors during 7 weeks of treatment compared to RF only, nanoconjugates only, and untreated controls ($P < .004$), and in some cases produced a complete response (data in press). In these *in vivo* experiments, no untoward or unexplained side effects were noted. We expect that as HCC-specific tumor targets are identified, a similar approach can be employed.

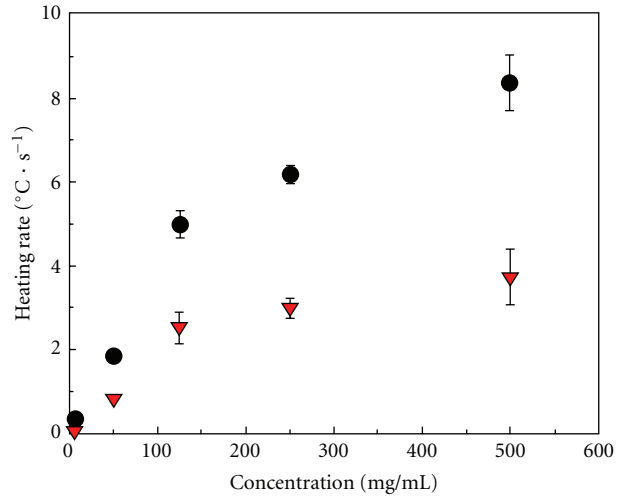


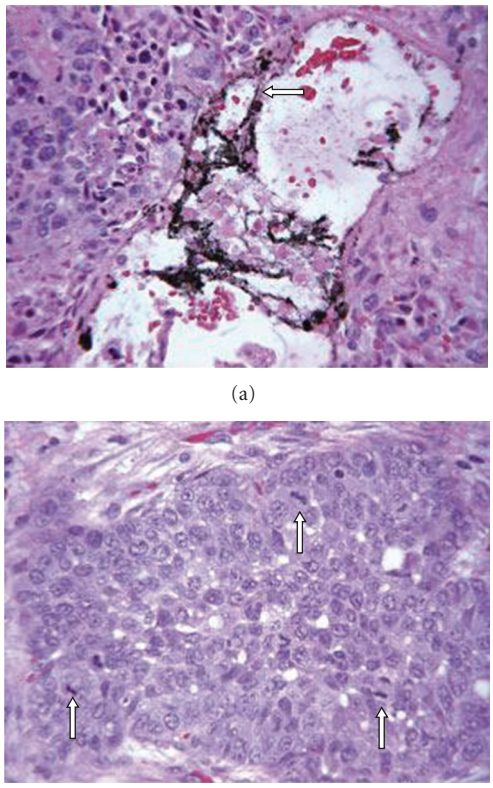

Figure 4: Concentration-dependent heating rate of Kentera SWNT suspensions under 600 W of RF generator output power. Suspensions exhibited nonlinear heating rates with increasing SWNT concentration. Shown are the averages of the heating rates for Kentera SWNTs (dots) and the calculated SWNT heating contribution (triangles). *Reproduced with permission from Cancer, vol. 110, no. 12, pp. 2654–2665, 2007.*

Table 1: Non-invasive RF field treatment of Hep3B cells: cell viability was assessed by Propidium Iodide-Fluorescent Activated Cell Sorting (PI-FACS) 18 hours after RF exposure.

| RF exposure (min) | Controls Cell death (%) | Pretreated with AuNP (67 $\mu$M) Cell death (%) | $P$ value |
|---|---|---|---|
| 5 | 75.0 ± 12.2 | 99.8 ± 3.1 | .4 |
| 2 | 21 ± 14.4 | 98.5 ± 0.5 | .001 |
| 1 | 17.6 ± 8.4 | 99.0 ± 0.2 | .001 |

## 8. Future Direction and Challenges

In this brief paper, we have summarized the grand opportunities and challenges, non-invasive RF-based treatment of



(a)

(b)

Figure 5: Photomicrographs of hepatic VX2 tumors from rabbits that received (a) or did not receive (b) intratumoral injection of Kentera single-walled carbon nanotubes (SWNTs) followed by 2 minutes of RF field treatment. SWNTs (arrow) can be identified surrounded by necrotic tumor. (Routine H & E stain, magnification, x400). *Reproduced with permission from Cancer, vol. 110, no. 12, pp. 2654–2665, 2007*

HCC presents. There areseveral advantages of using such an approach. Radio waves have well-documented safety in humans, mainly because of their minimal SAR. At the same time they have excellent whole body penetration reaching tumors in every possible location. Nanoparticles used to harness RF electromagnetic energy within the tumor are inexpensive and simple to synthesize with high reproducibility. They can be easily characterized using well-established methods. They are sufficiently small to navigate through the most compromised tumor vasculature. In addition to this, AuNPs are biocompatible, have not been associated with any acute or chronic toxicity in preclinical studies, and are already used clinically to treat severe rheumatoid arthritis. These features make it an attractive, safe, and effective treatment modality for HCC patients including those with hepatic dysfunction.

Identification of HCC-specific tumor targets is an area of active research inquiry. Attempts to characterize immunologic differences between human HCC cells and normal hepagtocytes led to the development of AF-20 and FB-50 monoclonal antibodies that recognize different domains on overexpressed aspartyl $\beta$-hydroxylase. However, these monoclonal antibodies are not commercially available, and their receptor-ligand interaction remains to be characterized. Similarly, another challenge is *in vivo* thermal dosimetry. The need to measure real-time temperature for treatments that employ hyperthermia has led to the development of magnetic resonance thermography. However it seems plausible that the interaction of the two magnetic fields will not allow utilization of magnetic resonance thermography for measurement of RF-based hyperthermia. Other techniques that allow real-time thermography need to be developed. Finally, we anticipate that long-term RF-induced hyperthermia-based treatment for HCC has the potential to induce thermotolerance as well as thermoresistance in some subsets of patients. Such patients may benefit from enhancing effects of chemotherapeutic agents using RF-based hyperthermia, which should also be investigated in the future.

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*Case Report*

# Single Port Laparoscopic Liver Resection for Hepatocellular Carcinoma: A Preliminary Report

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Single port laparoscopic surgery is an emerging technique, now commonly used in cholecystectomy. The experience of using this technique in liver resection for hepatocellular carcinoma is described in a series of 3 cases with single port laparoscopic liver resection performed during 2010. All patients were male aged 61 to 70 years, with several comorbidities. There were no complications in this early series. The length of hospital stay was 3–5 days. The blood loss was 200–450 mL, with operating time between 142 and 171 minutes. We conclude that this technique is feasible and safe to perform in experienced centers.

## 1. Introduction

Laparoscopic liver resection has been increasingly performed over the last two decades. The technique has improved since the first time it was published [1] in 1992. Each year, there has been considerable number of cases undergoing this technique. Consecutive reports have shown that liver resection can be done efficiently and safely using laparoscopic approach. Several potential advantages include less abdominal pain, less hospital stay, and some reports [2, 3] even suggest less operating time with less morbidity.

Single port laparoscopic surgery was reported as early as 1992 [4]. First described as an effort to reduce abdominal trauma in appendix removal, this approach has extended its indications to a variety of cases. One potential problem arising from this approach is the loss of triangular movement traditionally achieved with conventional laparoscopic surgery. In 2010, there were several publications [5–9] regarding single port laparoscopic liver resections. However these reports have limited coverage of this technique as a treatment for hepatocellular carcinoma (HCC). This study aims to report the feasibility and safety of single port laparoscopic liver resection technique for treatment of hepatocellular cancer in a single institution.

## 2. Methods

During 2010, all single port laparoscopic liver resection cases with proven histology findings of HCC were included in this paper. Demographic data, length of operation, operation technique, resection margin, blood loss, early post-op complications, and length of stay were evaluated for these patients. Postoperative followup was done until the end of 2010.

## 3. Surgical Technique

Patients were put under general anaesthesia in the French position. Incision was made according to the need to place the port. For GelPort (Applied Medical, Calif, USA), a 5 cm upper umbilical midline incision was made. For the SILS port (Covidien, Dublin, Ireland), a midline incision through the umbilicus measuring 2.5 cm was made. Port was inserted using open technique, and pneumoperitoneum of 12 mmHg was created using $CO_2$. A 30° laparoscopic camera was used for visual inspection of the abdominal cavity. A bendable and roticulating instrument (AutoSuture Roticulator Endo Grasp from Covidien, Dublin, Ireland) was used to manipulate the liver, together with the normal laparoscopic instruments. Liver was mobilized from falciform ligament and left

Table 1: Patient comorbidities.

| Case | Age | Gender | Comorbidities |
|---|---|---|---|
| 1 | 61 | Male | Ischemic heart disease with previous coronary artery bypass |
| | | | Hyperlipidaemia |
| | | | Type II diabetes mellitus |
| 2 | 69 | Male | Type II diabetes mellitus |
| | | | Hepatitis B carrier |
| | | | Ischemic heart disease |
| | | | Asthma |
| | | | Old cerebrovascular accident |
| | | | Hypertension |
| 3 | 70 | Male | Type II diabetes mellitus |
| | | | Hypertension |
| | | | Ischemic heart disease |
| | | | Beta thalassaemia trait |
| | | | Fatty liver |
| | | | Mild esophagitis |
| | | | Thrombocytopenia |
| | | | Renal calculi |

triangular ligament using harmonic scalpel and diathermy. Intraoperative ultrasound with laparoscopic ultrasound probe was done to assess the tumor, and margin of resection was marked using diathermy. Liver parenchyma was transected using Harmonic scalpel (Ethicon Endo-Surgery, Ohio, USA) and/or LigaSure (Covidien, Dublin, Ireland). Larger vascular structure such as the pedicle of liver segments and hepatic veins were divided using laparoscopic vascular stapler. Tissue glue was applied to the cut surface of liver. The specimen was retrieved using a plastic bag. Hemostasis was checked after desufflation of the abdomen. No drain was inserted at the end of the operation.

## 4. Results

In 2010, we have performed 3 cases of single port laparoscopic liver resection for HCC in our institution. All patients were male and had several comorbidities (Table 1).

Case 1 was known to have non viral hepatitis cirrhosis likely secondary to non alcoholic steatohepatitis for 3 years, with a family history of liver cancer. He was found to have a nodule in segment 2 on the followup of the CT scan. Previously before the operation, patient was independent. He was Child-Pugh class A, and the Model (MELD for End-stage Liver Disease) score before operation was 8. Platelet count was normal.

Case 2 has been diagnosed with HCC previously and underwent laparoscopic liver resection twice for segment 5 and right posterior resection, respectively. Previous resections were 2 years and 6 months before the single port resection. Patient was ambulating independently, with MELD score of 6 and Child-Pugh class A status. Platelets count before operation was normal.

Case 3 presented with lesion in segment 2 liver, found during investigation for thrombocytopenia. Patient was also known to have fatty liver. MELD score before operation was 6. The total platelet count was in low borderline of $163 \times 10^9$ /L. Patient was ambulating independently when admitted.

None of the operations were converted to open surgery. No additional port insertions were needed to complete the three operations. All patients stayed 1 night at the surgical high dependency unit and went to general ward the next day. Subsequent followup until December 2010 (7 months for case 1, 7 months for case 2, and 4 months for the last case) showed no recurrence of HCC. Detailed data on resection type, blood loss, operation duration, length of stay, complications, and resection margin can be seen in Table 2. There were no complications in this early series. The length of stay was 3–5 days. The blood loss was less than 500 mL in all cases. Operative time was less than 3 hours.

Although there is only one established cirrhosis for the nonneoplastic histopathology results for the resected specimen, case 2 shows occasional portal-portal fibrosis, and both cases without cirrhosis show portal chronic inflammation and macrovesicular steatosis.

## 5. Discussion

Laparoscopic liver surgery was firstly described by Gagner et al. [1] in 1992. Since that time, a number of studies [2, 3] regarding the feasibility and safety of the procedure have been published. During 2010, there have been several publications of the use of single port surgery for liver resection. The first report of this technique was by Aldrighetti et al. [5] in June 2010 who describes a left lateral sectionectomy for a single colorectal metastasis. The authors concluded that the approach is a feasible technique, but other benefits except cosmetic were questionable.

After the first report, several other publications reporting a single case or multiple case reports have been published. However, most of these cases were done for benign lesions or liver metastases. Only 1 case of single port liver resection from 5-case series reported by Gaujoux et al. [6] was done for hepatocellular carcinoma. Most reports for the single port laparoscopic liver resection were done for either benign lesions [6, 7] or metastatic lesions [5, 6, 8]

Single port laparoscopic liver resection is a new and emerging technique. With the development of special instruments to facilitate this technique, liver resection has become feasible and safe, but surgeons have been slow in applying this technique for HCC due to the presence of cirrhosis and concern regarding the oncological safety of the technique. The difficulty encountered when using single port laparoscopy is the loss of instrument triangulation, something that is crucial in a conventional laparoscopy. However, this setback can be overcome using new instruments with

Table 2: Operative parameters.

| Case | Resection Type | Tumor size | Cirrhosis | Blood loss | Length of operation (min) | Length of stay | Complications | Resection margin |
|---|---|---|---|---|---|---|---|---|
| 1 | Left lateral sectionectomy | 3.5 cm | + | 450 | 171 | 4 days | Nil | 2.5 cm |
| 2 | Segment 3 liver resection | 2 cm | − | 200 | 142 | 3 days | Nil | 0.4 cm |
| 3 | Left lateral sectionectomy | 4.5 cm | − | 300 | 159 | 5 days | Nil | 0.7 cm |

bending and angulating capability. Single port laparoscopy also requires the surgeon to do some cross-handling of the instruments that can facilitate the triangulation inside the abdominal cavity.

Starting in 2008, single port laparoscopic cholecystectomy has also been done regularly at our centre. Our centre's initial experience of single incision laparoscopic cholecystectomy [10] showed that there is no significant difference regarding pain and analgesia requirement between this technique and the conventional technique. Although there is still insufficient data to actually validate the clinical benefits of this technique over the conventional technique, the single port laparoscopy cholecystectomy feasibility is already established [11]. Our centre has begun offering the single incision laparoscopy cholecystectomy for patients on regular basis and has already exceeded 100 cases for the last 2 years.

In our centre, laparoscopic liver resections have been performed since 2005. Since then, more than 100 cases of laparoscopic liver resections have been done with good results. Combining this technique with the single port laparoscopic cholecystectomy experience in our centre, the single port liver resection was started in 2010.

Our experience shows that the single port laparoscopic liver resection approach can be done with reasonable operating time. Previous publications [5–7] reported that operative time for single port liver resection ranged from 55 minutes to 145 minutes. These results were comparable to our experience, with time range of 142–171 minutes. In our series, there is a slightly higher blood loss compared to other publications [5–7] (20–80 mL). All our patients were on anticoagulant therapy prior to their surgery, and this possibly explains the higher blood loss in our experience. The other reason for the difference was likely due to the size of the tumor and the underlying cirrhotic liver in one of our 3 patients, resulting in difficulties to achieve hemostasis.

Left segmental/sectional resection of the liver has been the main type of resection for single port laparoscopic liver surgery. Patients with lesions limited to the left side of the liver are appropriate for this technique, as reported in our series. This type of resection is best suited for single port technique because the instruments are already aligned to the liver transection plane and the specimen is small enough to be retrieved through a small incision (less than 5 cm). Of all the published single port liver resection cases [5–9], none were converted to open surgery. The postoperative hospital stay was also shorter. Our experience in this small series has been the same. As for the resection margin for the specimen, the result showed that a considerable free margin can be achieved. This indicates that the technique is not only feasible but also safe to perform in experienced centers.

## 6. Conclusion

This early experience with single-port liver resection for HCC suggests that this operation is safe and feasible in selected cases of HCC in a unit with experience in laparoscopic liver resection and single-port surgery.

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*Review Article*

# Summary of the 2010 AHPBA/SSO/SSAT Consensus Conference on HCC

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Under the auspices of the American Hepato-Pancreato-Biliary Association, an expert consensus conference was convened in January 2010 on the multidisciplinary management of hepatocellular carcinoma. The goals of the conference were to address knowledge gaps in the optimal preparation of patients with HCC for operative therapy, best methods to control HCC while awaiting liver transplantation, and developing a multidisciplinary approach to these patients with implementation of novel systemic therapies.

## 1. Introduction

HCC has emerged as the 5th most common cancer in the world and its incidence is increasing in the Western world [1, 2] In January 2010, the American Hepato-Pancreato-Biliary Association (AHPBA) convened a consensus conference on the multidisciplinary management of hepatocellular cancer (HCC) cosponsored by the Society of Surgical Oncology, the Society for surgery of the Alimentary Tract and the The University of Texas MD Anderson Cancer center [3]. The methods used in the consensus conference have been previously described. Briefly consultation within the three sponsoring organizations identified experts to participate in the conference. Each expert was asked to present on a given area and to outline two or three consensus statements, which were then reviewed by a panel of content experts and the audience. After the symposium, the consensus statements were summarized by the speakers and session cochairs with input from the corresponding session cochairs. The meeting was divided into three sessions (1) pretreatment assessment, (2) surgical treatment, and (3) combined modality therapy [3]. The following paper provides a concise summary of the expert consensus statements resulting from the three sessions.

## 2. Pretreatment Assessment of Hepatocellular Carcinoma

Currently, there are 18 HCC scoring or staging systems used in the world, but based on current knowledge and experience no single staging system is applicable to all patients [4]. Staging systems used should combine extent of liver disease, general health, and tumor markers as features to provide guidance in prognosis and treatment. However, the use of regional staging systems should be discouraged because it precludes comparison between centers. Most staging systems studied perform poorly when used in patients with a wide spectrum of disease, and the discriminatory performance of different staging systems appears to be treatment, region, and stage specific. Given these limitations, the expert consensus was that the Barcelona Clinic liver cancer (BCLC) is appropriate for patients with advanced liver disease who are not candidates for resection and/or transplantation. BCLC also provides a reasonable guide for patients in stages B and C with the caveat that resection may be considered for some of these patients. The AJCC/UICC classification is valid in the West and East for patients undergoing liver resection, and should be coupled with the fibrosis score. Pathological outcome should be reported using the AJCC/UICC system

following resection or liver transplantation. Finally accurate staging varies based on the modalities used, and optimal staging guidelines that may include biomarkers should be established to allow for more precise comparisons between different treatment regimens [4].

*2.1. Pretreatment Imaging.* Imaging is an integral component of pretreatment assessment of HCC and severity of liver disease. Recommendations regarding imaging were that both Dual CT and MRI should be used for pretreatment staging in HCC; however, MRI has the best performance characteristics for the detection of HCC. The use of Dual CT is also limited by repeated radiation exposure due to the frequency and length of follow-up imaging required in the management of patients with HCC and cirrhosis. Ultrasound or contrast-enhanced ultrasound could be useful for HCC screening; however, the data was insufficient to make a recommendation. Both MRI and CT have limited sensitivity and specificity for detection of lesions <1 cm; however, the new liver MR liver-specific agents are promising for HCC detection and characterization of small lesions. Image subtraction and diffusion weighted imaging should be used as markers of treatment efficacy rather than lesion size. Background liver fibrosis and cirrhosis may be also assessed by functional MRI which utilizes hepatocyte-specific contrast medium [4–6].

*2.2. Role of Portal Vein Embolization.* Portal vein embolization (PVE) has emerged as an important technique of increasing FLR (future liver remnant) in patients undergoing major hepatic resections [7–10]. The consensus regarding PVE was that patients with potentially resectable disease should have volumetric analysis of the total liver volume (TLV) and the anticipated FLR. If major hepatic resection is indicated, portal vein embolization may be appropriate when FLR < 20% of TLV in normal liver, <30% of TLV in chemotherapy associated injured liver, and <40% of TLV in patients with cirrhosis. Imaging is indicated 3-4 weeks after PVE and resection is safe when FLR volume reaches the target. Combination transarterial chemoembolization (TACE) with lipiodol and an anticancer agent followed by PVE should be considered for patients with chronic liver disease being considered for major resection due to increased hypertrophy and higher tumor responses compared to PVE alone [4, 11].

*2.3. Defining Criteria for Resectability.* The definition for resectability in HCC broadly includes two main considerations: liver function and tumor characteristics. The MELD score is useful in determining patients who can safely undergo major hepatic resection [12]. Minor resection in Child-Pugh class A patients with portal hypertension, ascites, bilirubin > 2 mg/dL is contraindicated. Resection should be considered in patients without portal hypertension and bilirubin < 1 mg/dL. Utilizing strict tumor size to determine resectability was found to be unwarranted. Multifocal tumors should be considered for resection, whereas multinodular tumors meeting the Milan criteria should be considered for transplantation given the high recurrence rates [4].

## 3. Surgical Treatment of HCC

Surgical management of HCC involves both nonresectional ablative techniques and surgical resection. Nonresectional ablative therapies have emerged as effective treatment options for patients with HCC with radiofrequency ablation (RFA) being the most commonly used technique. Percutaneous RFA has been found to induce significant tumor necrosis in small tumors away from vascular structures. Additionally, long-term survival rates after RFA are comparable to resection or liver transplant, (OLT) in patients with small HCC <2 cm [13, 14]. However this assertion is still to be determined in large randomized trials. Therefore, RFA is not recommended in resectable patients with tumors >4 cm or in HCC close to major vascular structure, but may be considered for small tumors away from vascular structures. Newer ablative therapies such as microwave ablation may be more effective in treating larger tumors and tumors close to vessels. However, current data regarding this microwave ablation and other ablative techniques such as high-intensity focused ultrasound and electropolation is immature and therefore definitive conclusions are not possible [15].

Hepatic resection is the primary treatment for HCC in selected patients with reported 5yr overall survivals of 25%–50% [16]. Selection for resection is based on the extent of the tumor and the severity of liver disease. Multiple tumors and/or portal hypertension in patients with Child-Pugh class A liver dysfunction can undergo resection with acceptable outcomes [17]. Resection with wide margins (1-2 cm) is the treatment of choice for HCC in patients without cirrhosis or for selected patients with cirrhosis without portal hypertension [16, 18]. Minimizing blood loss and performing limited resections is associated with better perioperative outcome, with most centers reporting mortality rates <5% [19]. The efficacy of resection in patients with large tumors and major vascular invasion is unclear, and decisions for surgical therapy in this group of patients must be made on an individual basis [15, 20]. Laparoscopic liver resection has been found to be feasible without compromising oncological outcome in limited clinical reports [21, 22].

Liver transplantation is the optimal treatment for HCC patients meeting the Milan criteria with cirrhosis where the 5 yr overall survival ranges from 60% to 80% with excellent disease-free survival [23]. However, given the limitations in available organs, the dropout rate, and the economic impact of OLT, other alternatives such as resection with equivalent outcomes should be considered in appropriate patients. OLT in patients exceeding the Milan criteria should be considered on a selective basis given the excellent outcomes observed by centers using an extended criterion [24]. Patients beyond the Milan criteria may be downstaged using locoregional therapies. Following a period of observation after downstaging, patients who meet Milan criteria may be considered for OLT [15].

Bridge therapies are often used to prevent progression of HCC while on the transplant list. The specific aims are: (1) avoid drop out due to HCC progression, (2) increase tumor-free survival after OLT, (3) down stage advanced HCC to enable liver transplantation, and (4) avoid delay of OLT after

favorable response [25]. The common therapies utilized are RFA, TACE, percutaneous ethanol injections (PEI) and liver resection [25–29]. TACE and RFA should be considered to bridge patients due to the low morbidity and the favorable responses associated with these techniques that may reduce drop out in patients with an expected wait period of greater than 6 month prior to OLT. Liver resection should also be considered for appropriate patients where it may delay and/or avoid the need for OLT [15].

## 4. Nonoperative Therapies for Combined Modality Treatment of HCC

Most patients with HCC present with advanced liver disease and are therefore not candidates for liver transplantation, resection, or ablative procedures. However, most patients may benefit from palliative procedures that include TACE, transarterial radioembolization (TARE), external beam radiotherapy, and systemic therapy with sorafenib. Patient selection for any of these therapies is based on patient and tumor factors and decisions regarding treatment approaches should be made in a multidisciplinary setting that includes a hepatologist, interventional radiologist, and a surgeon [30].

TACE has been shown in randomized trials to increase time to progression and overall survival in patients with unresectable HCC compared to best supportive therapy or transarterial embolization [31, 32]. Based on this, TACE is a standard for intermediate-\advanced-stage unresectable HCC even in the setting of portal vein thrombosis (excluding main portal vein) where there is a proven survival benefit. It is also useful in predicting tumor biology in the pretransplant setting when used for bridging or downstaging patients. Emerging data regarding the use of drug eluting microspheres TACE are encouraging due to the comparable efficacy with TACE and the potential for decreased toxicity [30].

Sorafenib which is an anti-VEGF receptor and raf kinase inhibitor is approved for the treatment of unresectable HCC and is the standard agent for systemic therapy of advanced HCC based on a level 1 data [33]. Radiographic responses to sorafenib are a poor parameter to determine response to therapy. Tumor necrosis as determined by triphasic CT may be an accurate surrogate marker of efficacy but further data is required. The extent of cirrhosis appears to influence the outcomes of sorafenib therapy. Newer novel agents require further study before recommendations can be made regarding their use [30].

The use of yttrium 90 radioembolization is safe and efficacious in well-selected groups of patient where acceptable response rates and improvements in overall survival have been reported [34]. The subsets of patients where this modality should be considered are patients being downstaged or bridged with the intention of OLT, patients with malignant portal vein thrombosis where both TACE and OLT are contraindicated, and patients with advanced disease [30, 35, 36].

Recently, there has been a resurgent interest in the use of radiotherapy for HCC, driven by technological advances and an improved understanding of hepatic tolerance to radiotherapy. External beam radiation therapy and photon irradiation have been shown to induce acceptable response rates and provide local control to unresectable tumors [37]. With improved understanding of hepatic tolerance rates, radiotherapy will further expand the treatment options for patients with HCC, and multimodal strategies that include radiotherapy merit further study [30].

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*Research Article*

# Liver Surgery for Hepatocellular Carcinoma: Laparoscopic versus Open Approach

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In this study, we try to compare the benefit of laparoscopic versus open operative procedures. *Patients and Methods*. One hundred and sixteen patients underwent laparoscopic liver resection (LR) and another 208 patients went for open liver resection (OR) for hepatocellular carcinoma (HCC). Patients' selection for open or laparoscopic approach was not randomized. *Results*. The CLIP score for LR and OR was $0.59 \pm 0.75$ and $0.86 \pm 1.04$, respectively, ($P = .016$). The operation time was $156.3 \pm 308.2$ and $190.9 \pm 79.2$ min for LR and OR groups, respectively. The necessity for blood transfusion was found in 8 patients (6.9%) and 106 patients (50.9%) for LR and OR groups. Patients resumed full diet on the 2nd and 3rd postoperative day, and the average length of hospital stay was 6 days and 12 days for LR and OR groups. The complication rate and mortality rate were 0% and 6.0%, 2.9% and 30.2% for LR and OR groups, respectively. The 1-yr, 3-yr, and 5-yr survival rate was 87.0%, 70.4%, 62.2% and 83.2%, 76.0%, 71.8% for LR and OR group, respectively, of non-significant difference. From these results, HCC patients accepted laparoscopic or open approach were of no significant differences between their survival rates.

## 1. Introduction

Hepatocellular carcinoma (HCC) is a well-known disease in Taiwan. To date, the literature on laparoscopic hepatic surgery is not common and believed this technique is an innovation [1, 2]. In 1998, we started to apply laparoscopic approach for liver surgery on liver cancer [2]. In the study of Santambrogio et al. [3], evaluation by laparoscopic echography is indispensable to guarantee precise determination of the segmental tumor location and the relationship of the tumor to adjacent vascular and biliary structure which were important in the perioperative liver dissection.

With the improvement of laparoscopic technique and the development of new technology and equipment, laparoscopic liver resection is feasible and safe in experienced surgeons. In 2000, Descottes et al. [4] had reported right liver lobectomy and believed the use of this new technical approach offers many advantages but require extensive experience in hepatobiliary surgery and laparoscopic skills. In addition, the caudate lobe alone could be removed without scarifying other parts of the liver reported by Dulucq et al. [5]. Therefore, the laparoscopic technique was accepted for major liver resection gradually in some institutions [6].

Unlike laparoscopic cholecystectomy, laparoscopic hepatectomy has technical difficulties. The expansion of laparoscopic liver surgery will depend on the ability of expert surgeons and technological advances to address the management of bleeding and hemostasis [7]. As we had known, the open hepatic resection by large skin incision causes severe postoperative pain and longer recovery time usually. In addition to the benefits shared by all laparoscopic procedures, laparoscopic liver surgery also has theoretical advantages in some patients of HCC. Therefore, the aim of this study is to compare the results of laparoscopic procedure with open technique in the patients of HCC.

## 2. Patients and Methods

*2.1. Patients' Data and Indications.* One hundred and sixteen patients (92 male and 24 female) were encountered and

underwent laparoscopic liver resection and another 208 patients (156 male and 52 female) went for traditional resection un-randomized from 1998 to 2006. The criteria for liver resection were HCC with final pathological diagnosis. The basic data and underlying condition of liver diseases were shown in Table 1.

*2.2. Laparoscopic Approach Procedures.* Patients were in supine position under general anesthesia and the trocar insertion sites depended on the site of tumor. Usually, it was necessary to insert four trocars to have an optional operative manipulation. The first trocar was placed by small incision below the umbilicus technique for pneumo-peritoneum creation. The abdominal pressure was maintained low at the level of 8–12 mmHg in addition to abdominal lifting if necessary. The general condition of the liver could be evaluated directly from the laparoscopic examination and then to decide the following procedure. The site or extension of the tumors and its relationship to the vasculature were confirmed by laparoscopic ultrasonography. The line of intended transection and tumor feeding vessels and hepatic veins were marked on the liver surface with diathermy. Microwave coagulation along the resection line was performed first before dissecting the liver parenchyma. With this technique, risk of bleeding will be less during dissection. For the left-sided resections, the round, Falciform, and left triangular ligaments and the lesser omentum were divided. All the transection lines were punctured with laparoscopic microwave tissue coagulator to minimize bleeding during the liver dissection. Ultrasonic dissector system (CUSA) was used and branched vessels, and ducts were clipped and transected. The critical point at the left hepatic artery required double clipping. However, the left portal vein and left hepatic vein were ligated with silk and large clips. The surgical field was irrigated and checked bleeders or bile leak, and residual fluid was removed by suction. The electric coagulator was applied for ensuring hemostasis on the resection surface. After dissecting the left liver completely, the specimen could be removed by widening the epigastric port wound. Finally, a drainage tube was placed for postoperative drainage. The surgical procedure, postoperative course, and outpatient followup at 1, 3, and 5 years were evaluated periodically. The following data were collected prospectively: including duration of surgery, blood loss, perioperative transfusions, surgical events, postoperative complications, hospital stay, and survival rate.

*2.3. Biostatistics Analysis.* The clinical patients' features and postoperative results, all values, were expressed as means with standard deviations. The Student $t$-test and one-way analysis of variance (ANOVA) were used. The Kaplan-Meier method was employed to measure survival curve, and log-rank test was used to delineate a comparison between the survival rates of LR and OR groups. SPSS (versionb12.0) for Windows XP was used for data analysis. A $P$ value of less than.05 was considered statistical significantly.

## 3. Results

*3.1. Intraoperative Results.* The laparoscopic procedure was completed in 116 patients. All patients who underwent laparoscopic liver resection included one segment or less in 97 patients and left lateral segmentectomy (removal of segment 2 & 3) in seven, left lobectomy (removal of segment 2, 3 & 4) in four, and right anterior sectorectomy in eight patients. The lesions were located in the right liver in 61 patients and in the left liver in 55 patients. The type of operations of LR and OR was shown in Table 2. Conversion to open laparotomy occurred in 6 patients (5.2%) due to the anatomic limitation. Mean tumor size measured on the surgical specimen was $2.5 \pm 1.2$ and $5.4 \pm 3.5$ cm for the LR and OR groups, respectively. A margin of at least 1 cm beyond tumor limits was obtained in our patients who underwent surgery for malignancy except the situation of the base of the tumor adjacent to the main vessels. Mean surgical time and blood loss for LR and OR is shown in Table 2. There were 8 in 116 patients (6.9%) who needed blood transfusion. There were no signs suggestive of gas embolism in any of our patients.

*3.2. Postoperative Results.* There was no operative mortality in LR group but 2.9% (6/202) in OR group ($P = .092$). Postoperative complications consisted of 7 and 63 patients in the LR and OR group ($P = .001$). Cirrhotic patients developed transient ascites in 2 in LR and 26 in OR group ($P = .002$) but were well controlled with medication. There were no cases of postoperative bleeding or bile leak in LR group but six and four patients in OR group. Mean hospital stay of the whole series was $6.2 \pm 3$ days for LR group and $12.4 \pm 6.8$ days for OR group with a significant difference ($P = .001$). After a mean followup of 94 months, no port-site metastasis was observed in any patient who underwent surgery for malignant disease. The 1-year, 3-year, and 5-year survival rate were found to be 87.0%, 70.4%, 62.2% and 83.2%, 76.0%, 71.8% for the LR and TR groups, respectively, of no significant difference ($P = .291$) as shown in the Figure 1. In addition, no tumor recurrence could be attributed to the laparoscopic approach during the follow-up period.

## 4. Discussion

In 1993, Nord and Brady [8] started to use laparoscope for liver surgery with the improvement of laparoscopic techniques and the development of new and dedicated technologies. Usually, limited liver resections were performed in the early stage, and advancing laparoscopic anatomical liver resections were still in development. Hilscher et al. [9] had reported their initiated formal laparoscopic liver resections in selected 20 patients and one bi-segmentectomy with unevenly results in 1998. However, most of their patients were metastatic liver tumors from the colon cancer and those livers were less cirrhosis. Far from being a routine technique in liver surgery, the laparoscopic approach to formal liver resections may be a promising procedure in selected cases where the tumor can be removed by a limited resection. Most

Table 1: Preoperative clinical demographic data.

| Variable | | Laparoscopy ($N = 116$) | Traditional ($N = 208$) | $P$ |
|---|---|---|---|---|
| Sex | Male | 92 | 156 | .459 |
| | Female | 24 | 52 | |
| Age | Total | 58.31 ± 12.7 | 57.9 ± 11.2 | .800 |
| | Male | 57.0 ± 12.2 | 56.9 ± 11.8 | .965 |
| | Female | 63.2 ± 13.8 | 60.9 ± 8.6 | .389 |
| Body mass index (kg/m$^2$) | | 25.0 ± 3.4 | 23.7 ± 3.4 | .001* |
| HBsAG | No | 42 | 84 | .535 |
| | Yes | 74 | 124 | |
| Anti-HCV | No | 75 | 130 | .791 |
| | Yes | 41 | 78 | |
| Alpha-fetoprotein (ng/mL) | | 890.8 ± 3660.0 | 14561.3 ± 123371.4 | .234 |
| GOT (U/L) | | 67.8 ± 49.5 | 64.4 ± 52.3 | .570 |
| GPT (U/L) | | 64.5 ± 62.4 | 62.2 ± 55.0 | .736 |
| Alkaline phosphatase (U/L) | | 101.7 ± 58.7 | 123.4 ± 111.7 | .052 |
| Total bilirubin (mg/dL) | | 1.27 ± 1.18 | 0.95 ± 0.77 | .003* |
| Albumin (gm/dL) | | 3.59 ± 0.61 | 3.86 ± 0.58 | <.001* |
| Platelet ($10^3$ uL) | | 41.0 ± 30.4 | 29.4 ± 23.1 | <.001* |
| BUN (mg/dL) | | 18.2 ± 9.9 | 17.6 ± 10.6 | .635 |
| Serum creatinine (mg/dL) | | 1.14 ± 0.49 | 1.22 ± 1.04 | .431 |
| Prothrombin activity (%) | | 0.916 ± 0.090 | 0.952 ± 0.099 | .001* |
| ASA class | 1 | 51 | 88 | .845 |
| | 2 | 51 | 100 | |
| | 3 | 13 | 19 | |
| | 4 | 1 | 1 | |
| Child-Pugh classification | A | 98 | 197 | .008* |
| | B | 17 | 10 | |
| | C | 1 | 1 | |
| CLIP score | | 0.59 ± 0.75 | 0.86 ± 1.04 | .016* |
| TNM stage | I | 53 | 84 | .001* |
| | II | 58 | 76 | |
| | III | 32 | 38 | |
| | IV | 2 | 10 | |

Table 2: Comparative data of laparoscopy and traditional groups.

| Variable | | Laparoscopy ($N = 116$) | Traditional ($N = 208$) | $P$ |
|---|---|---|---|---|
| Tumor size (cm) | | 2.5 ± 1.2 | 5.4 ± 3.5 | .001 |
| Type of resection | | | | |
| 1 Segment | | 97 (83.6%) | 38(18.3%) | <.001* |
| 2 Segment | | 19 (16.4%) | 170(81.7%) | |
| Operation time (minutes) | | 156.3 ± 308.2 | 190.9 ± 79.2 | .126 |
| Blood loss (mL) | | 138.9 ± 336.0 | 1147.4 ± 1649.4 | <.001* |
| Transfusion | No | 108 | 102 | <.001* |
| | Yes | 8 | 106 | |
| Blood transfused (mL) | | 47.4 ± 174.2 | 658.7 ± 1298.3 | <.001* |
| Mortality | No | 116 | 202 | .092 |
| | Yes | 0 | 6 | |
| Complication | No | 109 | 145 | <.001* |
| | Yes | 7 | 63 | |

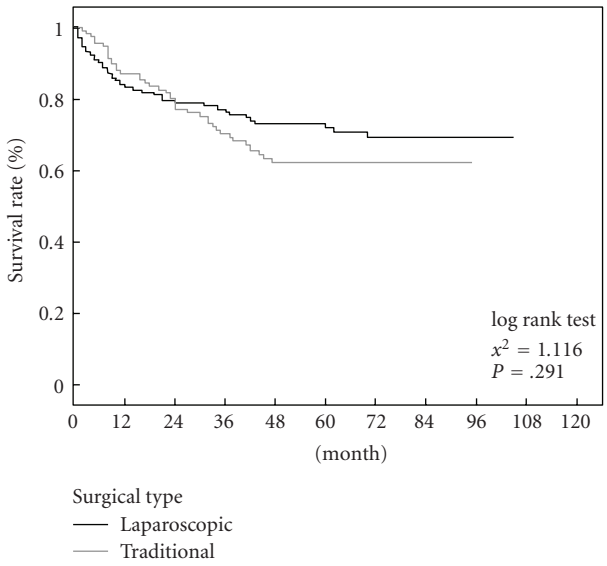


Figure 1: The survival curve of patients with HCC was treated by laparoscopic or open liver resection. Open method had the better result after 24 months postoperatively, but there was no significant difference totally ($P = .291$).

liver surgeons are thinking about the intraoperative bleeding, and it is difficult to handle. Kaneko et al. [10] reported that three patients underwent left lateral segmentectomy and eight underwent partial hepatectomy. They still believed that the differences were seen in blood loss, and postoperative pain was minimal compared with open hepatectomy. With this technique, postoperative recovery was swift and smooth and the patients were satisfied with the operation [11]. Therefore, laparoscopic approach to left lateral sectorectomy or right hepatectomy was believed to be safe and could be considered as a routine in selected patients recently [6, 12]. Even laparoscopic redo surgery for recurrent HCC in cirrhotic patients is a feasible procedure with good short-term outcomes [13].

The most important factors in the selection of candidates for laparoscopic resection were tumor's nature (benign of malignant) and anatomical location of the tumor [14, 15]. In our experience, we believed that lesions of the left liver lobe (II and III) and the anterior sector (IVa, V, and VI) constitute a good indication for laparoscopic approach, whereas lesions of the posterior and superior liver segments (I, IVc, VII, and VIII) are technically demanding and should only be approached with extreme caution or with hand-assisted method. Another factor in the selection for laparoscopic surgery is small tumor size, as in the most of the reported series (less than 5 cm on average). They were $2.5 \pm 1.2$ cm in our series and most of our cases were peripheral and protruding from the hepatic parenchyma. For the traditional hepatectomy, the size of the tumor was $5.4 \pm 3.5$ cm ($P < .001$). Therefore, limited resection (less one segment) was found in 97 cases (83.6%) in our series, compared with that of traditional method which was 38 cases (18.3%) ($P < .001$). The mean postoperative hospital stay was 6 days and 12 days for the laparoscopic and traditional liver resection, respectively, in our series. In comparing with the report of Morino et al. [15], the postoperative hospital stay was 6.4 days (range 2–16) in the laparoscopic group, 5.7 days for noncirrhotic patients and 12.6 days for cirrhotic ones. In general, the hospital stay was short in patients treated by laparoscopic approach. Concerning the mean operating time it was 160.5 minutes and the conversion rate was 8% as reported by the National Registry reported from Spain [16]. Analgesia was administered for less than 48 hours in 55% and there was no mortality in our series. We strongly believed that the laparoscopic approach can reduce blood loss and postoperative hospital stay as well. One of the reason for this result was the limited resections were major in LR group.

Intraoperative bleeding was the most concern in this laparoscopic liver resection. In our series, eight patients (8/108) need blood transfusion. Management of bleeding during dissection requires technical experiences and more importantly, adequate preoperative evaluation is the best guarantee. The microwave coagulator and CUSA were proved useful during laparoscopic resection because it can coagulate and dissect the hepatic parenchyma to achieve adequate hemostasis during the procedures. In addition, the potential risk of gas embolism led some authors to use gasless suspension laparoscopy [17]. However, precautions such as low abdominal pressure monitoring at the level of 6–8 m are warranted [16, 18, 19]. In our experience, it will be safe if the pneumoperitoneum was set at the level of 6–10 mmHg. In addition, no port-site metastases were observed in our patients and also mentioned by Cherqui et al. [20].

Laparoscopic liver resection for patients of HCC with chronic liver disease is associated with lower morbidity than open resections which were usually reported [15, 21, 22], and results were similar in our series. In the report of Buell et al. [22], the complications included reoperation for hemorrhage, bile leakage, and even death from hepatic failure. Mean length of stay was 2.9 days (range = 1–14 days). In a larger series of 243 hepatectomies carried out, 113 (46.5%) were performed by laparoscopy [23]. Concerning the survival rate, another retrospective study was performed in eleven surgical centers in Europe regarding their experience with laparoscopic resection of liver malignancies, 37 patients with HCC were included, conducted by multicenter European study [24]. During a mean followup of 14 months, the 2-year disease-free survival was 44% for patients with HCC. No port-site metastases were observed during followup. The 3-year overall and disease-free survival rates for patients with HCC (mean follow-up 40 months) were 85% and 68% reported by Vibert et al. [23] and 93% and 64%, respectively, by Cherui et al. [25]. The 5-year overall cumulative survival rate for the 69 patients was 63.9%. The 5-year cumulative survival rate for patients with HCC less than 2 cm in diameter was 76.0%, and 56.3% for patients with HCC more than 2 cm in diameter [25]. It seemed to us that laparoscopic procedures were best suited for the patients of well-differentiated HCC [25, 26]. After a mean followup of 94 months in our series, there was no difference in survival rate between the two groups. The 5-year survival rate was found to be 62.2% and 71.8% for the laparoscopic and traditional methods, respectively, without

significant difference ($P = .291$) in this series. It did not mean the laparoscopic method was better than that of formal open method because the tumor size was smaller in the laparoscopic group. However, the unexpected diagnosis of early HCC could be obtained only by laparoscopic technique in our experiences.

The surgical technique is an important factor in preventing intraoperative and postoperative complications in liver surgery. Laparoscopic approach in the extended hepatectomy could be performed due to the accumulation of experience and improvement of instruments nowadays [27]. Various techniques have been developed for safe dissection of the liver parenchyma. Therefore, hand-assisted laparoscopic liver resection is a more feasible procedure for removal of two segments of liver more or less [28]. Hand-port procedure could provide direct feeling with the surgeon's hand and makes possible a procedure that is almost identical to open surgery. In this method, there is a better visualization of the surgical field and dissection margin, and immediate hemostasis is also achieved by manually depressing the bleeding point. Laparoscopic liver resection using the Hand-port system is feasible for selected patients with lesions even in the posterior portion of the right hepatic lobe requiring limited resection [29]. In addition to the hand-assisted, laparoscopic assisted could be accepted recently and become more popular [30]. From the report of Inagaki et al. [31] with liver resection using the laparoscopy-assisted and total laparoscopic methods, there were no differences in the operation times, the transfusion amounts, the starting days of the patients' diets, the complication rates, or the durations of the hospital stay between the laparoscopic or open methods groups. Both the laparoscopy-assisted method and the total laparoscopic method are feasible to use for performing anatomical liver resection at present. There was no difference in the postoperative adverse event and extent of oncologic clearance due to either the improvement of surgeons' skills or the development of technology [10, 32, 33].

In conclusion, laparoscopic hepatectomy is beneficial for patient life quality as a minimally invasive procedure. Evolution of laparoscopic hepatectomy will depend on the development of new instrumentations. Laparoscopic hepatectomy is more feasible and with a low morbidity and mortality rate comparable to open procedures. However, prospective randomized trials are still needed to confirm those results, especially for resection of primary or metastasis liver malignant tumors.

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*Review Article*

# Radiofrequency Ablation of Hepatocellular Carcinoma: A Literature Review

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Radiofrequency ablation (RFA) of liver cancers can be performed safely using percutaneous, laparoscopic, or open surgical techniques, and much of the impetus for the use of RFA has come from cohort series that have provided an evidence base for this technique. Here, we give an overview of the current status of radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC), including its physical properties, to assess the characteristics that make this technique applicable in clinical practice. We review the technical development of probe design and summarize current indications and outcomes of reported clinical use. An accurate evaluation of treatment response is very important to secure successful RFA therapy since a sufficient safety margin (at least 0.5 cm) can prevent local tumor recurrences. We also provide a profile of side effects and information on the integration of this technique into the general management of patients with HCC. To minimize complications of RFA, physicians should be familiar with each feature of complication. Appropriate management of complications is essential for successful RFA treatment. Moreover, adjuvant therapy, such as molecular targeted therapies following curative therapy, is expected to further improve survival after RFA.

## 1. Introduction

Hepatic resection forms part of the conventional treatment for patients with hepatocellular carcinoma (HCC); however, the majority of primary liver cancers are not suitable for curative resection at the time of diagnosis. Difficulties of surgical resection may be related to size, site, and number of tumors, vascular and extrahepatic involvement as well as liver function of the patient [1–4]. There is a need to develop a simple and effective technique for the treatment of unresectable tumors within the liver. Therefore, local ablative techniques (percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT), and radiofrequency ablation (RFA)) have emerged in clinical practice to expand the pool of patients considered for liver-directed therapies [5–8]. Especially, RFA is not associated with some of the side effects of other ablative techniques [9]. Thus, RFA is currently performed widely due to the ease of use, safety, reasonable cost, and applicability to minimally invasive techniques [10].

This paper reviews the evidence supporting the use of RFA for HCC.

## 2. Background

*2.1. Localized Application of Radiofrequency Energy.* RFA is a localized thermal treatment technique designed to induce tumor destruction by heating the tumor tissue to temperatures that exceed 60°C [11]. The alternating current of radiofrequency waves passing down from an uninsulated electrode tip into the surrounding tissues generates changes in the direction of ions and creates ionic agitation and frictional heating. This tissue heating then drives extracellular and intracellular water out of the tissue, resulting in tissue destruction by coagulative necrosis [12, 13]. When tumor cells are heated above 45–50°C, intracellular proteins are denatured and cell membranes are destroyed through dissolution and melting of lipid bilayers. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60°C.

Percutaneous RFA under local anesthesia was feasible, although intraoperative RFA under general anesthesia was also performed to prevent severe pain and discomfort during the procedure.

*2.2. RFA Electrodes and Generators.* Three types of RF electrodes are currently available commercially: two brands of retractable needle electrodes (model 70 and model 90 Starburst XL needles, RITA Medical Systems, Mountain View, CA; LeVeen needle electrode, Boston Scientific, Boston, MA) and an internally cooled electrode (Cool-Tip RF electrode; Radionics, Burlington, MA) [14].

The needle electrodes of RITA consist of a 14-gauge insulated outer needle that houses nine retractable curved electrodes of various lengths. When the electrodes are extended, the device assumes the approximate configuration of a Christmas tree. Nine of the electrodes are hollow and contain thermocouples in their tips in order to measure the temperature of adjacent tissue. The alternating electric current generator comes in a 250 W model at 460 kHz (Model 1500X RF Generator, RITA Medical Systems). The ablation algorithm is based on the temperature at the tips of the electrodes. After the ablation cycle is completed, a temperature reading from the extended electrodes in excess of 50°C at 1 min is considered to indicate satisfactory ablation.

Another RFA device (LeVeen Needle Electrode; Radiotherapeutics) has retractable curved electrodes and an insulated 17-gauge outer needle that houses 10 solid retractable curved electrodes that, when deployed, assume the configuration of an umbrella. The electrodes are manufactured in different lengths (2 to 4.0 cm umbrella diameter). The alternating electric current generator is 200 W operated at 480 kHz (RF 3000; Boston Scientific). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out.

The third RFA device (Cool-Tip radiofrequency electrode; Radionics) has an insulated hollow 17-gauge needle with an exposed needle tip of variable length (2 or 3 cm). The tip of the needle contains a thermocouple to record the temperature of adjacent tissue. The shaft of the needle has two internal channels that allow the needle to be perfused with chilled water. In an attempt to further increase the size of the ablation area, the manufacturer placed three of the cooled needles in a parallel triangular cluster with a common hub. The generator has a peak power output of 200 W and is operated at 480 kHz (CC-1; Radionics). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60°C.

*2.3. Treatment Algorithm in Japan and the West.* RFA is basically recommended for HCC nodules with a maximum diameter of 3 cm in patients with not more than three tumors who are contraindicated for surgery, although the typical treatment algorithms in Japan, North America, and Europe are each slightly different [35].

One of the major treatment algorithms in Japan is the "consensus-based clinical practice manual for HCC" [14, 36] edited by the Japan Society of Hepatology (JSH). This consensus recommends (1) hepatectomy for a single tumor regardless of tumor size, but local treatment may be selected for a tumor 2 cm or smaller in Child-Pugh B patients; (2) hepatectomy or local treatment when there are 2 or 3 tumors and the tumor size is within 3 cm; (3) liver transplantation for Child-Pugh C patients with 3 or fewer tumors 3 cm or smaller or a single tumor with a tumor size within 5 cm (Milan Criteria); (4) RFA combined with transcatheter arterial chemoembolization (TACE) is recommended for tumors more than 3 cm in diameter. RFA is also recommended for 4 or more nodules where applicable.

In Europe and North America, the algorithm established by the American Association of the Study of the Liver Disease (AASLD) [37] recommends local treatment for 3 or fewer 3 cm or smaller early-stage HCCs and 2-cm or smaller very-early-stage HCCs with complications, such as portal hypertension.

*2.4. Assessment of Technical Effectiveness.* The assessment of the therapeutic effect of RFA is very important. The technical effectiveness of ablation is commonly assessed by findings on contrast-enhanced CT or MRI. A tumor was considered to have been successfully ablated when there were no longer any enhanced regions within the entire tumor during the arterial phase and at least a 0.5 cm margin of apparently normal hepatic tissue surrounding the tumor during the portal phase [38–40]. Failure to establish a sufficient ablative safety margin was shown to be an independently significant risk factor for local tumor progression on multivariate analysis [41]. Part of the tumor was diagnosed as remaining viable when images of the ablated area showed nodular peripheral enhancement [42].

Basically, the local recurrence rate following a single RFA treatment depends on how strictly the therapeutic effect is assessed. In cases of HCC in which local curative therapy was achieved by securing a safety margin, the 4-year survival rate was relatively high, at 66%–82% (results in Japan) [35, 43].

## 3. Clinical Outcomes

*3.1. Percutaneous Approach*

*3.1.1. Survival: Comparison with Those after Resection.* A randomized control trial (RCT) has shown that RFA achieved survival rates similar to those achieved by resection (Table 1) [15]. Chen et al. conducted RCT on 180 patients with a solitary HCC $\leq$5 cm indicated to receive either percutaneous RFA or surgical resection [15]. This study showed that percutaneous RFA achieved the same overall and disease-free survival rates as surgical resection for patients with small solitary HCC. The 1- and 4-year overall survival rates after percutaneous RFA and surgery were 95.8%, 67.9% and 93.3%, 64.0%, respectively. The corresponding disease-free survival rates were 85.9%, 46.4% and 86.6%, 51.6%, respectively. Recently, Huang et al. reported an RCT trial in which the 1-, 3-, and 5-year overall survival rates for the RFA group and the RES group were 86.96%, 69.57%, 54.78% and 98.26%, 92.17%, 75.65%, respectively. Overall survival and recurrence-free survival were significantly higher in the

Table 1: Survivals: RFA versus hepatic resection for HCC.

| Author/Year | Study type | *n* (RFA/resection) | Mean tumor size (cm) (RFA/resection) | Overall survival (%) (RFA versus resection) | *P* |
|---|---|---|---|---|---|
| Chen et al. [15], 2006 | RCT | 90/90 | ND/ND | 65.9 versus 64.0 (4-year) | NS |
| Huang et al. [16], 2010 | RCT | 115/115 | ND/ND | 54.78 versus 75.65 (5-year) | .001 |
| Vivarelli et al. [17], 2004 | Retrospective | 79/79 | ND/ND | 33 versus 65 (3-year) | .002 |
| Montorsi et al. [18], 2005 | Prospective | 58/40 | ND/ND | 30 versus 53 (4-year) | .018 |
| Ogihara et al. [19], 2005 | Retrospective | 40/47 | 4.6/7.4 | 39 versus 31 (5-year) | .79 |
| Wakai et al. [20], 2006 | Retrospective | 64/85 | ND/ND | 30 versus 53 (10-year) | .012 |
| Guglielmi et al. [21], 2008 | Retrospective | 23/33 | ND/ND | 45 versus 55 (5-year) | .7 |
| Abu-Hilal et al. [22], 2008 | Retrospective | 34/34 | 3.0/3.8 | 57 versus 56 (5-year) | .3 |
| Hiraoka et al. [23], 2008 | Retrospective | 105/59 | ND/ND | 59.3 versus 59.4 (5-year) | NS |
| Ueno et al. [24], 2009 | Retrospective | 123/110 | 2.0/2.7 | 63 versus 80 (5-year) | .06 |
| Takayama et al. [25], 2009 | Retrospective | 1315/1235 | 1.6/1.8 | 95 versus 94 (2-year) | .28 |

HCC: hepatocellular carcinoma; ND: not described; NS: not significant; RFA: radiofrequency ablation.

Table 2: Local tumor progression rates after RFA for HCC.

| Author | Year | *n* | Tumor size (mean, cm) | Follow-up period (mean, months) | Local tumor progression rate (%) |
|---|---|---|---|---|---|
| Rossi et al. [26] | 1996 | 41 | 2.3 | 22.6 | 5.0 |
| Buscarimi et al. [27] | 2001 | 60 | ND | 26.8 | 14 |
| Choi et al. [28] | 2004 | 53 | 2.1 | 23 | 21 |
| Lu et al. [29] | 2005 | 87 | 2.5 | 12.7 | 5.8 |
| Shiina et al. [30] | 2005 | 118 | ND | 34.8 | 1.7 |
| Solmi et al. [31] | 2006 | 63 | 2.8 | 32.3 | 41 |
| Hänsler et al. [32] | 2007 | 21 | 4.2 | ND | 21 |
| Waki et al. [33] | 2010 | 88 | ND | 36 | 4.8 |
| Li et al. [34] | 2010 | 117 | 2.4 | 21 | 9.4 |

HCC: hepatocellular carcinoma; ND: not described; RFA: radiofrequency ablation.

surgical resection group than in the RFA group ($P = .001$, $P = .017$). However, percutaneous RFA can be expected to have an advantage over liver resection in providing a better short-term postoperative result because local ablative therapy is a less invasive procedure [16–25].

*3.1.2. Local Controllability (Local Tumor Progression).* The local recurrence rate after RFA for HCC ranged from 1.7% to 41% [26–34] (Table 2). Local tumor progression is related to incomplete tumor ablation. It is often difficult to obtain a specific safety margin in three dimensions all around a large tumor. Some researchers reported that the most important factor associated with failure of local tumor control could be tumor size [8, 36–38]. In Table 2, local tumor progression did not necessarily depend on the tumor size; however, recurrence could occur even after a sufficient margin had been ensured. It is considered that local recurrence appears to arise from residual cancer after RFA while recurrence from a microsatellite or by microvascular invasion other than the main nodule may also appear as a late local recurrence. The local tumor progression rate can differ markedly depending on whether or not a 5 mm circumferential safety margin has been secured. Nishijima et al. categorized the presence of no margin, a partially lacking margin, margin narrower than 5 mm, and complete margin wider than 5 mm as R0, R1, R2, and R3 on the assessment of the therapeutic effect of RFA, respectively, and found significant differences in the local recurrence rate between R0 and R1 and between R2 and R3. The local recurrence rate significantly differed between patients with and without a sufficient safety margin [44].

Therefore, ensuring a safety margin in RFA is important for not only the simultaneous treatment of microsatellite lesions, but also to ensure sufficient tumor ablation on the assumption of a partial volume effect-associated limitation on evaluation of the therapeutic effect by imaging.

*3.1.3. Advances of Techniques: Large HCC.* Tumor size is an important factor influencing the local recurrence rate after RFA [45]. To increase the size of the coagulation zone in RFA, physicians have tried using vascular occlusion during RFA because vascular occlusion reduces heat dispersion. It was shown in the consensus meeting "HCC Treatment" at the 45th Annual Meeting of the JSH in Kobe in 2009 [46] that about 90% of physicians performing RFA employ lipiodol TACE-preceded RFA for 3 cm or larger HCCs. Lipiodol TACE-preceded RFA is relatively curative and can be readily performed for the following reasons: (1) lipiodol regurgitates into the portal branches via the peribiliary venous plexus, causing a transient state of liver infarction, which reduces the cooling effect, expanding the ablative area, and resulting in (2) coagulation of satellite lesions [43]. Peng et al. reported a series of 120 patients with HCC, and the 1-, 3-, 5-year overall survival rates for TACE-preceded RFA and RFA groups were 93%, 75%, 50%, and 89%, 64%, 42%, respectively ($P = .045$) [47]. Yamakado et al. reported that the survival rates of large HCC cases treated with resection and lipiodol TACE-preceded RFA were almost equivalent [48]. TACE combined with RFA therapy might improve the overall survival status for patients with large HCCs (Table 3) [47, 49–52].

*3.1.4. Advanced Techniques: Tumors Abutting the Diaphragm and Gastrointestinal Tract.* Ultrasound- (US-) guided procedures are necessary but limited for tumors located under the diaphragm. However, saline solution injection into the pleural cavity can separate the lung and liver on B-mode US, that is, artificial pleural effusion acts as an acoustic window. There are reports on the feasibility and safety of RFA with artificially induced pleural effusion for HCC located in the right subphrenic region [53–56]. In a series of 24 patients with HCC located in the hepatic dome, 200–1100 mL of 5% glucose solution was infused intrathoracically to separate the lung and liver, thus, complete tumor necrosis in a single session was achieved in 96.4% [56].

Artificial preparation of a space between the intestine and nodule by infusing normal saline or 5% glucose (artificial ascites method) for treatment has recently become possible [57, 58]. These techniques markedly expanded the indication for RFA. Laparoscopic resection or laparotomic RFA had to be inevitably performed in patients with HCC nodules <2.0 cm in diameter before the introduction of artificial ascites, but more than 90% of cases are now treatable by the "artificial ascites method".

*3.1.5. Advanced Techniques: Cases That Are Unclear on B-Mode US.* Multiple RFA sessions for HCCs were frequently required because of HCC nodules that are unclear on B-mode US. Under CT fluoroscopy using either CT arteriography or iodized oil injection, we can target and puncture hepatic malignancies using a percutaneous ethanol injection needle. Real-time CT fluoroscopy is useful to guide the needle puncture and to monitor ethanol injection in small hepatic malignancies [67]. Another merit is that the efficacy of treatment can be evaluated using contrast enhanced CT immediately after treatment.

Contrast enhanced harmonic US imaging is able to evaluate small hypervascular HCCs even when B-mode US cannot adequately characterize the tumors [68–72]. The microbubbles of these contrast agents provide stable nonlinear oscillation in a low-power acoustic field because of the hard shells of these bubbles, producing great detail in the harmonic signals in real time [71–73]. It has been reported that contrast harmonic sonography-guided RFA is an efficient approach for guiding further ablation of hepatic malignancies that are not clearly demarcated by B-mode US [74–78].

Virtual CT sonography using magnetic navigation (Real-time Virtual Sonography (RVS); HITACHI Medico, Tokyo, Japan) provides cross sectional images of CT volume data corresponding to the angle of the transducer in the magnetic field in real-time. This imaging technique displays a real-time synchronized multiplanar CT image in precisely the same slice of the US plane. Thus, RVS can be used for real-time needle insertion guidance, especially for nodules demonstrated on CT, but not on US [79, 80].

*3.2. Laparoscopic/Open Surgical Approach.* The use of a laparoscopic or open approach allows repeated placement of RFA electrodes at multiple sites to ablate larger tumors [59–66] (Table 4). Moreover, a hand-assisted technique can be applied safely and effectively to laparoscopic liver surgery and offers the advantages of intraoperative US, which provides better resolution of the number and location of liver tumors. The postoperative recovery of patients was shorter compared with that after an open surgical approach. Ishiko et al. reported that the surgical procedures consisted of 5 RFA sessions for tumors in the caudate lobe with hand-assisted laparoscopic surgery (HALS) and a postoperative CT scan demonstrated sufficient ablation in all patients and there was no surgical mortality [63]. The HALS approach has several advantages; it facilitates and expedites the procedure, reduces the stress factor on the surgeon, greatly improves exposure, and facilitates immediate and efficient control of bleeding vessels with the internal hand. However, the local treatment failure rate of the laparoscopic approach was higher in patients with HCC nodules situated deep within the liver and measuring 4 cm or more in diameter [81]. Great difficulty can be encountered during treatment of lesions in contact with the diaphragm.

Although more invasive, open RFA can be performed more easily, and the puncture course of RF needle can be more widely selected than that during laparoscopic approach. Some have reported that patients undergoing radical open RFA demonstrated few ablation site recurrences even though the nodules measured more than 4 cm in diameter and/or there were more than three nodules [59, 62, 65].

*3.3. Complications.* A recent review indicated that complication rates for percutaneous, laparoscopic, and open RFA of hepatic tumors in 3670 patients were 7.2%, 9.5%, and

Table 3: Survivals: RFA combined with TACE versus RFA alone for HCC.

| Author/year | *n* (TACE+RFA/RFA) | Tumor size (mean, cm) (TACE+RFA/RFA) | Overall survival (%) (TACE+RFA/RFA) | *P* |
|---|---|---|---|---|
| Kitamoto et al. [49]/2003 | 10/16 | 3.9/3.4 | ND | |
| Wang et al. [50]/2007 | 43/40 | ND | 68.3/57.6 (1-year) | <.05 |
| Shibata et al. [51]/2009 | 46/43 | ND | 84.8/84.5 (3-year) | .515 |
| Morimoto et al. [52]/2010 | 19/18 | 3.6/3.7 | 93/80 (3-year) | .369 |
| Peng et al. [47]/2010 | 120/120 | ND | 50/42 (5-year) | .045 |

HCC: hepatocellular carcinoma; ND: not described; RFA: radiofrequency ablation, TACE: trans catheter arterial chemoembolization.

Table 4: Laparoscopic/open RFA for liver malignancies: local tumor progressions and survivals.

| Author/year | Arms | *n* | Tumor size (mean, cm) | Follow-up period (mean, months) | Local tumor progression | Survival (%) |
|---|---|---|---|---|---|---|
| Topal et al. [59]/2003 | LS/open | 9/9 | 3.8/3.5 | 12.2 | 1/9, 0/9 | ND |
| Berber et al. [60]/2005 | LS | 66 | 4.1 | 25.3 | ND | 38% (3-year) |
| Hildebrand et al. [61]/2007 | LS | 14 | ND | 23.2 | 1/14 | ND |
| Minami et al. [62]/2007 | open | 30 | 3.2 | 18.9 | 1/30 | 71.6% (3-year) |
| Ishiko et al. [63]/2008 | HALS | 5 | ND | 32.2 | 1/5 | ND |
| Ballem et al. [64]/2008 | LS | 104 | 3.5 | 23 | ND | 21% (3-year) |
| Tanaka et al. [65]/2009 | open | 26 | ND | ND | 1/26 | ND |
| Salama et al. [66]/2010 | LS | 72 | ND | 14.3 | 2/72 | ND |

HALS: hand-assisted laparoscopic surgery; LS: laparoscopy; ND: not described; RFA: radiofrequency ablation.

9.9%, respectively [82]. Overall, the frequency of major complications of percutaneous RFA ranged from 0.6%–8.9%, which was higher than that of PEI, but generally less than that of MCT [43]. Complications of percutaneous RFA reported in 2320 patients treated at 41 different hospitals in Italy indicate that the mortality rate was 0.3% with an overall complication rate of 7.1% [83, 84]. The authors described major complications (2.4% incidence) including death, hemorrhage, RFA needle-track seeding, RFA lesion abscess, perforation of gastrointestinal viscus, liver failure, biloma, biliary stricture, portal vein thrombosis, and hemothorax or pneumothorax requiring drainage, and minor complications (4.7% incidence) including pain, fever, and asymptomatic pleural effusion. Although Llovet et al. [85] reported that dissemination along puncture route was observed in 12.5% of their patients, dissemination might not occur at such a high frequency. This complication was almost absent in many reports from Japan [43].

Theoretically, a tumor that is contiguous to a large vessel is more likely to have some viable tumor cells following local thermal therapy because there is a significant tissue cooling effect caused by blood circulation of normal body temperature. Thus, the effort to thoroughly ablate the lesion with a safety margin under such conditions increases the total number of electrode insertions, and this may increase the risk of complications. Some investigators have suggested that tumor location is closely related to the risk of major complications. Central tumors close to the hepatic hilum were reported to be unsuitable for percutaneous RFA because of the risk of injuring adjacent bile ducts [7]. Moreover, peripheral tumors adjacent to extrahepatic organs were also suggested to be unsuitable because of the risk of heat injuries, such as intestinal perforation and pleural effusion [84, 86]. However, Teratani et al. reported that there was no difference in early complication rates according to tumor location [87]. The effort to achieve thorough ablation increased the total number of electrode insertions, and this may have led to an increase in complications.

Not only elevating the survival rate and reducing the incidence of local recurrence but also avoiding complications as much as possible are major tasks. To minimize complications of RFA, knowledge of risk factors and prevention methods is required. In addition, because early and accurate diagnosis is necessary for the appropriate management of complications, physicians should be familiar with all features of complication.

## 4. Future Perspective

Currently, a multicenter randomized controlled study (prospective randomized study of surgery or RFA for early HCC: SURF Trial) is underway in Japan, involving patients with 3 or fewer tumors 3 cm or smaller for which both hepatectomy and RFA are applicable [88], and a large global study is currently underway (the Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of HepatocellularCarcinoma

(STORM) trial), looking at the efficacy of sorafenib therapy after potentially curative treatment with liver resection or RFA.

## 5. Conclusion

Here, we have assessed the role of RFA in the overall therapeutic strategy for patients with HCC and highlighted deficiencies in current knowledge. We intend to strive for a balanced discussion between the tendency to overemphasize the potential advantages of RFA and the tendency to understate a potentially useful treatment. Percutaneous RFA can achieve the same overall and disease-free survival rates as surgical resection for patients with small HCC, while causing few side effects. Percutaneous RFA combined with TACE will make the treatment of larger tumors a clinically viable treatment alternative. The use of a laparoscopic or open approach allows repeated placement of RFA electrodes at multiple sites to ablate larger tumors. In addition, an accurate evaluation of treatment response is very important to secure successful RFA therapy since a sufficient safety margin (at least 0.5 cm) can prevent local tumor recurrence. Adjuvant therapy, such as molecular targeted therapies following curative therapy, is expected to further improve survival after RFA.

## Authors' Contributions

Y. Minami drafted the paper and wrote the final version of the paper. M. Kudo reviewed and approved the final version of the paper.

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*Review Article*

# Early Hepatocellular Carcinoma: Transplantation versus Resection: The Case for Liver Resection

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The optimal surgical treatment of hepatocellular carcinoma on well-compensated cirrhosis is controversial. Advocates of liver transplantation cite better long-term survival, lower risk of recurrence, and the ability of transplantation to treat both the HCC and the underlying liver cirrhosis. Transplantation, however, is not universally available to all appropriate-risk candidates because of a lack of sufficient organ donors and in addition suffers from the disadvantages of requiring a more complex pre- and postoperative management associated with risks of inaccessibility, noncompliance, and late complications. Resection, by contrast, is much more easily and widely available, avoids many of those risks, is by many accounts as effective at achieving similar long-term survival, and still allows for safe, subsequent liver transplantation in cases of recurrence. Here, arguments are made in favor of resection being easier, safer, simpler, and comparably effective in the treatment of HCC relative to transplantation, and therefore being the optimal initial treatment in cases of hepatocellular carcinoma on well-compensated cirrhosis.

## 1. Introduction

Hepatocellular carcinoma (HCC) is the seventh most common cancer worldwide, one of the most common causes of cancer death worldwide, and its incidence is increasing [1–3]. The rate of cancer death from primary liver cancer (90% of which is HCC [4]) in the United States has increased by over 40% in recent decades [2]. Risk factors for the development of HCC include hepatitis (most commonly hepatitis B virus (HBV) or hepatitis C virus (HCV)), steatohepatitis, cirrhosis, hepatotoxins, and less commonly hereditary diseases such as hemochromatosis and alpha-1 antitrypsin deficiency. HCC uncommonly arises in healthy liver parenchyma. HBV is the most common underlying liver disease, and chronic carriers have a logarithmically increased risk of developing HCC compared to the general population [4].

## 2. The Debate

There is currently no consensus regarding the best surgical treatment for patients with well-compensated cirrhosis and early HCC within the Milan criteria (a single tumor <5 cm in maximum diameter, or 2-3 tumors each <3 cm, without lymphovascular invasion [5, 6]). While transplantation is clearly better for patients with severe cirrhosis and early HCC, and resection is better than transplantation for resectable but extra-Milan-criteria HCC on mild cirrhosis, on the middle ground—early HCC with mild cirrhosis—wages the debate between transplantation and resection.

## 3. Advantages of Liver Transplantation

The ability to treat with a single intervention not only the HCC but also the underlying oncogenic liver disease from which it arose—and by extension, from which other tumors may arise—is one of the greatest advantages of liver transplantation over resection. In high-volume centers, liver transplantation achieves this goal with acceptable morbidity and mortality (Table 1).

Furthermore, not only is liver transplantation relatively safe, but compared with resection, it has been reported to produce a longer 5-year survival and a lower rate of recurrence (Table 1). The reasons for these improved results compared to resection are difficult to discern, however, and may be related to a truly superior extirpation of gross and microscopic disease or to selection bias, especially as might

Table 1: Series comparing RSX and LT for HCC on cirrhosis.

| First author [ref] | Year | N RSX | N LT | Mb (%) RSX | Mb (%) LT | Mt (%) RSX | Mt (%) LT | Overall 5-YS RSX | Overall 5-YS LT | Rec (%) RSX | Rec (%) LT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Iwatsuki$^{wi/o}$ [46] | 1991 | 17** | 71** | NR | NR | NR | NR | 0% | 41% | 50 | 43 |
| Ringe$^{wi/o}$ [47] | 1991 | 131** | 61** | NR | NR | $15^{30\text{-d},*}$ | $15^{30\text{-d},*}$ | 36% | 15% | NR | NR |
| Vargas$^{wi}$ [48] | 1995 | 35 | 11 | NR | NR | NR | NR | 58% 1-YS | 81% 1-YS | 40 | 0 |
| Tan$^{wi/o}$ [49] | 1995 | 12 | 15 | $33^{NR}$ | $13^{NR}$ | $8.3^{NR}$ | $6.7^{NR}$ | 33% 3-YS | 63% 3-YS | 45 | 15 |
| Michel$^{wi/o}$ [50] | 1997 | 102 | 113 | $39^{NR}$ | $38^{NR}$ | $8.8^{NR}$ | $22^{NR}$ | 31% | 32% | 86 | 30 |
| Philosophe$^{wi/o}$ [51] | 1998 | 67** | 58** | NR | NR | $44^{30\text{-d}}$ | $13^{30\text{-d}}$ | 38% | 45% | 55 | 20 |
| Colella$^{wi/o}$ [52] | 1998 | 41 | 55 | NR | NR | NR | NR | 44% | 68% | NR | NR |
| Mazziotti$^{NR}$ [53] | 1998 | 238 | 41 | $42^{NR}$ | $80^{NR}$ | $4.6^{30\text{-d}}$ | $6.2^{30\text{-d}}$ | 41% | 69% | NR | NR |
| Otto$^{wi/o}$ [54] | 1998 | 52 | 50 | NR | NR | $21^{30\text{-d}}$ | $8.0^{30\text{-d}}$ | 37% | 44% | 21 | 8.0 |
| Weimann$^{NR}$ [55] | 1999 | 32 | 31 | NR | NR | $13^{30\text{-d}}$ | $10^{30\text{-d}}$ | 34% | 63% | 19 | 0 |
| Yamamoto$^{wi/o}$ [25] | 1999 | 294 | 270 | NR | NR | $1.4^{30\text{-d}}$ | $7.8^{30\text{-d}}$ | 47% | 54% | NR | NR |
| Llovet$^{wi}$ [19] | 1999 | 77 | 87 | NR | NR | $3.9^{90\text{-d}}$ | $2.3^{90\text{-d}}$ | 51% | 69% | 57 | 3.4 |
| Figueras$^{wi/o}$ [56] | 2000 | 35 | 85 | NR | $6.7^{NR}$ | NR | NR | 51% | 60% | 65 | 7.0 |
| De Carlis$^{wi/o}$ [57] | 2001 | 131 | 91 | NR | NR | $4.5^{90\text{-d}}$ | $18^{90\text{-d}}$ | 38% | 65% | 62 | 7.0 |
| Shabahang$^{NR}$ [58] | 2002 | 44 | 65 | NR | NR | $7.0^{NR}$ | $7.0^{NR}$ | 57% 3-YS | 66% 3-YS | NR | NR |
| Bigourdan$^{wi}$ [59] | 2003 | 20 | 17 | $30^{30\text{-d}}$ | $47^{30\text{-d}}$ | $5.0^{30\text{-d}}$ | $0^{30\text{-d}}$ | 36% | 71% | 30 | 18 |
| Pierie$^{NR}$ [60] | 2005 | 81 | 33*** | NR | NR | $20^{30\text{-d}}$ | $9.0^{30\text{-d}}$ | 10% | 19% | NR | NR |
| Margarit$^{wi}$ [61] | 2005 | 37 | 36 | NR | NR | $2.7^{30\text{-d}}$ | $5.6^{30\text{-d}}$ | 78% | 50% | 59 | 11 |
| Poon$^{wi}$ [62] | 2007 | 204 | 43 | $35^{30\text{-d}}$ | $44^{30\text{-d}}$ | $3.4^{H}$ | $0^{H}$ | 68% | 81% | NR | NR |
| Cillo$^{wi/o}$ [63] | 2007 | 131 | 40 | NR | NR | $5.3^{90\text{-d}}$ | $7.5^{90\text{-d}}$ | 31% | 63% | 53 | 5.0 |
| Del Gaudio$^{wi}$ [22] | 2008 | 80 | 293 | NR | $79^{NR}$ | $0^{NR}$ | $5.0^{NR}$ | 66% | 58% | 59 | 46 |
| Bellavance$^{wi}$ [64] | 2008 | 245 | 134 | $49^{30\text{-d}}$ | $65^{30\text{-d}}$ | $1.6^{30\text{-d}}$ | $1.5^{30\text{-d}}$ | 46% | 66% | 50 | 14 |
| Sotiropoulo$^{wi/o}$ [65] | 2009 | 61 | 60 | $38^{30\text{-d}}$ | $38^{30\text{-d}}$ | $23^{30\text{-d}}$ | $8.0^{30\text{-d}}$ | 23% | 59% | NR | NR |
| Zhou$^{wi}$ [66] | 2010 | 1018 | 89 | NR | NR | $0.69^{NR}$ | $4.5^{NR}$ | 70% | 89% | NR | NR |

Abbreviations: RSX: resection; LT: liver transplantation; YS: year-survival; Mb: morbidity; MT: mortality; Rec: recurrence.
*RSX and LT combined.
**Cirrhotic and noncirrhotic livers combined.
***33 wait-list patients (22 transplanted patients).
$^{wi}$All patients within Milan criteria.
$^{wi/o}$Some patients within and some outside of Milan criteria.
$^{NR}$Milan criteria not reported.
$^{H}$Hospital mortality (during same admission for same treatment).

occur from inappropriate stratification based on stage of disease. Staging of HCC is in fact plagued by an inordinate number of staging systems. At the time of the recent American Hepato-Pancreato-Biliary Association/American Joint Commission on Cancer (AHPBA/AJCC) Consensus Conference on Multidisciplinary Treatment of HCC staging [7], there were 18 different staging or scoring systems—or versions thereof—in use around the world. A major reason that HCC staging is difficult is that, to a greater extent in HCC compared with other cancers, prognosis after surgical treatment of HCC depends not only on tumor factors, such as size, number, and invasiveness (as are used in AJCC staging), but also on factors related to patient comorbidities, performance status, and quality-of-life scores, factors related to liver disease, factors related to etiology of disease (e.g., alcohol versus hepatitis B versus hepatitis C), and interactions between these groups of factors [7]. Whatever the reason—selection bias or a true finding—the many available data suggest that the rates of long-term survival and recurrence after transplantation are superior to those observed following resection (Table 1).

In the early history of liver transplantation from the 1960s through the 1980s, transplantation was considered to be indicated for primary liver tumors not resectable by subtotal techniques [8–10]. However, recurrence rates as high as 82% [10] and single-digit 5-year survival rates [9] were disappointing. Subsequently, the observation [10–12] that small HCC identified on pathologic evaluation

of explanted livers transplanted for other indications were associated with low recurrence rates and long-term survival led to the development of the above-mentioned Milan criteria. Patients meeting these criteria in the original study by Mazzaferro et al. had overall and recurrence-free 4-years survival rates of 85% and 92% percent, respectively, following liver transplantation [6]. These results have since been corroborated in subsequent series published in the 2000s, with recurrence rates as low as 2% and 5-year survival rates as high as 89% following liver transplantation for HCC (Table 1).

## 4. Advantages of Resection

*4.1. Easier.* Unfortunately, the high 5-year survival rates and the low recurrence rates possible following liver transplantation are available only to those patients waiting for a graft who actually get one, whereas resection is more easily and immediately available to all acceptable-risk patients. In fact, the national median waiting times based on Organ Procurement and Transplantation Network (OPTN) data as of December 2010 range from 140 days for American Indians to 651 days for Hispanics [13], during which time patients may drop out because of tumor or comorbid progression, death, or other reasons. Depending on the time period, type of analysis, and dropout criteria [14], the 1-year dropout rate for patients with HCC awaiting liver transplantation ranges from 12% to 38% [14–18]. When these dropouts were considered in one of the first intention-to-treat analyses [19], the 2-year survival decreased significantly from 84% to 54%. Although subsequent intention-to-treat studies accounting for dropouts have reported good 4-year survival rates of approximately 60% following transplantation for HCC [17, 18], other factors are not accounted for, such as socioeconomic barriers that may prevent many patients ever from being listed for transplantation. Resection, by contrast, is available more easily, widely, and immediately to all patients who can tolerate the operation. Not only is resection a modality that is easier for patients to obtain, but it is easier for surgeons to perform, since it almost never requires venovenous bypass and does not require transplantation fellowship training, which some but not all hepatobiliary fellowships include. Resection, however, should not necessarily be viewed as a mutually exclusive modality but rather a complementary one, since its easy availability makes it effective not only in achieving long-term survival, but also effective for use as both a selection tool for transplantation, and a bridge to transplantation, as discussed below.

*4.2. Effective.* Given the absence of randomized controlled trials comparing resection and transplantation, estimates of their relative effectiveness must at least be based on similar patient populations to avoid selection bias. To that end, several groups have studied transplantation-eligible patients, that is, patients meeting the Milan criteria for transplantation, who underwent resection, not transplantation. Such transplantation-eligible patients undergoing resection had 5-year survival rates of 70% at two large hepatobiliary centers [20, 21], a rate comparable with some of the best reported following liver transplantation (Table 1). In a more recent intention-to-treat analysis of 80 transplantation-eligible HCC patients who underwent resection compared to 293 patients listed for transplantation, 5-year survival was similar (66% and 58%, resp.) [22]. This is consistent with the observation in a 2009 review of nearly 60 series of resection and/or transplantation that the weighted mean of reported 5-year survival rates is similar for resection and transplantation: 48% and 52%, respectively [23].

Not only is resection effective at producing a 5-year survival comparable to that of transplantation, but in cases of recurrence—which is uniformly higher following resection compared with transplantation (Table 1)—transplantation remains an option. This strategy of salvage liver transplantation (SLT) has the advantage of limiting the impact on the available pool of donors since the majority of transplantation-eligible patients undergoing resection without recurrence would not draw from this valuable and limited resource of liver grafts.

Salvage transplantation was formally proposed first in 1998 by Llovet et al. [24], although several other authors were also studying this strategy around the same time [25–27]. Two simultaneously published articles in Annals of Surgery, by Adam et al. [28] and Belghiti el al. [29], popularized the approach in 2003, reporting disparate conclusions. Adam et al. compared 17 patients who underwent SLT for recurrence of HCC after resection with 195 patients following primary liver transplantation (PLT) and found significantly higher mortality (23.5%), shorter survival, and more recurrence in SLT patients compared to PLT [28]. Belghiti et al., by contrast, included an intention-to-treat analysis and found similar rates of complications, 5-year survival, and recurrence [29]. These latter results of Belghiti et al. have more recently been corroborated by other groups. Del Gaudio et al. reviewed the results of 227 cirrhotic patients with transplantation-eligible HCC: 80 who underwent liver resection and 147 liver transplantation [22]. Among the liver-resection patients, 49% recurred and of those who recurred, 69% were within the Milan criteria for transplantation, of whom 10 underwent SLT. Compared with patients who underwent primary transplantation, SLT patients had similar rates of complications, 5-year survival, and recurrence [22]. Cherqui et al. studied 67 transplantation-eligible patients who underwent resection and found that of 36 (54%) patients with a recurrence, 16 (44%) who underwent SLT had a 5-year survival rate of 70% [30].

*De principe* SLT is another strategy to minimize use of scarce liver grafts by using resection as a tool to select patients who, based on pathologic evaluation of the specimen, have risk factors for recurrence (e.g., microscopic vascular invasion, the presence of previously unrecognized small satellite nodules). The Barcelona Clinic Liver Cancer group has employed this strategy, finding it to be an effective way to improve the outcome of resected patients [31]. Of 17 patients who were candidates for either resection or transplantation, but who underwent resection, 8 were deemed high-risk and therefore offered immediate transplantation. Of 6 who agreed to *de prinicipe* SLT, 5 were transplanted and although 4 of these 5 had no pretransplantation evidence of HCC,

4 indeed were found to harbor unrecognized HCC in the explanted liver but were free of disease at a median follow up of 45 months [31].

The use of resection as an effective tool to select patients for *de prinicipe* SLT was corroborated by Scatton et al. who studied 93 patients who underwent curative-intent surgery for HCC, primary resection in 20 (all 20 of whom had well-compensated cirrhosis with a Model for End-Stage Liver Disease score of 8) and primary transplantation in 73 [32]. Six of the 20 resection patients underwent *de principe* SLT and 14 underwent SLT for actual recurrence. Not all 20 were within the Milan criteria at resection: Twelve (9 SLT and 3 *de principe*) were within and 8 (5 SLT and 3 *de principe*) were beyond the Milan criteria. The 20 patients undergoing resection followed by transplantation and the 73 undergoing PLT had 5-year survival rates (55% and 66%, resp.) that were statistically similar [32]. This study supports the notion that pathologic examination of resected specimens allows determination of which patients benefit most from an eventual transplantation, and allows the opportunity to perform it preemptively.

*4.3. Safer.* Not only is liver resection easier and as effective as primary transplantation, it is also likely safer. Although this claim is made with the understanding that there are no randomized controlled trials to support it, it is intuitively true, given that all transplantations are major and complex operations, even when done for small tumors. A liver resection for a small tumor, in a liver with well-compensated cirrhosis, however, is in general a lower-risk procedure, and can sometimes even be performed laparoscopically. In fact, a series of 163 liver resections for HCC (74% on cirrhosis) performed at 3 large European centers recently reported median operative time of 180 min, blood loss of 250 mL, and tumor size 3.6 cm, with a mean length of stay of 7 days [33]. A recent review of nearly 60 series of either transplantation, resection, or direct comparisons of the two modalities in the treatment of early HCC found that the weighted means of postoperative morbidity rates was nearly identical (44% for resection and 45% for transplantation), but mortality following transplantation was 60% higher than following resection (8% and 5%, resp.) [23].

While both resection and transplantation may be performed safely, resection has the additional advantage of delaying need for and risks associated with immunosuppression. These risks include toxicities (especially nephrotoxicity), infectious complications, and posttransplantation *de novo* neoplasms, among others. Nephrotoxicity is common after liver transplantation and adversely affects graft and patient survival [34]. Immunosuppression-related posttransplantation infection is a significant problem that is entirely avoided with resection. In a series of 1000 liver transplantations treated with tacrolilmus immunosuppression, posttransplantation infection was the most common cause of death (34% of 360 deaths) [35]. In cases of HCV-related HCC, reinfection of a new liver graft following transplantation is universal and serum HCV levels have been shown to increase 4- to 100-fold during treatment for acute rejection [36]. Posttransplantation neoplasms occur at a rate several-fold higher than age- and sex-matched individuals [37], and include skin cancers and lymphoma (up to 10-fold risk) [37–40], myelodysplastic syndrome [41], and other extrahepatic cancers, such as those of the head and neck, lung, and gastrointestinal tract [42].

*4.4. Simpler.* In addition to being safer, easier, and comparably effective relative to transplantation, resection has the advantage of simpler preoperative and postoperative management. Any patient being evaluated for either modality requires extensive workup regarding HCC and comorbid factors, but transplantation requires in addition an extensive preoperative process that includes myriad wait-list issues, psychosocial evaluation of recipients and live donors, and the universal emergent nature of the operations.

Bryce et al. [43] have studied the impact of sociodemographic factors on access to transplantation services and identified six stages that a patient must pass through prior to transplantation: disease occurrence, disease progression, disease diagnosis, referral for transplantation, listing for transplantation, and finally organ transplantation. Reasons preventing patients from completing all of these stages are numerous and include medical unsuitability for a transplantation, refusal of treatment, disparities/bias, and death. Using Pennsylvania state databases to collect sociodemographic and socioeconomic information, they linked data to records from five centers responsible for 95% of liver transplantations in Pennsylvania, and found that patients were significantly less likely to undergo evaluation, wait-listing, and transplantation if they were women, African American, or lacked commercial insurance [43]. Furthermore, these differences were greater during the early stages of the preoperative process (referral and listing) than for the final transplantation stage, where national oversight and review occur [43].

Postoperative management is similarly complex and requires a higher level of dedication, compliance, and investment of time, energy, and attention on the part of the patient than is possible for many patients, especially those of lower socioeconomic status. Noncompliance with immunosuppressive regimens and follow-up schedules has obvious risk for graft rejection and systemic toxicity and is more common in patients of low socioeconomic status [44]. Furthermore, for reasons that are not well defined, low-socioeconomic patients may also have worse survival following transplantation for HCC. In a study of 4735 patients identified in the OPTN database, although the survival of all patients with HCC improved *over time* regardless of racial, ethnic, and income groups, African American and low-income individuals had significantly poorer long-term survival compared to other socioeconomic groups [45].

## 5. Conclusion

Although liver transplantation provides the best recurrence-free survival and the best chance for a cure of HCC on well-compensated cirrhosis, due to the complete removal of all hepatic HCC disease and all oncogenic cirrhotic liver, the current (and likely future) shortage of available grafts,

and the increased risks and complexities associated with the pre-, intra-, and postoperative course of liver transplantation counterbalance this advantage of transplantation. Furthermore, in cases of recurrence (or high risk thereof)—the one clear disadvantage of resection—transplantation remains a safe option. Taken together, these arguments suggest that resection is easier, safer, simpler, and as effective compared with transplantation and therefore is the optimal first choice for patients with early HCC on well-compensated cirrhosis.

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*Review Article*

# APASL and AASLD Consensus Guidelines on Imaging Diagnosis of Hepatocellular Carcinoma: A Review

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Consensus guidelines for radiological diagnosis of hepatocellular carcinoma (HCC) have been drafted by several large international working groups. This article reviews the similarities and differences between the most recent guidelines proposed by the American Association for Study of Liver Diseases and the Asian Pacific Association for the Study of the Liver. Current evidence for the various imaging modalities for diagnosis of HCC and their relevance to the consensus guidelines are reviewed.

## 1. Introduction

Consensus guidelines have been drafted by several large international working groups on different occasions in an attempt to standardise the surveillance, diagnosis, and management of HCC. Of the major working groups, the European Association for the Study of the Liver was the first to establish consensus guidelines on the clinical management of HCC following the Barcelona European Association for the Study of the Liver (EASL) Conference in 2000 [1]. The American Association for Study of Liver Diseases (AASLD) adapted these recommendations to issue a set of consensus recommendations in 2005 [2]. This was more recently updated in 2010 [3]. The Asian Pacific Association for the Study of the Liver (APASL) itself also developed a set of consensus recommendations in December 2008 [4].

The rationale for a set of guidelines on management of the growing problem of HCC is several fold. Firstly, it aims to maximise healthcare resources when targeting large populations at risk, based on current evidence-based practice. Secondly, it allows for a standardised method of diagnosis in the era of computed tomography (CT) and magnetic resonance imaging (MRI). Lastly, it provides clinicians with a guide to the treatment of HCC.

Establishing universal guidelines for imaging diagnosis of HCC can be challenging, particularly in the lesions that do not display classical imaging features. Nevertheless, imaging diagnosis of HCC is important because it is noninvasive, given that the incidence of needle tract tumour seeding following biopsy of HCC is small but not negligible (overall 2.7%, or 0.9% per year) [5], while the risk of significant haemorrhage-related complications following image guided liver biopsy is 0.5% (based on a retrospective review of 3636 percutaneous core biopsies performed at a single institution) [6]. Furthermore, it allows for proper delineation of extent of disease, which impacts on the type of treatment, including local ablative therapy, such as radiofrequency ablation, transhepatic arterial chemo-embolisation (TACE), surgery or transplant. It can allow for accurate localisation of tumour foci, making it possible for local ablative therapies and proper surgical planning.

The purpose of this paper is to review the similarities and differences between the more recent guidelines on radiological diagnosis of HCC as proposed by the APASL and the AASLD.

## 2. Radiological Diagnosis of HCC

The use of imaging in HCC diagnosis can be best divided into two main categories. The first is in the surveillance of patients at high-risk for developing HCC. The second is

in the diagnosis of HCC based on an abnormal screening test.

## 3. Surveillance

Prospective screening of patients at high-risk of developing HCC increases the proportion diagnosed with potentially curable disease. A screening strategy should focus on those patients with chronic HBV or HCV virus infection that has progressed to cirrhosis since more than 40% of these patients will develop HCC [7].

As for the time interval between surveillance tests, both the AASLD and APASL recommend measurement of serum alpha-fetoprotein (AFP) levels combined with grey-scale ultrasound (US) of the liver for surveillance of HCC [3, 4] at 6-monthly intervals for HBV carriers and patients with chronic hepatitis, since it has been shown on metaregression analysis to demonstrate a significantly higher sensitivity for early HCC with US every 6 months than with annual surveillance [8, 9]. Although detailed discussion regarding the serological markers for HCC are beyond the scope of this paper, brief mention needs to be made with regards to AFP since it is the single most commonly used serologic marker for HCC.

As with all diagnostic tests, the sensitivity profile of AFP is reduced when a higher threshold is applied in order to improve specificity. On its own, AFP is not sufficient as a screening test for HCC [10]. Taking the most commonly report cut-off of 20 ng/mL, AFP carries a sensitivity of 41–65% and a specificity of 80–94% [11]. Particularly in high-risk patients, it has a low positive predictive value of around 25% [12].

US screening is superior to alpha-fetoprotein assay for detection of HCC [13]. Combined AFP and US further increases detection rate [14]. As such, combined use of AFP monitoring and US is recommended, in patients with chronic HCV [15, 16] as well as HBV, where it has been found to reduce mortality (37–41%) [17, 18]. Despite the higher sensitivity and specificity of CT and MRI for detection of HCC [19], these have not been validated for and are therefore not currently recommended for screening.

## 4. Imaging Diagnosis

A feature common to the APASL and AASLD guidelines is that the recommendations for imaging diagnosis of HCC are to be interpreted in the context of patients at high-risk for HCC [3, 4]. This would include patients with liver cirrhosis and those with chronic HBV infection without definite cirrhosis. It is important to make this distinction, since the guidelines may not necessarily apply to the general population.

*4.1. Classical Imaging Features.* There is little disagreement between the consensus guidelines of the APASL and the AASLD on the definition of imaging features of classical HCC. The presence of arterial hypervascularity and washout are generally considered to be highly specific for the diagnosis of HCC, and shall henceforth be referred to as "classical imaging features" [20]. In particular, this enables differentiation from intrahepatic cholangiocarcinoma, which shows delayed enhancement [21]. At the time of the EASL guidelines in 2001, the importance of "washout" was not fully appreciated, hence not included. However, this is now specifically emphasized as a crucial feature in the APASL and AASLD guidelines.

Arterial hypervascularity is defined as increased enhancement of the lesion in the hepatic arterial phase of imaging relative to the background liver. This is based on the fact that HCC receives predominant vascular supply via the hepatic artery. A precontrast and a dynamic postcontrast scan of the liver is necessary to demonstrate this on imaging.

"Washout" of the lesion is based on the fact that HCC contains predominantly arterial blood and so, by the time portal venous and delayed images are acquired, the lesion is observed to be hypoattenuating on CT (or in the case of US, "hypoechoeic" and in the case of MRI, "hypointense") to the surrounding liver at the portal venous or equilibrium phase. Washout can be explained in terms of tracer kinetic modeling of a lesion with high proportion of intravascular space [22] For demonstration of washout, the delayed phase has been shown to be superior to the portal venous phase, both for CT and MRI; this is estimated at 2-3 minutes following injection of intravenous contrast agents [23, 24]. The timing of the scans are important, and this has led to the recommendation that imaging be performed in specialised centers [25].

The presence of elevated AFP greater than 200 ng/mL is no longer required under the revised AASLD guidelines, as it is recognised that there are inherent false-positives (in cirrhotic patients) and false negatives [3, 25]. Detailed discussion on the role of AFP is beyond the scope of this paper, although the limitations of AFP as a serologic marker for HCC has previously been alluded to.

Despite the abundant use of multidetector row technology, CT may underestimate the extent of disease in around 50% of cases [26]. Although it has been established in that MRI is superior in the detection of HCCs, particularly the lesions smaller than 2 cm in size [27, 28], neither the APASL nor the AASLD recommends the use of MRI over CT for staging of disease. In the study by Pitton et al. where direct comparison between MRI and 64-row CT, MRI was significantly more sensitive in detecting tumour nodules [29]. However, the decision to use MRI over CT can be limited by its relatively high cost and technical demand.

*4.2. Atypical Imaging Features—AASLD Guidelines.* Most of the differences between the AASLD and APASL guidelines for the radiological diagnosis of HCC lie in the approach to lesions that do not demonstrate the classical imaging features of HCC. The AASLD essentially does not recognise use of nonvascular imaging criteria, and in the absence of the classical arterial hypervascularity and venous washout pattern of HCC, further evaluation is necessary. While this makes the AASLD guidelines more applicable to transplant guidelines (Milan and UCSF criteria), where diagnoses were based on vascular enhancement pattern of HCCs [30, 31], it may also lead to understaging of disease [3].

Often, the lesions that do not conform to the classical imaging features are better differentiated and smaller than 2 cm in size. These "early" HCCs have been shown to contain not only fewer portal tracts but also fewer arterioles [32]. This is reflected by their atypical imaging appearances, where 87% of well-differentiated lesions and 41–62% of lesions smaller than 2 cm showed either absence of arterial hypervascularity, venous washout, or both (Figure 1) [33, 34]. Importantly, these are the lesions that should be the target of surveillance and diagnoses, since they can be ablated with high likelihood of cure [25].

Conversely, for the larger lesions, even in the absence of the classical imaging features, size alone is a risk factor [34]. In the series by Yu et al. in patients with known HBV-induced cirrhosis, lesions with a spherical contour greater than 2 cm were found to have high malignant potential, despite lack of arterial hypervascularity [35]. Indeed, the classical enhancement features for HCC in large lesions may be confounded by the presence of central necrosis and lesion heterogeneity ("nodule-in-nodule" appearance) [36].

In the revised AASLD guidelines, lesion size continues to predominate, though less so compared to the earlier edition. In the earlier AASLD guidelines, any lesion greater than 2 cm in size and demonstrates classical imaging features can be treated without biopsy. For lesions that were between 1 to 2 cm in size, two imaging modalities, rather than one, with classical features were needed to confirm the presence of HCC and avoid biopsy. This has been recently revised such that any lesion larger than 1 cm that demonstrate the classical pattern of HCC can be deemed as such and treated accordingly without biopsy. This is because as with the larger lesions, the approach of using a single imaging technique for lesions that are between 1 to 2 cm yields acceptable results [37–39].

In the presence of atypical findings from a single imaging test (CT or MRI), the AASLD recommends a different imaging modality (CT or MRI) for further assessment. This has been validated by Khalili et al. in which single imaging scans were found to have similar specificity (91–99%) to two coincidental positive scans (91–100%) with much less resource utilization and higher sensitivity (74–89% versus 53–62%) [38]. However, if atypical findings are again demonstrated, biopsy is recommended. Biopsy restores the specificity of imaging to 100% where any of the findings are atypical [40]. Note that contrast-enhanced ultrasound (CEUS) is not considered to be specific enough (besides the fact that the CEUS agents are not commercially available in the United States) and is excluded from the revised AASLD guidelines [3].

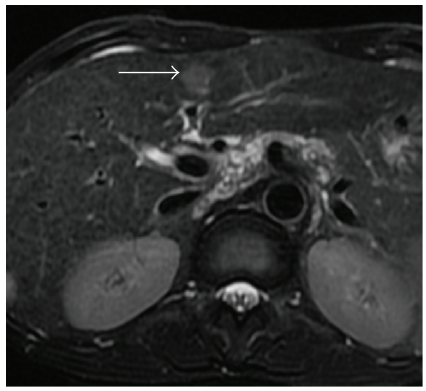
Even though the majority of cirrhotic nodules smaller than 1 cm are benign [3], Kim et al. found that in patients with mild cirrhosis related to HBV, HCCs were present in two-thirds of hypervascular lesions smaller than 1 cm [41]. As such, in lesions smaller than 1 cm, the specificity of imaging for HCC is limited [42], and based on AASLD guidelines, these cannot be regarded as HCC, regardless of the enhancement pattern. A foreseeable problem with imposing this size criteria is that it can pose dilemma in clinical practice, since it has been shown that subcentimetre lesions can be diagnosed, particularly with MRI [43].

Instead of aggressively chasing the diagnosis through biopsy for lesions smaller than 1 cm (which in itself can be technically challenging due to size), close interval followup in 3 months using the modality that best depicts the lesion is recommended. Here, the guidelines may be debated. It has been suggested that for among hypervascular nodules smaller than 1 cm, those smaller than 5 mm, are subcapsular in location, wedge shaped, or ill defined (more likely to represent vascular shunts) a 6-month followup is sufficient, but when the nodule is round, oval, intraparenchymal, or in a dominant mass (more suspcious for HCC), closer imaging followup at 3-monthly intervals should be performed [44]. This may reduce unnecessary imaging but requires further validation. Typically, nodules are declared benign only if they regress or remain stable for two years, since HCC nodules can grow very slowly [2].

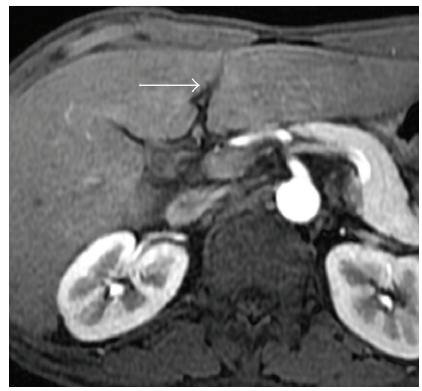
*4.3. Atypical Imaging Features—APASL Guidelines.* The APASL guidelines approach the atypical lesions in different manners. Essentially, these focus on Kupffer cell density as a marker of benignity. It has been shown that Kupffer cell density decreases with dedifferentiation of the cirrhotic nodule [45, 46] and is reflected by two different classes of imaging contrast agents. The first is a second generation CEUS agent containing perfluorobutane microbubbles (Sonazoid, GE Healthcare); its use is currently limited as it is not available outside of Japan. The other is superparamagnetic iron oxide (SPIO) MR contrast agents, namely ferucarbotran (Resovist, Bayer) and ferumoxide (Feridex, AMAG pharmaceuticals). Since normal liver tissue contains Kupffer cells, which are in turn part of the reticuloendothelial system, malignant lesions can be reliably differentiated from nontumourous liver based on the fact that they do not contain Kupffer cells.

The APASL guidelines basically divides the atypical lesions into those that are hypervascular (and do not demonstrate washout) and those that are hypovascular (and do not show arterial hypervascularity). For hypervascular lesions that do not demonstrate washout, early HCCs can be reliably differentiated from focal nodular hyperplasia and arterioportal shunts based on differential uptake of Kupffer-specific contrast agents. On the parenchymal phase of imaging, HCCs should appear as unenhanced areas on CEUS and as T2*-hyperintense lesions on SPIO-enhanced MRI. However, a foreseeable limitation is in the characterisation of other hypervascular malignancies, such as neuroendocrine carcinoma metastases.

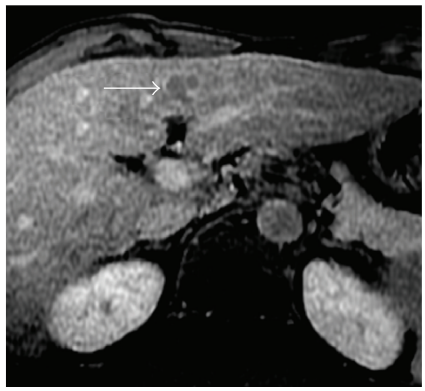
The approach to the hypovascular lesion is a little more complex, while at the same time, the differential list for this includes a larger group of hepatic malignancies, including intrahepatic cholangiocarcinoma and metastases. Basically, if the lesion is initially shown to be hypovascular on CT and MRI, CEUS may be attempted to demonstrate enhancement in the hepatic arterial phase. If this is shown to be true, the lesion may be deemed HCC. Alternatively, if Kupffer-specific imaging demonstrates a relative lack of uptake, the lesion can be regarded as HCC. Again, the limitation of



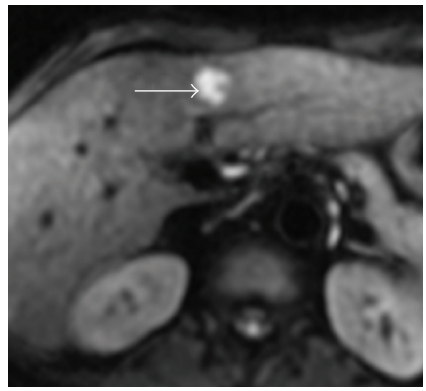
(a) Axial fat-saturated respiratory triggered T2-weighted fast spin echo image (TE 80 msec) shows a mildly hyperintense 1.2 cm lesion (arrow) in segment 4



(b) Axial contrast-enhanced fat-suppressed T1-weighted spoiled gradient recalled echo (LAVA) image of the liver at the same level, taken at 20 seconds following injection of standard dose of intravenous contrast (Dotarem, Guerbet) shows no appreciable enhancement in the expected site of the lesion (arrow)



(c) Axial LAVA image in the delayed phase (180 seconds postinjection) shows the lesion (arrow) as hypointense to the surrounding liver, consistent with washout



(d) On the axial DW image (b = 500 s/mm$^2$), the lesion (arrow) is hyperintense. This was correspondingly hypointense on the ADC map (not shown), consistent with restricted diffusion

Figure 1: HIV positive patient with chronic HBV infection without known liver cirrhosis. By the AASLD and APASL guidelines, this lesion would require further evaluation. CT done prior to the MRI also failed to demonstrate arterial hypervascularity. Note, however, that the lesion showed suspicious features on T2-weighted and DW imaging. The lesion was biopsied percutaneously under ultrasound guidance and showed to represent a well-differentiated HCC.

such an approach is that the other concomitant hypovascular lesions such as adenocarcinoma metastases are not definitely excluded.

Although CT arterial portography and CT hepatic arteriography (CTPA and CTHA) are considered to be significantly more sensitive for demonstrating the early vascular changes in small HCCs [47], these are invasive and the expertise for these procedures is not readily available in many centres around the world.

The ensuing sections will briefly review various imaging modalities used in diagnosis and assessment of HCC; some of these are included in the current APASL guidelines, the rest are meant to inform the reader of recent advances in imaging of HCC that may potentially be integrated into future diagnostic imaging algorithms.

*4.4. Kupffer Specific Imaging: Sonazoid CEUS and SPIO Agents.* Given that the APASL recommends the use of Kupffer-specific agents (Sonazoid and SPIO agents) for lesion characterisation, a more detailed discussion on the utility of these contrast agents needs to be made. However, in part because neither Sonazoid nor currently commercially available SPIO agents are approved by the United States Food and Drug Administration (FDA) for clinical use, these are not included under the diagnostic algorithm by the AASLD. CEUS on its own is an accepted imaging modality for HCC diagnosis under the APASL guidelines and this has been validated even for lesions smaller than 2 cm [37]. Jang et al. showed that the sensitivity, specificity, and accuracy of CEUS for diagnosing HCC was 87%, 100%, and 93%, respectively, [48].

Inherently, the enhancement patterns of lesions on CEUS reflect tumour microvascular morphology, making it a valuable method for predicting the histological grade [49] while providing valuable information for antiangiogenic therapy [50]. The keys limitations of CEUS are that it is operator dependent and has decreased sensitivity in obese patients and lesions far from the skin surface [51]. Furthermore, the phenomenon of "washout" on CEUS is less specific for HCC than it is with CT or MRI, due to significant overlap between nearly all malignant and some benign lesions. Washout in CT or MRI is determined by contrast dynamics in both the intravascular space and the interstitium whereas CEUS washout is predominantly related to contrast dynamics in the intravascular space (Figure 2). Moderately differentiated HCC generally shows classic enhancement features, while well-differentiated and poorly differentiated tumours account for most atypical variations [52].

Adding Kupffer-specific phase imaging to CEUS protocols may yield additional information that can be used to further assess histologic grades of tumour and enable better characterisation among dysplastic nodules, moderately-differentiated and poorly differentiated HCCs [45]. As with SPIO imaging, Kupffer-specific imaging enables detection of all moderately and poorly differentiated HCCs [46]. The reader should however bear in mind that these findings are read in the context of patients at high-risk for HCC development. Kupffer phase imaging itself remains nonspecific, since even benign lesions, such as haemangiomas, that do not contain Kupffer cells, will appear as hypoechoeic on Kupffer-specific phase of CEUS.

Similarly, use of SPIO has been shown in multiple studies to improve accuracy of MRI for detection of HCCs. However, detailed discussion of the SPIO agents will be avoided since these are currently out of production, except to say that experience with SPIO agents thus far had been promising and that it potentially improves imaging detection of HCCs [40, 53, 54]. Combined gadolinium chelate and SPIO MRI, termed "double contrast" MRI, is technically more cumbersome, even though it appears to increase the tumour to liver contrast to noise ratio, and therefore sensitivity, over multiphasic CT [55, 56] routine Gd-enhanced MRI [57], or SPIO-enhanced MRI [58, 59].

### *4.5. Imaging of Tumour Thrombosis in HCC: Worth a Look?*

Although important for staging and treatment decision making, assessment of portal vein thrombosis for tumour involvement is currently not considered in both the APASL or AASLD guideline recommendations. Image guided percutaneous biopsy of suspected portal vein tumour thrombosis is feasible but invasive [60]. It may be possible to apply the same (AASLD or APASL) criteria used in diagnosis of HCC nodules to the vessel of interest to determine tumour involvement, but this does not appear to have been well studied. Separate guideline recommendations may be necessary.

Various noninvasive techniques have been investigated, and among them, CEUS appears to show fairly good success [61], superior to that of CT [62]. CEUS itself carries a sensitivity of 88% for diagnosing malignant portal vein thrombosis [63]. Combining CEUS and CT, Sorrentino and colleagues found 100% positive predictive value if both imaging modalities demonstrated arterial hypervascularity within the thrombi. In that study, the overall sensitivity of imaging for malignant thrombosis was 75% [64]. In the small series by Sun et al. 18-FDG PET may discriminate between benign and malignant portal vein thrombi but larger numbers are necessary [65]. Based on the absolute ADC values, diffusion-weighted (DW) MRI shows promise for discriminating between bland and tumour portal vein thrombi [66], but has not been fully validated.

### *4.6. Hepatocyte-Specific MRI Agents, DW MRI and Positron Emission Tomography (PET): On the Horizon?*

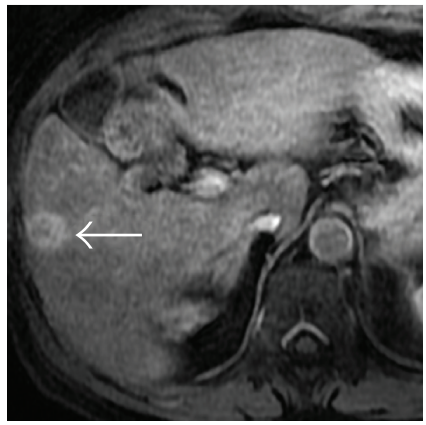
Functional imaging of HCC is fast becoming a reality and a brief mention of some of these techniques shall be made. Hepatocyte-specific gadolinium chelate agents are relatively new and are not currently included in the guideline recommendations. Gadoxetic acid (Gd-EOB-DTPA, Primovist, Bayer) and gadopentetate dimeglumine (Gd-BOPTA, Multihance, Bracco) are two such contrast agents that have been shown to improve diagnosis of HCC, showing diagnostic performance similar to or better than SPIO [67, 68] and comparable to double contrast MRI [69].

Hepatocyte-specific gadolinium chelate agents allow for multiphasic dynamic contrast-enhanced MR imaging to be combined with the hepatocyte-specific phase. These require delayed scanning of approximately 20 minutes in the case of Gd-EOB-DTPA and 60–120 mins in the case of Gd-BOPTA to provide maximal lesion to liver contrast [70]. Specifically, they may be used to differentiate HCCs from the arterial enhancing pseudolesions and are recommended for diagnosis of focal nodular hyperplasia [71, 72]. Like SPIO agents, they may allow for characterisation of the degree of tumour differentiation [73].

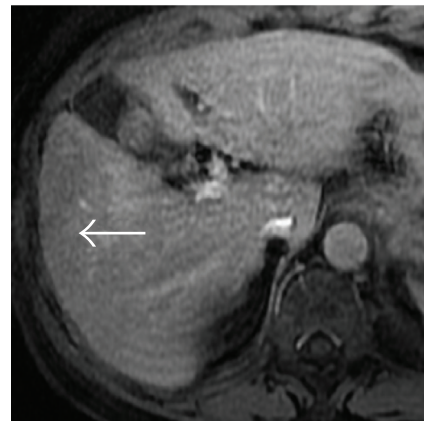
Gd-BOPTA-enhanced MRI with hepatocyte-specific phase imaging improves diagnosis over routine multiphasic CT or MRI [74], with quoted sensitivity and specificity rates of 97% and 88%, respectively, [75, 76] (Figure 3). Gd-EOB-DTPA-enhanced MRI is also superior to CT, with reported accuracy of 0.88, compared to 0.74 in CT [77–79]. Between the two agents, Gd-EOB-DTPA was more sensitive than Gd-BOPTA for HCC detection (86% compared to 64%) [80], perhaps related to the fact that the extent of hepatobiliary uptake is considerably less with Gd-BOPTA (5% versus 50%).

Combining Gd-EOB-DTPA-enhanced MRI and Sonazoid CEUS detected 73% of the nodules not detectable by multiphasic CT [81]. It may also be combined with diffusion-weighted (DW) MRI to improve diagnosis [82]. However, assessment for lesions smaller than 1 cm can be still poor (sensitivity of 29–43%) [83], and hence further experience is necessary with these hepatocyte-specific agents before they are included in imaging guidelines.

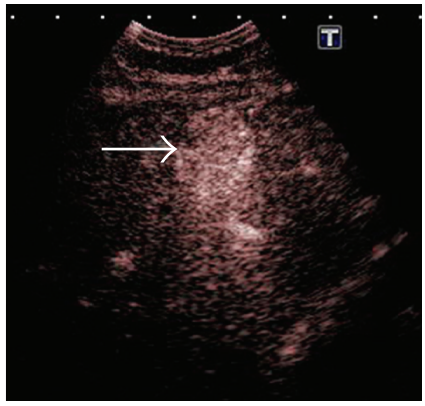
DW MRI studies the random motion of water molecules and shows promise for detection and characterisation as well



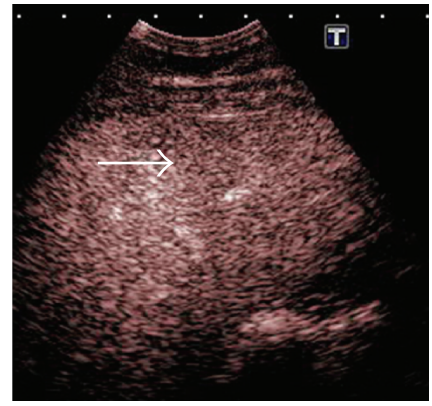
(a) Axial LAVA image in the arterial phase shows a hypervascular lesion (arrow) in segment 5/6



(b) Axial LAVA image at 3 minute delay shows no significant washout in the expected location (arrow) of the lesion. This would be deemed atypical based on consensus criteria



(c) CEUS (SonoVue, Bracco) demonstrates avid arterial enhancement within the lesion (arrow) at 18 seconds

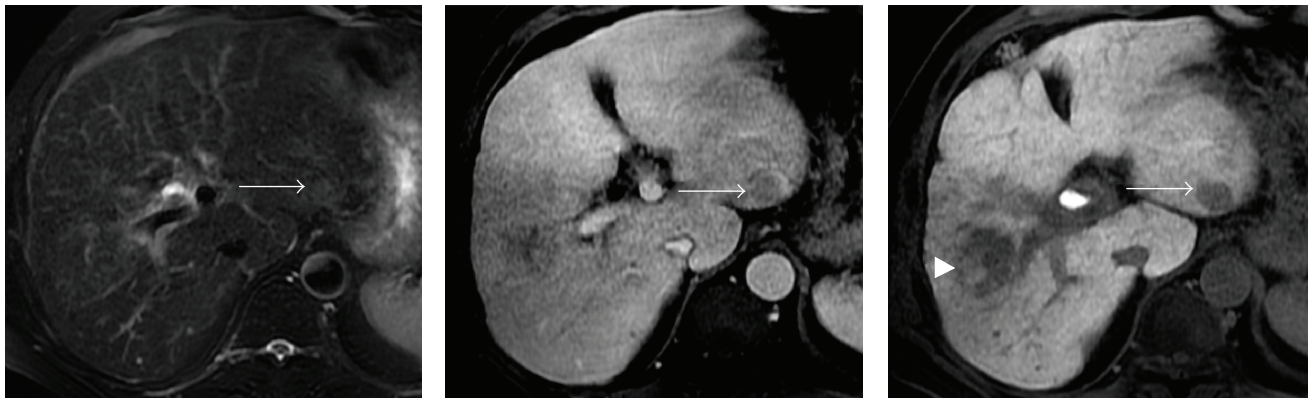


(d) The lesion showed rapid washout, become mildly hypoechoeic (arrow) to the surrounding liver at 35 seconds, consistent with HCC. CEUS is not considered in the revised AASLD guidelines; by APASL criteria, this satisfies criteria for HCC. Histology confirmed moderately differentiated HCC

Figure 2: Patient with chronic HCV infection found to have a 2 cm hypoechoeic nodule on surveillence ultrasound scan. Both CEUS and multiphasic contrast-enhanced MRI were performed.

as posttreatment assessment of tumours [84]. It improves MR detection of HCCs, particularly in lesions smaller than 2 cm [85], with sensitivities of 84–98% compared to 76–85% for multiphasic MRI alone [86–88]. Potentially, objective measurement of the apparent diffusion coefficient (ADC) may allow for distinction between the different tumour grades [89, 90]. It can be combined with SPIO-enhanced MRI, raising sensitivity from 66% to 70%, while maintaining high specificity of 98% [91]. DW MRI also shows potential for assessment of treatment response to local ablative therapies [88, 92]. Its role in the diagnostic algorithm is not certain at this point, although, given the promising results and its ease of implementation in routine clinical practice (due to fast acquisition times, no needs for additional hardware and ease of interpretation), incorporation into future guidelines is anticipated.

$^{18}$Fluorodeoxyglucose (FDG) PET is generally accepted to have low sensitivity (50–68%) for intrahepatic HCC [93–95] and is therefore not considered to be useful for diagnosis of HCC, except perhaps in cases of poorly differentiated HCC where it may show better results [96]. Dual tracer imaging with the addition of $^{11}$C-acetate improves sensitivity for intrahepatic disease from 37–49% for 18-FDG and 11-C alone to 90% when combined [97]. The role of 18-FDG is limited to evaluation of extrahepatic disease [98], with sensitivity of 13–84%, depending on the size of the lesions [99]. Newer tracers such as $^{18}$F-choline [100] and$^{18}$F-thymidine [101] have shown slightly better results, but further experience is needed. At present, PET plays a small role in imaging assessment of HCC, but tumour-specific tracers may be the key to its use in future.



(a) Axial fat-saturated respiratory triggered T2-weighted fast spin echo image (TE 80 msec) does not reveal abnormal signal focus in the left lobe, even on retrospective review

(b) Axial LAVA image in the portal venous phase shows a questionable focus of mixed intensity (arrow) in segment 3. This was mainly due to pulsation artefact from the abdominal aorta. No enhancement was seen in the corresponding section on hepatic arterial phase imaging (not shown)

(c) Axial LAVA hepatocyte-specific phase image at 20 min post injection confirms the presence of a 2.2 cm lesion (arrow) in the subcapsular region of segment 3. Given the size, HCC is highly suspected, even in the absence of classical imaging features. Note partially treated lesion in the right lobe (arrowhead)

Figure 3: Chronic HBV patient with known multifocal HCC presumed to be confined to the right lobe, completed one session of TACE. US suggested possible nodule in the left hepatic lobe, but this was occult on multiphasic CT. MRI with standard dose of Gd-EOB-DTPA was performed.

## 5. Summary

Our understanding of the pathophysiology of HCC has improved tremendously over the past decade. This has been paralleled by advancements in US, CT and MRI technology, along with development of various Kupffer- and hepatocyte-specific imaging contrast agents. As the treatment of HCC becomes more sophisticated, a greater need for highly accurate diagnosis is necessary. The consensus recommendations by the AASLD and APASL on the radiological diagnosis of HCC underscore the push for noninvasive diagnosis of HCC in avoidance of biopsy.

While there is general consensus with regards to the surveillance for HCCs in high-risk patients, pertinent differences in the recommendations for imaging diagnosis of HCC exist. These reflect the differences in the availability of diagnostic imaging resources in different regions. For example, Sonazoid is not available for use outside of Japan and is therefore unique to the APASL guidelines. In a way, they also point to differences in practice patterns and the controversies in our understanding of "early" HCC. The AASLD guidelines demand that the classical enhancement features of HCC are demonstrated, accepting that this may limit sensitivity; biopsy is regarded as a means to restore sensitivity. On the other hand, the APASL guidelines emphasizes the use of Kuppfer specific imaging techniques to improve diagnostic performance.

With rapid and continual improvement in diagnostic imaging modalities and validation of these guidelines, further refinements to the diagnostic algorithm can be expected in the near future. At present few of the established techniques have fallen out of favour; SPIO agents are on the decline due to decreased clinical usage, while double contrast MRI, CTHA and CTAP are cumbersome to perform and not compatible with routine clinical practice.

Hepatocyte-specific MRI contrast agents are increasingly used in the United States, Europe and parts of Asia, as well as DW imaging, which is now already widely applied in routine clinical practice, demonstrate great promise to improve current methods of imaging diagnosis. However, before these can be incorporated into the imaging algorithms, validation of their utility is necessary. Similarly, the utility of imaging for other important aspects of HCC management, such as for noninvasive diagnosis of portal vein tumour thrombosis, may also need to be addressed in time to come.

## Conflict of Interests

The authors have no conflict of interests to declare.

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*Case Report*

# Liver Resection after Downstaging Hepatocellular Carcinoma with Sorafenib

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*Background*. Sorafenib is a molecular-targeted therapy used in palliative treatment of advanced hepatocellular carcinoma in Child A patients. *Aims*. To address the question of sorafenib as neoadjuvant treatment. *Methods*. We describe the cases of 2 patients who had surgery after sorafenib. *Results*. The patients had a large hepatocellular carcinoma in the right liver with venous neoplastic thrombi (1 in the right portal branch, 1 in the right hepatic vein). After 9 months of sorafenib, reassessment showed that tumours had decreased in size with a necrotic component. A right hepatectomy with thrombectomy was performed, and histopathology showed 35% to 60% necrosis. One patient had a recurrence after 6 months and had another liver resection; they are both recurrence-free since then. *Conclusion*. Sorafenib can downstage hepatocellular carcinoma and thus could represent a bridge to surgery. It may be possible to select patients in good general condition with partial regression of the tumour with sorafenib for a treatment in a curative intent.

## 1. Introduction

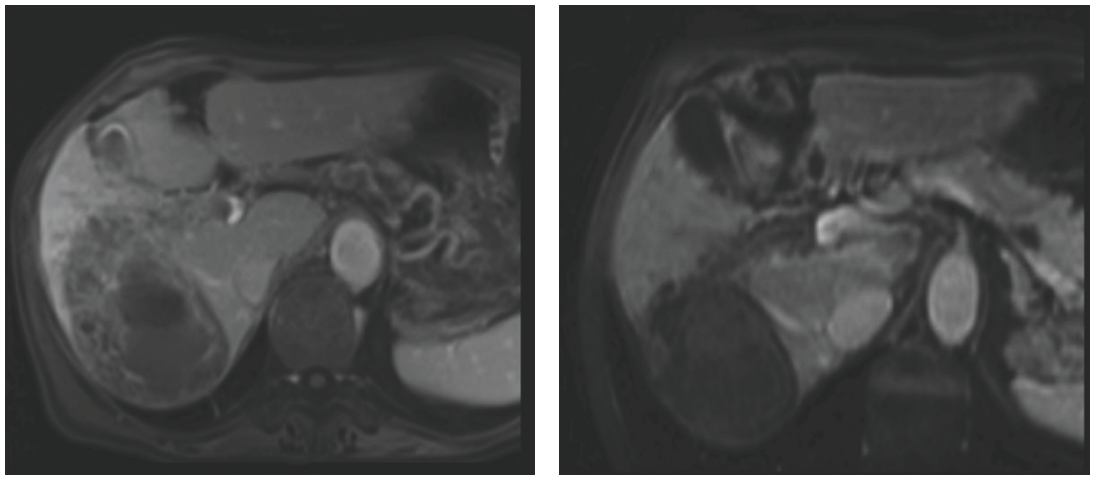
Hepatocellular carcinoma (HCC) represents one of the highest causes of cancer-related death. Recent advances have been made for advanced HCC (extrahepatic spread or major vascular invasion) with molecular-targeted therapies [1] such as sorafenib (Nexavar, Bayer), which has been indicated as a palliative therapy in Child A patients since a benefit in median survival and time to radiologic progression has been shown in 2 large international trials [1, 2].

We report here the cases of 2 patients who were treated with sorafenib with a palliative intent but eventually had a resection after good clinical and radiological response. This is, to our knowledge, the first report of resection surgery after sorafenib.

## 2. Case Reports

*2.1. Case 1.* A 56-year-old man presented with asthenia, right subscapular pain, weight loss, and malaise with hypoglycaemia. He had a significant history of chronic alcoholism. The laboratory tests showed normal platelet count, polycythaemia, prothrombin time of 79%, liver cytolysis, and cholestasis with total bilirubin of 43 $\mu$mol/L. Alpha-foeto-protein (AFP) was 282,500 ng/mL, and anti-HCV antibodies were positive with high virus levels. MRI (Magnetic Resonance Imaging) showed (Figure 1(a)) a 120 mm hypervascular tumour of the right liver with a right portal branch tumoral thrombosis reaching the bifurcation. There was no sign of extra-abdominal spread. The lesion had all radiological features of HCC (i.e., hypervascular with portal phase washout). The middle hepatic vein was free of invasion.

The HCC was considered as nonresectable because of the extension of the portal thrombus and its neoplastic features [3], and a palliative treatment with sorafenib (800 mg per day, total dose received = 216 g) was initiated. Nine months later, the patient was in a better general condition. Sorafenib was well tolerated (neither gastrointestinal symptoms nor



(a) (b)

Figure 1: *MRI of patient 1.* (a) Before treatment. (b) After 9 months of treatment with sorafenib.

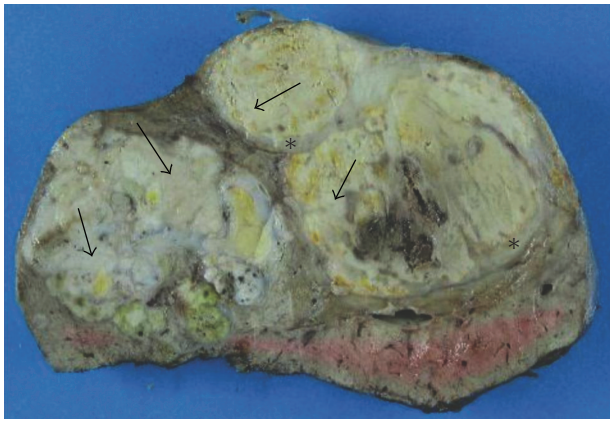


Figure 2: *Macroscopic aspect of patient 1's surgical specimen.* Transverse section of the liver after fixation in 4% formaldehyde. The tumour has several nodules, with a focal capsule (∗), and white areas corresponding to necrosis (arrows).

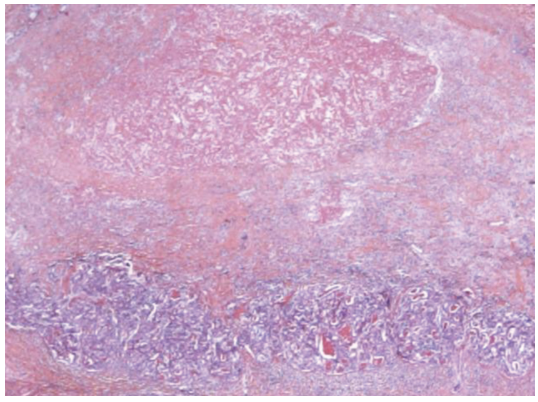


Figure 3: *Microscopic examination of patient 1's specimen* at ∗10 magnification after hemalun eosin safran coloration. Bottom of the figure shows the HCC with a pseudoglandular aspect; top shows an eosinophilic irregular area corresponding to necrosis.

skin rash or hand-foot syndrome). Hemoglobin was normal; there still were cytolysis and cholestasis; AFP was 15,600 ng/mL.

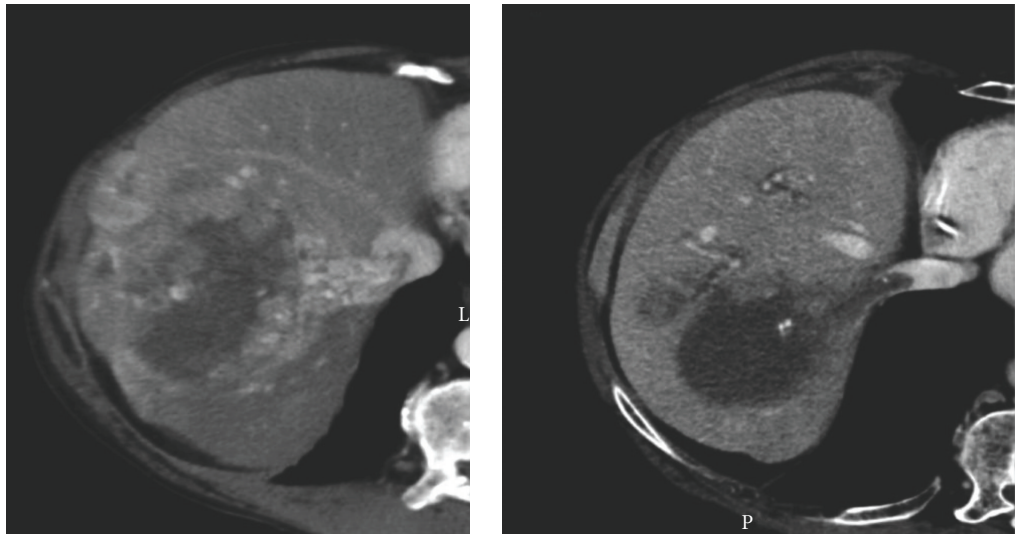
An MRI (Magnetic Resonance Imaging) (Figure 1(b)) and a new CT scan showed a 88 mm in diameter tumour (decrease in size of 27%) with a necrotic component. The portal thrombus was necrotic as well, and the left portal branch was still free of invasion. The response was classified treatment effect (TE) 3 (partial response) in the RECICL classification [4]. A biopsy in the left lobe found chronic hepatitis lesions without cirrhosis (METAVIR score A1F1). A surgical treatment was proposed 1 month after cessation of sorafenib.

At laparotomy, neither ascitis nor peritoneal carcinomatosis was seen. Frozen biopsies of hilar adenomegalies were performed to rule out an extrahepatic spread and showed no malignant cells. The main tumour was found in segments VI, VII, and VIII with daughter lesions. The liver appeared to be fibrous but not cirrhotic. We performed a right hepatectomy extended to a part of segment IV with a total of 30 minutes pedicular clamping and the use of hanging manoeuvre.

The macroscopic (Figure 2) and microscopic (Figure 3) histopathological examination showed an HCC with a pseudoglandular aspect and necrosis (around 35% of the tumour). Microvascular emboli were found. There were no tumour cells on resection margins (<1 mm between tumour and resection limits). The right portal branch thrombus was totally necrotic. Nontumoural liver was METAVIR A1F3/F4.

The postoperative course was uneventful. One year later, the patient had a recurrence in the anterior segment IV that was previously left in place. A partial segmentectomy was performed, and the patient is in remission 6 months after the second surgery.

*2.2. Case 2.* The second case is a 68-year-old male patient with a Child-Pugh A cirrhosis of alcoholic origin, weaned for 1 year and with grade 1 oesophageal varices. Pain in




(a) (b)

Figure 4: *CT scan of patient 2.* (a) CT scan before treatment. (b) Reassessment CT scan after 9 months of treatment with sorafenib.

Table 1: Summarize of patients' characteristics.

| Case | Before treatment | | | Sorafenib | | Reassessment | | Histology | |
|---|---|---|---|---|---|---|---|---|---|
| | Size (mm) | Thrombus | AFP (ng/mL) | Daily dose (mg) | Time (months) | Size (mm) | AFP (ng/mL) | Thrombus | Tumour |
| 1 | 120∗80 | Right portal branch | 282,500 | 800 | 9 | 88∗60 | 15,600 | necrotic | 35% necrosis, thrombus necrotic |
| 2 | 100 | Right hepatic vein | 3,500 | 800 | 9 | 75 | 9 | necrotic | 60% necrosis, thrombus necrotic |

the right hypochondrial area revealed a 100 mm in diameter HCC taking up the whole right liver with a neoplastic thrombus of the right hepatic vein (Figure 4(a)). AFP was 3,500 ng/mL. After a multidisciplinary discussion, the patient was prescribed sorafenib (800 mg per day) with a palliative intent. No adverse effects were observed. Nine months later, AFP was 9 ng/mL, and a reassessment CT scan (Figure 4(b)) showed a 25% decrease of the tumour (75 mm); doppler ultrasound showed the thrombus to be necrotic. Considering this significant response to the sorafenib (TE3 response [3]), a resection surgery was proposed 1 month afterwards. A right hepatectomy with extraction of the thrombus was performed after a quick inferior vena cava clamping (to prevent spread during handling of the tumour). There was no complication in the postoperative course, and the patient was discharged at day 7.

A moderately differentiated hepatocellular carcinoma (grade III in Edmondson's classification) was found at histopathology, with a necrotic component at 60% and no vascular emboli. The right hepatic venous thrombus was totally necrotic.

The patient shows no recurrence 6 months after his operation.

## 3. Discussion

We showed through these 2 cases that sorafenib could make a difference for patients with advanced HCC and put them back on track for a curative treatment (Table 1).

*Sorafenib is an oral multikinase inhibitor of tumour growth and angiogenesis* that inhibits cell surface tyrosine kinase receptors (such as VEGFR and PDGFR) as well as flt-3 and c-kit and downstreams intracellular serine/threonine kinases in the ras/raf/MAPK cascade [5]. This targeted therapy is recommended to Child A patients with advanced HCC and World Health Organization performance status equal or inferior to 2 [6]. Additional tolerability data from Child B patients are still needed before sorafenib can be recommended to this category of patients.

*Histopathological examination* of the resected liver in our 2 cases shows 35% and 60% of *tumour necrosis*, and the right portal branch thrombi were totally necrotic. Some cases have already been reported in urology with the regression of a neoplastic vena cava thrombus in response to sorafenib [7]. Lately, Kudo and Ueshima reported the clinical experience of the use of sorafenib in Japan since it has been approved in May 2009 and described 15 *complete remissions* out of 3,700

patients [8]. We found as well in the literature a few case reports where *sorafenib allowed a good response and a second-step curative intent treatment*. Bathaix et al. [9] recently reported a case where sorafenib led to a very significant regression (about 90%) of the tumour, allowing treating the patient secondarily in a curative intent with transarterial chemoembolisation (TACE) and radiotherapy. Vagefi and Hirose [10] described the case of a patient who has been downstaged by sorafenib and subsequently radiofrequency ablation to the Milan criteria and is now on a waiting list for LT. Nevertheless, in none of these cases a liver resection has been performed after sorafenib, and necrosis has not been histologically proved. We demonstrate in our 2 case reports a correlation between clinical improvement, decrease in tumour size on MRI and CT-scan images, and necrosis component at histopathology.

However, an *accurate evaluation of the effect of sorafenib* and the selection criteria of good responders still need to be defined. One of the problems is that tumour size can remain the same or increase even if there is a good response to the drug, misleading the prescriber. Sorafenib induces early intralesional necrosis that could be detected with dynamic imaging with tumour perfusion and contrast diffusion [11], or gadolinium-injected MRI [12]. The RECICL classification proposed by the Liver Cancer Study Group of Japan [4] and based on the treatment effect on the tumour is useful after molecular-targeted therapy.

Trials are ongoing to evaluate sorafenib as an adjuvant treatment, the main one being the STORM study (http://clinicaltrials.gov/ct2/show/NCT00692770). Endpoints of this phase 3-randomized trial are efficacy and safety of sorafenib versus placebo in the adjuvant treatment of hepatocellular carcinoma after potentially curative treatment (surgical resection or local ablation). Here, patients did not receive any sorafenib postoperativly, as there still are no recommendations about its use as an adjuvant therapy. The S-TACE study (http://clinicaltrials.gov/ct2/show/NCT00478374) aims to evaluate the com-bination of TACE and sorafenib, and other trials want to assess the combination with systemic chemotherapy (http://clinicaltrials.gov/ct2/show/NCT00808145, and http://clinicaltrials.gov/ct2/show/NCT00844688). A current study is aiming to assess the antitumour activity of neoadjuvant sorafenib in patients with resectable HCC (http://clinicaltrials.gov/ct2/show/NCT01182272).

To our knowledge, there is no reported case in the literature about surgery after treatment with sorafenib. We did not observe more bleeding/adhesion during surgery; and none of our patients presented complications such as wound dehiscence or incisional hernia, but it should be taken into account that sorafenib is a VEGFR and PDGFR inhibitor and hence has antiangiogenic properties. The same postoperative complications related to a defect in wound healing might occur as with bevacizumab (Avastin); there are currently no recommendations from Bayer. However, the half-life of sorafenib is only 24 to 48 hours, and a period of 1 week without sorafenib before surgery should be enough to avoid sorafenib-related complications if there are any.

This case demonstrates that sorafenib could downstage HCC and thus represents a bridge to surgery. It might be possible to select patients in good general condition with partial regression of the tumour with sorafenib for a treatment in a curative intent: radiotherapy or radio frequency ablation, surgery, and liver transplantation. Especially, Child A patients who have been prescribed sorafenib in a palliative intent should be carefully reassessed as surgery (or other curative treatments) might still be feasible. The evaluation of sorafenib as a neoadjuvant treatment should be considered and randomized trials to be performed to assess this option. Standard radiologic evaluation should be defined after treatment with sorafenib.

## Abbreviations

HCC: Hepatocellular carcinoma
HCV: Hepatitis C virus
TACE: Transarterial chemo embolisation
CT-scan: Computed tomography scan
AFP: Alpha-foeto protein
MRI: Magnetic resonance imaging.

## Conflict of Interests

The authors declare no conflict of interest.

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