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AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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TOPIC HIGHLIGHT

2016 Hepatocellular Carcinoma: Global view

New advances in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the leading cause of deaths in cirrhotic patients and the third cause of cancer related deaths. Most HCC are associated with well known underlying risk factors, in fact, HCC arise in cirrhotic patients in up to 90% of cases, mainly due to chronic viral hepatitis and alcohol abuse. The worldwide prevention strategies are conducted to avoid the infection of new subjects and to minimize the risk of liver disease progression in infected patients. HCC is a condition which lends itself to surveillance as at-risk individuals can readily be identified. The American and European guidelines recommended implementation of surveillance programs with ultrasound every six months in patient at-risk for developing HCC. The diagnosis of HCC can be based on non-invasive criteria (only in cirrhotic patient) or pathology. Accurately staging patients is essential to oncology practice. The ideal tumour staging system in HCC needs to account for both tumour characteristics and liver function. Treatment allocation is based on several factors: Liver function, size and number of tumours, macrovascular invasion or extrahepatic spread. The recommendations in terms of selection for different treatment strategies must be based on evidence-based data. Resection, liver transplant and interventional radiology treatment are mainstays of HCC therapy and achieve the best outcomes in well-selected candidates. Chemoembolization is the most widely used treatment for unresectable HCC or progression after curative treatment. Finally, in patients with advanced HCC with preserved liver function, sorafenib is the only approved systemic drug that has demonstrated a survival benefit and is the standard of care in this group of patients.

Key words: Hepatocellular carcinoma; Surveillance; Staging system; Radiofrequency ablation; Liver surgery; Liver transplant; Transarterial chemoembolization

Core tip: Liver cancer is the fifth leading cause of cancer worldwide, and the third-leading cause of cancer death. Altouhg some risk factors have been classically associated with development of hepatocellular carcinoma (HCC), in the last years, also, some protective factors

have been described, like coffee drink, and drugs like statins and beta-blockers. The current European Association for the Study of Liver and American Association for the Study of Liver Diseases guidelines recomended the barcelona clinic liver cancer classification as staging system for prognosis prediction and treatment allocation The therapeutic approach in patients with HCC depends on factors such as liver function, tumour extension and comorbidities existence. Available treatments are: Surgical treatments, percutaneous ablation, chemoembolization, radioembolization and systemic treatment.

Pascual S, Herrera I, Irurzun J. New advances in hepatocellular carcinoma. *World J Hepatol* 2016; 8(9): 421-438 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i9/421.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i9.421

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading cancer in the world. It is an important health problem especially in high incidence areas. Nowadays the global incidence is still growing, but with the development of hepatitis B vaccine and the new therapies in hepatitis C virus (HCV), a gradual decline in the incidence is expected in the next decades. Another important issue is the high mortality of the patients with this tumour. In spite of well established surveillance programs in patients with chronic liver disease, most tumours are diagnosed in intermediate-advanced stage, and only palliative measured can be applied.

In the next pages we will review the risk factors associated with the development of HCC, the new advances in diagnosis imaging, the main prognosis classification and finally the therapeutic approach.

EPIDEMIOLOGY

Liver cancer is the fifth-leading cause of cancer diagnosed in men worldwide[1], and the seventh cause of cancer in women, representing about 7% of the total number of cancer diagnoses. Globally, liver cancer is the third-leading cause of cancer death, after lung and stomach[2,3]. The annual incidence of HCC is similar to the deaths per year that it generates, which point out the aggressiveness of this disease[1].

The HCC incidence increases progressively with advancing age in population with a peak at the age of 70-year-old[4]. In Chinese and black African population, mainly infected with hepatitis B virus (HBV), the patient are younger, and in Sub-Saharan Africa (an area with a high incidence of HBV infection) can appear in the third decade of life[5,6].

The incidence of HCC is highest in men, with a male to female ratio of 2.4 and this difference is even higher in populations with a high incidence of HCC, with an average of 3.7 to 1[3]. The differences in the geographical distribution of HCC reflects the differences in exposure to the hepatitis viruses and different environmental pathogens, so the incidence is highest in East Asia, Sub-Saharan Africa and Melanesia, with 85% of the total number of cases[2,3], while in most industrialized countries the incidence is low, except in the South of Europe[7]. Globally there is a growing incidence of the number cases of HCC, even in United States and Europe, mainly due to the high number of people infected with the virus of HCV in these areas[3]. The universal vaccination against HBV in children born after 1980 in some endemic countries has decrease the rate of HCC in children and it is expected a reduction of the incidence of this tumour in the future in these areas[8,9].

ETIOLOGY AND RISK FACTORS

Multiple risk factors have been associated with the development of HCC, being the most frequent chronic viral hepatitis (B and C), alcohol abuse, and exposure to aflatoxins, however, this can occur in people without any known risk factor[10].

Geographically in Africa and East Asia, the most frequently risk factor associated with HCC is chronic HBV infection, while in Western countries, HCV infection is the main risk factor[2]. Overall 54% of cases could be attributed to HBV infection, 31% to HCV infection and 15% to other causes. Cirrhosis is the main risk factor for the development of HCC and about 30%-35% of all cirrhotic patients will develop HCC in the course of their disease, which may be due to chronic viral hepatitis, alcohol, hereditary metabolic diseases, or autoimmune and non-alcoholic fatty liver disease[11]. It is estimated that the annual risk of developing HCC in the cirrhotic patients is between 1%-8% according to the aetiology[12]. The risk of developing HCC increases progressively in male patients, with advanced age, low platelet count, and oesophageal varices[13], as well as it has also been associated with increasing pressure portal[14], or with the degree of liver stiffness measured with transient elastography[15-17].

Viral hepatitis

HBV and HCV Chronic infection are the main risk factor for the development of HCC[18-21]. The higher prevalence of HBV infection occurs in China, Southeast Asia and Sub-Saharan Africa[8,21]. Globally, it is estimated that 54% of all liver cancers are attributable to HBV infection[22]. The prevalence of HCV infection is higher in Egypt, Japan and the South of Italy[21].

The development of HCC associated with HBV infection usually occurs in patients with cirrhosis, but it can appear in patients without cirrhosis[5,23-28]. So screening for HCC will be recommended in this group of patients. Some risk factors for the development of HCC have been identified in patients with chronic HBV infection: The presence of hepatitis virus e antigen (as an indicator of viral replication)[28], high viral load[29],

genotype C (which is the most prevalent in Asia)[30] and infection in early childhood or perinatal period[31-33]. Several studies have demonstrated that the treatment of chronic HBV hepatitis with interferon or nucleotide analogues (suppressing viral load) reduces the relative risk of developing HCC[31,34-43], but these benefits have not been observed in patients who develop resistance to the treatment. Some studies suggest that patients co-infected by HBV and HCV have greater risk of developing HCC[44-46].

There is a very well known association between HCV chronic infection and the development of HCC, in fact, the risk of developing HCC in these patients increase between 20 and 30 times[21,47-49]. In very few cases it may occur in patients with HCV infection and lower grades of hepatic fibrosis[13,50]. High viral loads and HCV genotype 1b infection have been associated with higher risk of HCC occurrence[51]. The levels of inflammatory markers of oxidative stress are higher in patients infected with HCV and HCC[52] and the immune response can be another cofactor in the progression from cirrhosis to HCC in HCV infected patient[53]. In patients with HVC infection who achieve sustained viral response after treatment, there is a decrease in the risk of HCC[54,55]. The universal analysis of blood donations for anti-HCV has resulted in a substantial decrease in the number of cases of hepatitis C in blood donors and the use of needles and disposable syringes and other changes in medical procedures have substantially reduced new infections by HCV. As well as HCV and HBV co-infection may increase the risk of developing cirrhosis and HCC[56], the HIV infection appears to be a cofactor that increases the risk of developing HCC in cirrhotic patients with viral hepatitis[57].

Schistosomiasis

The infection by trematode in blood is endemic in tropical areas of Africa, the Caribbean, Asia, and South America. The species of Schistosoma japonicum, already identified as possible human carcinogen, has been associated with risk of developing HCC in infected by HBV and HCV patients[58,59].

Toxins

The ingestion of food contaminated with aflatoxin B1 (fungi Aspergillus flavus and Aspergillus parasiticus), which can be found at staple foods of tropical and subtropical areas, is a co-factor of risk in the development of HCC, especially in some regions of Africa and Asia, associated with infection by HBV[60,61]. Several studies have shown increased HCC mortality in some rural Chinese areas associated with drinking water potentially contaminated with toxins of some algae (microcystins), with hepatotoxic effect[62,63]. Other studies have established a relationship between the consumption of betel nut, very common in Asia, with an increasing risk of developing cirrhosis and HCC[64,65].

Many studies have associated chronic alcohol consumption with the development of liver cirrhosis and HCC[66-72], although quantity of alcohol ingestion and duration of consumption that supposes a significant risk for developing HCC is unknown. It has been described a relationship between genetic polymorphisms of the enzymes involved in the metabolic pathway of ethanol and increased risk of HCC in excessive drinkers. An increased risk of HCC in heavy alcohol drinkers has been associated to the polymorphism of the aldehyde dehydrogenase and the dysfunction of the enzyme Glutatión S-transferasa[73,74]. Some studies have established that smoking is a significant co-factor in the development of HCC[66,75,76].

Diabetes mellitus and obesity

The obesity, diabetes and dyslipidemia have also been identified as cofactors of risk in the development of HCC, although the pathophysiological mechanisms have not been clarified. It is believed that the deposit of fat in the liver could alter some metabolic functions in patients with diabetes mellitus[77,78]. In these patients, liver steatosis can lead to a nonalcoholic fatty hepatitis, whose pathogenesis is unclear but it have been related to chronic inflammation, oxidative stress, insulin resistance and lipotoxicity, constituting a cofactor for the development of liver cirrhosis and HCC[79-82].

The metabolic syndrome, which is defined by the presence of central obesity, dyslipemia, hypertension, and impaired glucose metabolism, has also been associated with an increased risk of developing HCC[83].

Other causes of cirrhosis

Patients with hemochromatosis may develop HCC by up 45% cases, according to some studies, iron overload can lead to the development of cirrhosis and HCC in these patients[84]. The protein alpha-1-antitrypsin deficiency is a documented risk factor in the development of cirrhosis and HCC that also could be without cirrhosis[85]. Occasionally, patients with cirrhosis secondary to Wilson's disease, autoimmune hepatitis or primary biliary cirrhosis can develop HCC[86-88]. Several studies suggest that porphyria may increase the risk of developing HCC, even in patients without cirrhosis[89-97].

Other factors

A meta-analysis showed an increase of significant risk of any primary liver cancer, and also of HCC in patients with cholelithiasis[98]. The oral anticonceptive (OC) consumption has been rarely associated with the emergence of benign tumours of the liver in young women, like hepatic haemangioma, focal nodular hyperplasia and specially hepatocellular adenoma[99]. Some cases of malignant transformation of liver adenomas in women taking OC have been described[100,101], but subsequent studies did not corroborate these results[102]. Some studies have suggested that the excessive consumption of saturated fats and meat may increase the risk of HCC[103,104]. Although others authors have not found this association[105]. Nitrogenous compounds (used in smoked fish, cheeses, bacon, sausages and other foods)

may increase the risk of liver disease and cancer[106].

In an American study, individuals with a family history of first degree with liver cancer, had up to four times more likely to develop liver cancer than the general population, suggesting that certain shared genetic and environmental factors would influence the risk of developing liver cancer[107]. There is some evidence that there might be an association between a polymorphism of the gene of epidermal growth factor and the risk of developing HCC, although these data require further investigation[108-115].

PROTECTIVE FACTORS

Statins

The use of statins has been associated with a decrease in the risk of developing HCC[116,117]. In a meta-analysis, including 10 studies, the risk of developing HCC was lower in people taking statins[118].

Beta-blockers

A recent retrospective, observational study establishes the hypothesis that treatment with propranolol may reduce the risk of HCC in cirrhotic patients[119].

Diet

The consumption of fish, vegetables and omega-3 fatty acids has been associated with a lower risk of developing HCC in different studies[107,120,121]. Similarly, the increased consumption of vitamin E has also been associated with lower risk of HCC rate[122]. The Mediterranean diet, characterized by high consumption of vegetables, olive oil and cereals, with moderate wine consumption and fish, and low consumption of meat, is associated with a lower risk of HCC[123].

Coffee

There are several studies that have associated coffee consumption with a reduced risk of liver cancer including HCC. In a recent meta-analysis, taking more than two cups of coffee a day reduces risk of liver cancer of up to 43%, which could be related to its antioxidant effect[124-126].

SURVEILLANCE

Surveillance is cost effective in high risk cirrhotic patient, with an expected annual incidence of HCC exceeding 1%-5% per year, and in some cases of non-cirrhotic patients with HBV chronic infection. The problem is that most of the studies of surveillance of HCC in chronic liver disease have been developed in endemic Asian countries with high incidence of HBV infection. In fact, the only prospective study has been developed in China, exclusively in patients with HBV infection. In this study, the mortality related to HCC was lower in patients under HCC surveillance[127]. Other retrospective studies conducted in Europe and America also have showed a better prognosis in patients diagnosed in surveillance programs[128-130]. Both, European American and Asian guidelines recommended that patient with high risk of developing HCC should be entered into surveillance programs. This should be performed using ultrasonography every six months[131-133].

DIAGNOSIS OF HCC

According to the latest consensus conferences and practice guidelines, nowadays, to get to a definitive diagnosis of HCC, will not be necessary to perform a liver biopsy if the tumour is higher than 1 cm in diameter and the typical imaging features are present in a contrast enhanced study [dynamic computed tomography (CT) scan or magnetic resonance (MR)]. Thus, to properly documented the existence of HCC is required that the tumour enhances more intensely in the arterial phase than the surrounding liver and less than the surrounding liver in the venous phase. But these rules are only applicable if the patient has well diagnosed cirrhosis or a HBV chronic hepatitis. In any other cases (patient with typical lesion but without liver disease or patient with atypical lesion and cirrhosis), a liver biopsy must be performed to establish the diagnosis. The serum alphafetoprotein level has no longer be used for diagnosis of HCC, because is insufficiently sensitive or specific for use as a surveillance assay[130,131].

In order to reduce the variability in liver lesion interpretation and standardize the report from CT and MR information, the American College of Radiology has developed a new classification: Liver Imaging-Reporting and Data System (LI-RADS). The LI-RADS assigns imaging findings to one of five categories, allowing radiologist to stratify individual observations according to the level of concern HCC. So LR-1 is an observation definitively benign and LR-5 is definitively HCC. The intermediate stages correlates with probably benign (LR-2), intermediate possibility of being HCC (LR-3) and probably HCC (LR-4) according to radiological features, lesion diameter and contrast enhanced behaviour[134]. As has been described recently, the nodules both LI-RADS category 4 and category 5 have high specificity for HCC diagnosis, and in addition, a relevant proportion of lesions categorized as LI-RADS category 2 and 3 could be HCC and a liver biopsy should be recommended in such patients[135]. A consensus is necessary between different organizations in order to optimize reporting of CT and MR imaging features in the patients at risk for HCC[136].

STAGING

The main prognosis predictors of survival in patients with HCC are: Liver function, tumour burden (size and number of HCC nodules, vascular invasion), serum alpha-fetoprotein level and performance status. Nowadays, there is no universally adopted staging system for HCC. The most widely and accepted staging system in oncology, the classification of malignant tumours

Table 1 Factors included in each staging system

Staging system	Size	Nodules	Met	PVT	AFP	CH	Alb	Bil	ALP	Ascites	PS
TNM	Yes	Yes	Yes	No	No	No	No	No	No	No	No
Okuda	Yes	No	No	No	No	No	Yes	Yes	No	Yes	No
CLIP	Yes	No	No	Yes	Yes	Yes	No	No	No	No	No
FRENCH	No	No	No	Yes	Yes	No	No	Yes	Yes	No	Yes
BCLC	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes
JIS	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No
CUPI	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	No

Met: Metastasis; PVT: Portal vein thrombosis; AFP: Alfafetoproteina; Alb: Albumin; Bil: Bilirubin; ALP: Alkaline phosphatise; PS: Performance status; CLIP: Cancer of the Liver Italian Program; BCLC: Barcelona clinic liver cancer classification; CUPI: Chinese University Prognosis Index; JIS: The Japan Integrated Staging; TNM: Classification of malignant tumours; FRENCH: French classification of hepatocellular carcinomas; CH: Child-Pugh.

(TNM), has been adapted for HCC by the American Joint Committee on Cancer. Currently, the United Network for Organ Sharing, the organ allocation administration in United States of America, allocates donors organs for liver transplantation for the treatment of HCC based on the revised TNM classification. The problem of this system is that it does not incorporate any measure of liver function reserve, which is critical in HCC. Prognosis for HCC is impacted by local spread and hepatic dysfunction, and any staging system in HCC should include parameters that represent both aspects because an advanced liver disease can contraindicate any therapeutic approach as much as an advanced and extended HCC. The first staging system specifically designed for HCC was the Okuda classification[137], but other staging systems have been described in the last decades: Cancer of the Liver Italian Program[138], French classification[139], Barcelona clinic liver cancer classification (BCLC)[140], Chinese University Prognosis Index[141], the Japan Integrated Staging[142], which has been redefined including biomarkers and the Taipei Integrated Scoring System, based on total tumour volume[143]. In Table 1 are represents the parameters included in these staging system. Some of these classifications have been externally validated in separated groups.

The current European Association for the Study of Liver (EASL)-EORTC GP guidelines and the American Association for the Study of Liver Diseases (AASLD) guidelines endorse the BCLC classification and recommend the use of this staging system for prognosis prediction and treatment allocation[132,133]. The BCLC classification divides HCC patients in five stages, from (0, A, B, C, D) according to pre-established prognosis variables: Size and number of nodules, vascular invasion, performance status and Child-Pugh stage. The five stages are: 0 very early stage, A early, B intermediate, C advanced and D terminal and each stage represents the first approach to the evaluation of the patients with expected prognosis and initial treatment option to be considered. Early stage patients may be treated with potential curative treatment: Percutaneous ablation, surgery or liver transplant (LT). Intermediate stage patients may be treated with chemoembolization, advanced stages may be treated with systemic therapy (sorafenib) and in terminal patients only best supportive approach can be applied. But, as in all recommendations, the final treatment indication should take into account a detail evaluation of additional characteristics of the patients that imply a personalized decision making. So, a young patient with Child C and a small tumour should be considered for LT, not for best supportive care.

TREATMENT

The therapeutic approach in patients with HCC depends on several factors such as liver function, size and number of nodules, tumour extension, age and comorbidities existence. Currently, available treatments can be divided into surgical treatments (resection or transplantation), percutaneous ablation (Chemistry: Acid ethanol acetic or thermal: Microwave, laser, radiofrequency and cryoablation), chemoembolization, radioembolization and systemic treatment. The goal of curative treatments should be to obtain a complete response, according to modified RECIST radiological criteria[144,145]. The recommendation of selection for different treatment strategies are based on evidence-based data and local experience and capacities. Is advisable that any decision of treatment should be adopted by multidisciplinary HCC teams including hepatologist, oncologist, surgeons, radiologist and interventional radiologist. Properly allocate each treatment in each case is a crucial decision and is mandatory to warrant a good results in terms of survival, treatment morbidity and mortality and recurrence.

Surgery

As in any tumour, the surgical resection should be the first option to be considered in patients with HCC. The problem is the limitation that supposes the presence of liver cirrhosis, hypertension portal, coagulopathy, or hepatic dysfunction associated, that may contraindicate any surgery and resection of the tumour. The results of surgery to make appropriate estimated that survival at 5 years should reach 60% and 5 years tumour recurrence 70%, peri-operative mortality must be 2%-3% and less than 10% of transfusion requirements. Anatomic resection aiming 2 cm margins provides better results and survival but only could be applied in patients with preserved liver function. Adequate selection of patients for surgery involves a correct assessment of liver

Table 2 Reported 5-year overall survival and recurrence in patients undergoing liver transplant for hepatocellular carcinoma within Milan criteria

Ref.	*n*	5-yr overall survival	5-yr recurrence
Mazzaferro *et al*[155]	48	74%	8%
Bismuth *et al*[149]	45	74%	11%
Llovet *et al*[147]	79	75%	4%
Jonas *et al*[151]	120	71%	15%
Yao *et al*[158]	64	72%	6.5%
Marsh *et al*[153]	248	67%	3.6%
Herrero *et al*[154]	47	70%	8.5%
Mazzaferro *et al*[155]	444	73%	4.3%

function, using Model End Stage Liver Disease punctuation, Child-Pugh class or more sophisticated estimation with the measurement of indocyanine green retention rate or hepatic venous pressure gradient (HVPG). Portal hypertension is an independent prognosis factor in patients undergoing resection and the extensive assessment is recommended before surgery using the component of portal hypertension: Platelet counts, splenomegaly, esophageal varices, and/or HVPG. In practice, BCLC recommendation is to avoid surgery in patient with advanced liver insufficiency, hypertension portal or high bilirubin[146].

If the patient is properly selected, with preserved liver function and no clinically significant portal hypertension, the next step is to evaluate tumour extension: Size and number of nodules, vascular invasion and presence of microsatellites. Tumour size, multinodularity and vascular invasion, are well known predictors of recurrence and survival. Characteristically, microscopic vascular invasion is related to tumour size and involves 20% of tumours of 2 cm, 30%-60% of tumours 2-5 cm and up to 60%-90% of tumours up to 5 cm[147]. With all of this in mind, hepatic resection should be considered for small solitary tumours (and multifocal only if technically possible) with adequate hepatic function. In BCLC staging system, surgery is reserved for patient in the very/early stage, with well preserved liver function and a single tumour less than 2 cm, without portal hypertension and normal bilirubin.

LT

Since Mazafferro described the Milan criteria in 1996 (solitary tumour less than 50 mm in diameter or less than 3 tumours, and 30 mm in diameter each one, in the absence of extrahepatic vascular spread), numerous studies have validated the results of the initial study, both in terms of 5-year survival and recurrence of the tumour (Table 2)[148-155]. This study also allowed that transplantation became a feasible option for treatment in these patients, and also showed that to achieve acceptable rates of survival (*i.e.*, similar to that of the patients transplanted without HCC), the size and number of tumour should be limited. The situation of treatment of HCC has changed dramatically in the last decades. A better knowledge about the tumour behaviour, improvement in surgical techniques and radiological therapies together with a better selection of potential candidates to each treatment have allowed to improve the survival of patients with HCC. The optimisation of the criteria as well as the management of patient already listed for LT remains a source of debate. Important questions, like the expansion of eligibility criteria for LT beyond Milan criteria, the role of down-staging as a bridge to LT or the possible need of adjuvant therapies in patient in waiting list in order to avoid tumour progression and eventual drop-out, are still unresolved.

Expanded criteria for LT

Alternative eligibility criteria beyond Milan criteria have been proposed, and some of them have been incorporated into clinical practice. The main aim of all these new approaches is to permit the fair allocation of liver graft between more potential recipient with similar survival and tumour recurrences. Having in mind the recognised predictors of recurrence (size and number of nodules, presence of bi-lobar disease, tumour differentiation and presence of micro or macro vascular invasion or tumour satellites), some groups have proposed different expensive criteria. In fact, the limitation of some of the studies have been the used of pathological examination of the explants to determine the tumour burden (data that obviously is only disposable after the LT) instead of radiological staging, as it is showed in Table 3[155-162]. This fact, hinders the correct interpretation of the results a consequently the clinical application of the results. The University of California, San Francisco criteria constitutes a well recognised extension to Milan criteria and have been applied in clinical practice[151]. First published in 2001, demonstrated that patients with a single tumour less 65 mm in diameter, or 2-3 tumours each with less 45 mm diameter, with a total tumour diameter less than 80 mm, had similar survival than patients inside Milan criteria[155]. Subsequent studies (both prospective and retrospective) have reported favourable results with expanded criteria. A recent retrospective and multicentre study by Mazzaferro *et al*[155], have been performed introducing "up to seven" criteria: the sum of the number of tumour nodules and the diameter of the largest nodule (in centimetres) being less than 7[154]. These results have been externally validated in an independent cohort[162,163]. The international consensus conference for liver transplantation for HCC recommended to consider the LT in patients with HCC inside Milan criteria and only a modest expansion of the number of potential candidates may be considered outside Milan criteria[164].

Downstaging

Another important question is the role of downstaging in patients with HCC exceeding Milan criteria, using locoregional therapies: Radiofrequency ablation (RFA), transarterial chemoembolization (TACE), transarterial radioembolization or surgery. The objective of these therapies should be to decrease tumour size or number

Table 3 Summary of the characteristics of the published studies including patients within Milan criteria or with expanded criteria

Ref.	Patients MC/EC	HCC criteria	Staging method	Design	5-yr survival (%) MC/EC
Yao *et al*[158] UCSF criteria	46/14	1 < 6 cm 2-3 > 4, 5 cm Sum diameter < 8 cm	Explant	Retro	72
Herrero *et al*[154] Navarra Criteria	35/12	1 < 6 cm 2-3 < 5 cm	Rx	Pros	
Kneteman *et al*[157]	19/21 18/9	1 < 7.5 cm Multinodular < 5 cm	Explant Rx	Pros	87/83 (4-yr) 92/77
Yao *et al*[152]	130/38	1 < 6 cm 2-3 > 4, 5 cm Sum diameter < 8 cm	Rx	Pros	90/93
Silva *et al*[159] Valencia Criteria	231/26 254/27	1 < 5 cm 2-3 < 5 cm Sum diameter 10 cm	Explant Rx	Retro	62/69
Herrero *et al*[156]	59/26	1 < 6 cm 2-3 < 5 cm	Explant Rx	Pros	70/56 66/68
Mazzaferro *et al*[155] Metroticket	444/283	Sum nodules/size 7 cm	Explant	Retro	73/71
Fan *et al*[160] Shanghai Criteria	394/176	1 < 9 cm 2-3 < 5 cm Sum diameter 9 cm	Explant	Retro	51/65
Guiteau *et al*[161]	363/82	1 < 6 cm 2-3 < 5 cm Sum diameter 9 cm	Rx	Pros	73/71 (3-yr)

Staging method: Pre LT with radiological features (Rx) or post LT according to histopathological features (Explant). Study design: retrospective (Retros), prospective (Pros). MC: Milan criteria; EC: Expanded criteria; LT: Liver transplant; UCSF: University of California, San Francisco; HCC: Hepatocellular carcinoma.

of tumours in order to achieve a pre-established locally criteria acceptable for LT. Some of the studies have reported successfully results with this strategy achieving 5 years survival similar to that of patients with HCC who meet Milan criteria without requiring downstaging[165,166]. Nevertheless, there are some unresolved issues. The defined upper limit for size and number of nodules eligibility for downstaging and the possible role of alpha-fetoprotein has not been well defined. The assessment of adequate response is variable in the different reports, although the recommendation should be to consider the amount of available tumour according to modified RECIST criteria. Otherwise, the acceptable criteria previously defined as successful downstaging in each study, has been different, as well as the observation period recommended after the tumour has been down-staged, before considering for LT. The recommendation of Consensus Conference was that LT may be considered after successful downstaging, without evidence for preferring a specific locoregional therapy and using criteria including size and number of viable tumour[164].

Interventional radiology treatment

HCC is the tumour that takes the greatest advantage from interventional radiology therapies for several reasons: Not only surgical difficulties in cirrhotic patients, but also ablative and endovascular treatments have demonstrated high response rates and survival benefits.

Among all chemical ablative treatments, percutaneous ethanol injection (PEI) has a widespread use, although it has more difficulties to treat encapsulated tumours against other substances as acetic acid. PEI has been the most used ablative therapy until 1999[167], but it has been disregarded after the emergence of more sophisticated techniques. Despite it has also evolved with multi-pronged needles that minimize some PEI disadvantages as the need of multiple sessions[168], they have a limited use and nowadays PEI use is reserved for the treatment of HCC < 2 cm with unfavorable RFA locations (Figure 1).

Among 2000-2010 numerous cohort studies and some randomized control trials (RCTs) and meta-nalisis[169] demonstrated that RFA gets better control of the disease compared to PEI. It has the ability to create bigger necrosis, including a peripheral ring to the tumour, and therefore higher complete necrotic rates - even sustained necrosis - particularly in tumours < 3 cm, where ablation is more effective.

Initial complete response has demonstrated a positive impact on survival, although there still will be high recurrence rates, comparable to surgical resection. HCC usually appears in the setting of underlying chronic hepatic disease and this conditioned the appearance of new nodules, but there are also same segment recurrence nodules as a result of the growth of small peritumoral satellites or vascular microinvasion out of the ablated zone.

There are some researches[170,171] with specimen from surgery, about the distance of microsatellites depending on tumour size that come to the conclusion that a reasonable limit of RFA is 2, 5-3 cm in order to create a security margin of 5 mm. This makes us use RFA needles 1 or 2 numbers of ablation greater than the tumour diameter. Other strategies to increase the

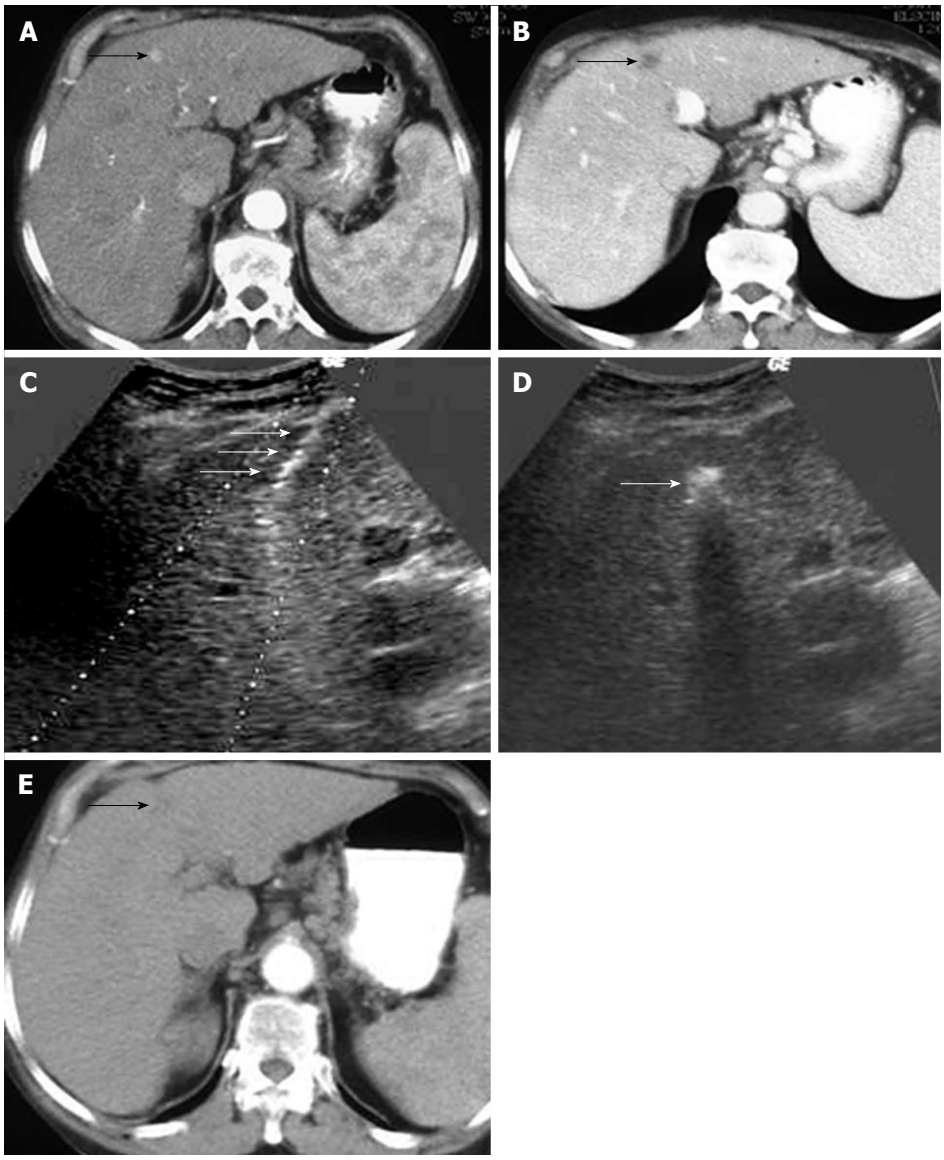

Figure 1 Ethanol injection treatment for hepatocellular carcinoma. A: Very early hepatocellular carcinoma pre-percutaneous ethanol injection treatment (Arterial phase); B: Very early hepatocellular carcinoma pre-percutaneous ethanol injection treatment (Portal phase); C: Percutaneous ethanol injection procedure (Ultrasound guidance fine needle puncture); D: Percutaneous ethanol injection procedure (Ethanol aggregation after ultrasound guidance percutaneous ethanol injection); E: Computed tomography control arterial phase after 1 year (Sustained complete response).

ablation zone are overlapping techniques or multi-pronged needles, but their clinical use is difficult and not widespread.

RFA creates a complete necrosis area with a predictable diameter, whenever is not affected by nearby medium-large-sized vessels that could condition the perfusion-mediated tissue cooling, known as the heat sink effect. This limitation and the presence of non-treated microsatellites make up their main theoretical limitations, but there are also others that limit their clinical use: Ultrasound visualization of the nodule within liver parenchyma (difficult at fatty liver, macronodular cirrhosis, Ⅷ segment nodules…) and the risk of damage of nearby organs (yuxtahiliar, gallbladder, stomach, duodenum, large intestine). This potential damage contraindicates RFA if we are not able to isolate them with sterile water instillation (spacing technique). Last, sub capsular tumours are not good indication of RFA due to the risk of tumoral seeding.

BCLC protocol last review[140] considered RFA as the first therapy at HCC < 2 cm, when a patient is not candidate to LT. This stage is also known as very early stage 0 or carcinoma *in situ*. RFA is also considered an alternative curative treatment at early stage (A) (single or 3 nodules ⩽ 3 cm), with survival benefit up to 70%.

Microwave ablation is emerging as an alternative to RFA with several advantages. It is able to induce greater intratumoral temperature and bigger ablation area during less time than RFA. Thus, it is less dependent from tissue impedance and less influenced by heat-sink effect. Nowadays, it has less scientific evidence than RFA and there is lack of comparative papers between both techniques, but it seems logical to use it at HCC nearby to large hepatic vessels.

Irreversible electroporation is the technique more expensive, less used in clinical practice and with less evidence, although it is not affected by heat-sink effect and it doesn't damage adjacent structures. Therefore, its use seems useful to treat complex location lesions[144,172].

TACE has been established by a meta-analysis of RCTs[173] as the standard of care for nonsurgical patients with large or multinodular noninvasive HCC isolated to the liver and with preserved liver function, known as intermediate stage HCC.

It is frequently used to control tumour progression (palliative treatment) as primary therapy or while waiting for liver transplantation, but some considerations has to be remarked. Intermediate stage is actually a heterogeneous group of patients and TACE benefit should be assessed in subgroups of patients as it has already been remarked[174]. Moreover, large series treated by TACE reported patients with single nodule stage A HCC[175,176].

This would be justified by the recent concept of treatment stage migration: If a subject in a given stage is not candidate to the recommended treatment, we should consider the treatment of the more advance stage[140]. In our experience more than 1/3 of patient candidates to RFA, due to ablation difficulties, were treated by TACE (Figure 2), as has also been remarked in the literature[177].

Thus, early stage HCCs have been treated with TACE with reported maintained complete responses and it has been suggested to include TACE as an alternative curative intention therapy (stage A), in selected patients and performed with a concrete technique[178].

TACE technique is an interesting underestimate debate. There are different accepted techniques to perform endovascular HCC treatments with no enough evidence to determine the best option and this implies huge difficulties to standardize the results. Bland embolization or simple chemoinfusion have evolved to combined techniques of intra-arterial chemotherapy followed by ischemic changes after intra-arterial embolic materials (TACE).

Conventional TACE involves the selective injection of a chemotherapeutic agent (usually Doxorrubicine) emulsified in a viscous carrier (lipiodol), followed by embolic material into the feeding arteries of the tumour.

It has been the most common way to perform TACE since the beginning of the century-validated with level 1 of evidence[173] - and is still acceptable with widespread use, above all in eastern countries. There are different ways to perform it regarding on how to mix lipiodol and contrast, being more or less selective and types of lipiodol aggregation. The optimal way should include filling of the "rear door of the tumour", *i.e.*, small portal drainage veins[179].

An alternative way to perform TACE is widespread in the clinical practice, known as drug-eluting beads-TACE (DEB-TACE). It concerns performed microspheres loaded with chemotherapeutic agents which allows the delivery of large amounts of drugs to the tumour for a prolonged period of time (improve antitumoral efficacy), thereby decreasing plasma levels of the chemotherapeutic agent and potentially systemic effects (better tolerance).

A prospective multi-institutional RCT (Precision V)[178] demonstrated significant better tolerance compared to cTACE, but only improved response in advanced disease (Child-Pugh B). Later several cohort studies and some RCTs favors DEB-TACE *vs* cTACE in response rates and survival, but nowadays it is a usual debate in HCC symposiums because more evidence is needed to evaluate the two modalities of TACE. Actually, DEB-TACE has implemented in the clinical practice of western countries based on some clear rationale: Maximize drug delivery, long lasting effect/slow and sustained release, tumour effect *vs* systemic side effects and better reproducibility.

Technical recommendations to perform it have been published to improve its efficacy, helping reproducibility and constitute clear working tendencies[180-182]: (1) Must use microcatheter with super-selective injection at feeding arteries; (2) Use angio-CT system technology for tumour targeting; (3) Mix beads with contrast 3-4:1 to increase visibility; (4) Avoid complete stasis (endpoint near stasis); (5) Inject slowly (1 mL/min) trying to introduce as much Doxorubicin as possible inside the tumour (maximum 150 mg); (6) Use of small size microspheres to increase penetrability. At present 100-300 μm are recommended, but the use of smaller beads (M1 70-150 μm) - commonly used at treating liver metastasis- is being evaluated in clinical trials. Many working groups have introduced them in their protocols, particularly with small size HCCs and they are extremely promising thanks to their bigger penetrability[183]; and (7) - Repeat TACE in 2-4 wk, if needed, to get initial complete response, which is being related to survival benefit[184].

Ablative therapies and chemoembolization form the interventional treatments recommended by BCLC staging and treatment strategy, with simplicity as one of its known advantages. Other classifications as Japanese guidelines[185] stands for suggest other treatment options together with first line therapies in different stages or subgroups of them.

The huge variability of patients with HCC makes necessary to create a tailored approach that nowadays it is an undeniable clinical tendency[186]. We should adjust to each patient the most suitable treatment for its particular case, after a multidisciplinary assessment. The combination of locoregional therapies sometimes offers this maximal flexibility. This approach seems to be particularly valuable in patients with multifocal disease and nodules > 3 cm.

Among combine therapies, there are more experience with the combination of TACE and RFA (TACE first). Therefore, perfusion tissue is reduced and heat loss by perfusion mediated tissue cooling is minimized making possible larger ablation zone with wider safety margin[187]. Thus, sometimes downstaging is possible, above all with HCC 3-5 cm.

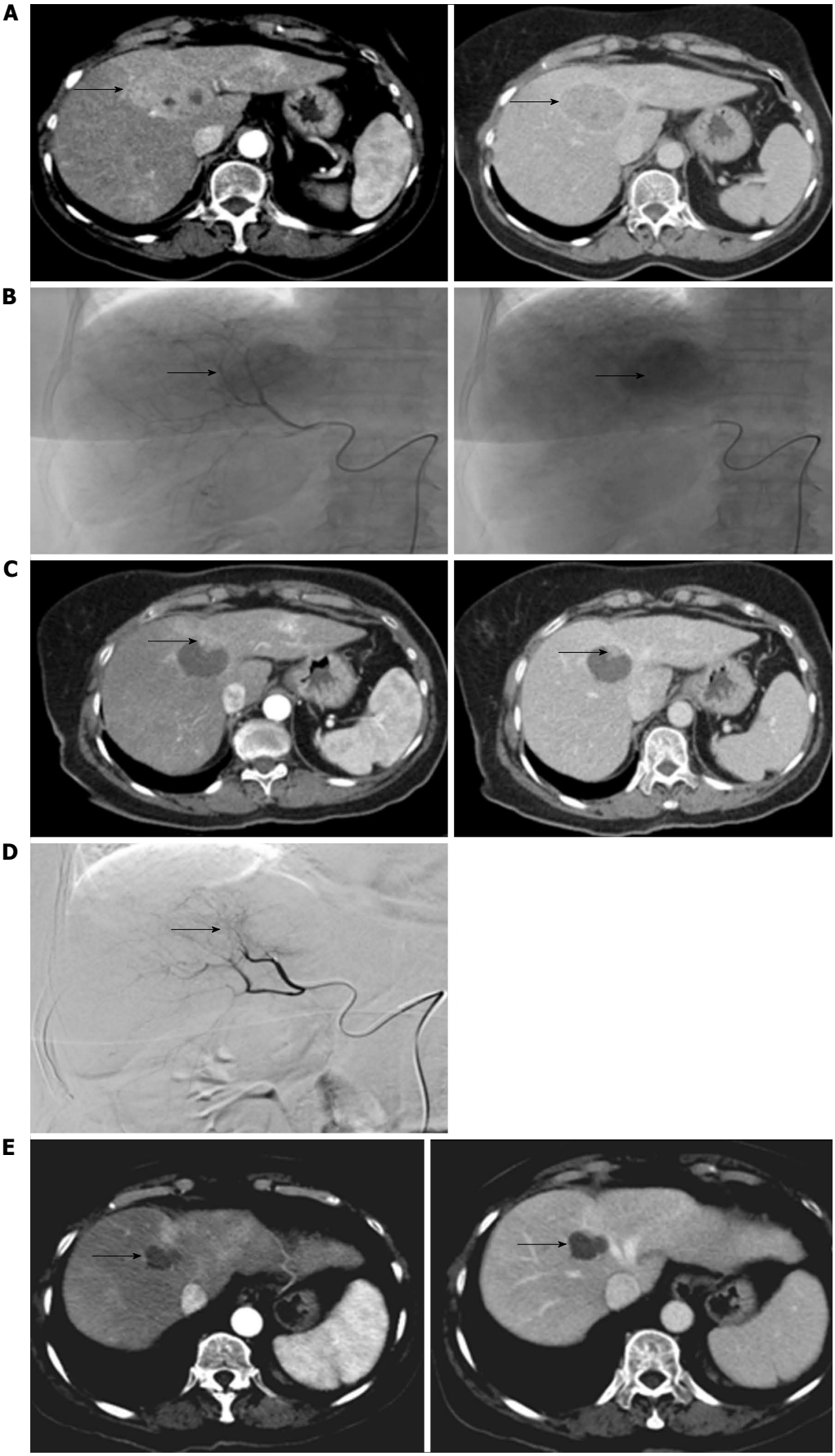

Figure 2 Transarterial chemoembolization for hepatocellular carcinoma. A: Four centimeter hepatocellular carcinoma S-IV. Arterial and venous phase computed tomography; B: First transarterial chemoembolization procedure; C: Small residual foci after 1 transarterial chemoembolization; D: Second transarterial chemoembolization; E: Complete response after 2 transarterial chemoembolization.

In the recent years, several groups perform RFA followed by TACE (RFA first). This way, TACE acts over a transitional zone with sub lethal hyperthermia and increase vascular permeability. This forms an increase delivery, uptake and susceptibility to chemotherapeutics ideal to treat microsatellites outside RFA zone[188].

Radioembolization is an alternative to TACE with less evidence and minor applicability. It needs to join interventional radiology and nuclear medicine units, which is restricted to only a few hospitals. Besides, technically is more complex than TACE and require an anatomical previous vascular map, because many times is necessary to embolize the arteries that communicate the target liver places with other adjacent organs as gallbladder or stomach that could be damaged.

Although is not included in the BCLC recommended treatments, it would be indicated in stage B HCC as an alternative to TACE and some stage C HCC with portal thrombosis that is not a contraindication of this technique. Some working groups consider it a first option in tumour > 5 cm or when > 4 nodules are present[174]. Ongoing RCTs are needed to unequivocally confirm the survival benefit provided by transarterial radioembolization in many cohort studies.

Sorafenib

Sorafenib is a small molecule that inhibits tumour-cell proliferation, tumour angiogenesis and it is a multi-tyrosine kinase inhibitor and nowadays is the only drug that have demonstrated survival benefits in patients with advanced HCC. The initial phase Ⅱ and phase Ⅲ studies showed positive results with better survival in patients treated with sorafenib. The benefit of sorafenib was to increase the median survival from 7.9 mo in the placebo group to 10.7 mo in the sorafenib group. In addition, sorafenib showed a significant benefit in terms of time to progression, but objective responses rates were low[189]. These results were corroborated in other phase Ⅲ study conducted in Asia[190]. This drug is only indicated in patients with preserved liver function and advanced disease not susceptible of other therapies and in this group of patients have an acceptable safety profile with manageable adverse events. The initial results were very promising because it was the first time that a systemic therapy demonstrated benefits effects in patients with HCC. Two subsequent trials, the Space (Sorafenib or placebo in combination with TACE for intermediate-stage HCC)[191] and the Storm (Sorafenib or placebo after resection or ablation to prevent recurrence of HCC)[192] have failed to demonstrated efficacy of sorafenib as adjuvant in combination with locally therapies. In the next years, new novel drugs, with a slightly different profile in terms of targets and intensity, have been tried both in first-line and second-line therapy. Until now, none of these drugs (sunitinib, brivanib, linifanib and combination of erlotinib and sorafenib) have proven to be better than sorafenib in first-line trials, in terms of survival. Second-line trails with brivanib, everolimus and ramucirumab have also failed to show benefits compared with placebo.

The EASL and AASLD recommend the use of sorafenib in patients with HCC advanced stage and preserved liver function.

CONCLUSION

HCC is a tumour with high incidence in patients with liver cirrhosis and is currently the leading cause of death in this group of patients. It is expected a decreases in incidence in the coming decades due to better management of patients infected with HBV and HCV. The vaccination against hepatitis B, the extended use of antiviral drugs with a high genetic barrier, which remain at undetectable viral load levels and the higher rate of sustained viral response in patients with chronic HCV with the new generation of antiviral drugs will reduce the incidence of this tumour in the future. On the other hand, increasingly numbers of studies have identified protective factors such as treatment with beta-blockers or statins, and perhaps in the future the use of some of these drugs will be recommended in selected cirrhotic patients. On the other hand, the improvement in the quality of imaging techniques allows establishing a diagnosis without histological confirmation in a high percentage of patients. New radiologic classifications, although promising, need more studies to be accepted universally. Once confirmed the diagnosis, the staging of the tumour allows us to decide the best therapeutic approach. Although several prognostic classifications have been described, the BCLC classification has been supported by American and European clinical practice guidelines. In addition, it allows deciding the best therapy according to the stage. The mainstays of treatment of HCC are surgery, radiological approach and systemic drugs. Since it is the treatment of choice to better outcomes in terms of survival, the indications of liver transplantation are in constant review. The expanded criteria and the downstaging have helped to expand the number of patients who are eligible for this option, with acceptable survival and recurrence after the transplant. On the other hand, the percutaneous ablative techniques have obtained good results in terms of response and survival, similar to surgical resection, in selected cases. In patients at intermediate stages, chemoembolization with particles has improved the results against the conventional chemoembolization with a similar rate of adverse effects. Sorafenib is the only systemic drug that has demonstrated survival benefits in advanced-stage patients and therefore remains the standard of care in this group. So far, any drug has shown survival benefits in second-line therapy after progression with sorafenib.

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TOPIC HIGHLIGHT

2016 Hepatocellular Carcinoma: Global view

Preoperative portal vein embolization for hepatocellular carcinoma: Consensus and controversy

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Abstract

Thirty years have passed since the first report of portal vein embolization (PVE), and this procedure is widely adopted as a preoperative treatment procedure for patients with a small future liver remnant (FLR). PVE has been shown to be useful in patients with hepatocellular carcinoma (HCC) and chronic liver disease. However, special caution is needed when PVE is applied prior to subsequent major hepatic resection in cases with cirrhotic livers, and volumetric analysis of the liver segments in addition to evaluation of the liver functional reserve before PVE is mandatory in such cases. Advances in the embolic material and selection of the treatment approach, and combined use of PVE and transcatheter arterial embolization/chemoembolization have yielded improved outcomes after PVE and major hepatic resections. A novel procedure termed the associating liver partition and portal vein ligation for staged hepatectomy has been gaining attention because of the rapid hypertrophy of the FLR observed in patients undergoing this procedure, however, application of this technique in HCC patients requires special caution, as it has been shown to be associated with a high morbidity and mortality even in cases with essentially healthy livers.

Key words: Hepatocellular carcinoma; Future liver remnant; Poral vein embolization; Liver functional reserve; The associating liver partition and portal vein ligation for staged hepatectomy

Core tip: Preoperative portal vein embolization (PVE) has been developed to secure the safety of a major hepatic resection by inducing the hypertrophy of the future liver remnant. PVE has been shown to be useful for patients with hepatocellular carcinoma and chronic liver disease. However, the indications should be carefully judged based on the volumetric analysis and evaluation of the liver functional reserve. Recently, a novel technique called the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been introduced to gain a rapid hypertrophy of the future liver remnant; however, at present, data supporting ALPPS in hepatocellular carcinoma with

cirrhosis are still very weak.

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INTRODUCTION

Currently, hepatic resection is the treatment of choice for large hepatocellular carcinomas (HCC), colorectal liver metastases (CLM) and hilar cholangiocarcinomas, and extensive liver resection is often required in patients with these malignancies. Preoperative portal vein embolization (PVE), which induces atrophy of the liver segments to be resected and hypertrophy of the future liver remnant (FLR), has been introduced in an attempt to expand the indications for major (the resection of 3 or more Couinaud segments[1]) hepatic resection and prevent postoperative liver insufficiency. Thirty years have passed since the first report of PVE by Makuuchi *et al*[2], and the usefulness of PVE is currently widely accepted. However, the beneficial effect of preoperative PVE may be impaired in patients with chronic liver disease, especially liver cirrhosis[3], and caution is required when PVE is applied in patients with large HCCs and underlying liver cirrhosis. In such patients, volumetric analysis of the liver segments in addition to evaluation of the liver functional reserve is mandatory[4]. On the other hand, some European groups have recently advocated the usefulness of a new procedure termed the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS)[5], as this procedure has been shown to induce rapid hypertrophy of the FLR within a short interval[6]. However, application of ALPPS to HCC patients with underlying liver cirrhosis is debatable from the point of view of the safety. In this manuscript, we have reviewed the recent advances in preoperative PVE and other procedures aimed at increasing the FLR.

HISTORY OF PVE

In the first report, Makuuchi *et al*[7] applied preoperative PVE for patients with hilar cholangiocarcinoma. They stated that the purposes of PVE were: (1) to initiate compensatory hypertrophy of the FLR; and (2) to avoid a sudden increase of the portal venous pressure during and after the surgery[7]. The second goal is especially important in HCC patients with portal hypertension, where PVE may serve as a preoperative "tolerance test"; if the FLR cannot tolerate the higher portal pressure induced by PVE, sufficient hypertrophy of the FLR cannot be expected. Two approaches were used for PVE: Transileocolic portal embolization (TIPE) *via* laparotomy under general anesthesia, and percutaneous transhepatic portal embolization (PTPE) using a puncture technique with ultrasonic guidance under local anesthesia. The embolic material consisted of a mixture of absorbable gelatin powder, contrast material, and antibiotics.

Kinoshita *et al*[8] performed selective PVE (THPE), wherein they used a contralateral approach to occlude the portal vein branch bearing the HCC tumor. The aim of selective PVE was to enhance the effect of transcatheter arterial embolization (TAE) and the accompanying hypertrophy of the nonembolized segments. They used gelatin sponge, thrombin mixed with glucose, or an adhesive mixture of fibrin with contrast material as the embolic material.

Subsequently, the indication of preoperative PVE was expanded to other liver tumors, including CLM and HCC without cirrhosis. Among patients with CLM, PVE is indicated in patients with: (1) small multiple lesions of the right lobe; or (2) a small solitary tumor located adjacent to the hilum of the liver[9,10]. Reports dealing with PVE for HCC with underlying cirrhosis or chronic hepatitis were at first mainly small patient series from Asian countries, while documentations of large patient series have appeared after the year 2000[11-18]. The indications for PVE in cases of HCC is determined by the relationship between the liver functional reserve and the volumetric ratio of the FLR to the total liver volume. In general, major hepatic resection is contraindicated in Child-Pugh class B or C patients; these patients are therefore also not suitable candidates for PVE. In addition, Child-Pugh class A patients should undergo assessment by the indocyanine green retention rate at 15 min (ICG-R15). An ICG-R15 value of > 20% is generally considered as a contraindication for major hepatic resection and therefore also for PVE (Figure 1)[4].

MODIFICATION OF PVE

Approach

Several approaches have been advocated for PVE, which can be mainly categorized as TIPE or PTPE; the PTPE approach is further subdivided into an ipsilateral approach and a contralateral approach. TIPE is a safe approach; complete portography can be achieved using this approach, and insertion of the catheter into the segmental portal branches is relatively easy; however, it requires general anesthesia and laparotomy, and carries the risk of post-PVE bowel obstruction.

PTPE can be performed under local anesthesia, and is therefore considered to be a less invasive procedure; however, the possible risk of hemorrhage/subcapsular hematoma or peritonitis cannot be ignored, and if the contralateral approach is selected, injury to the vessels in the FLR may make the subsequent liver resection impossible. A meta-analysis showed that despite the absence of any significant difference in the rate of major complications between TIPE and PTPE, the rate for minor complications was significantly higher for PTPE[19].

Nagino *et al*[20] recommended the ipsilateral approach occluded the right anterior and posterior portal branches using different types of catheters. This technique is

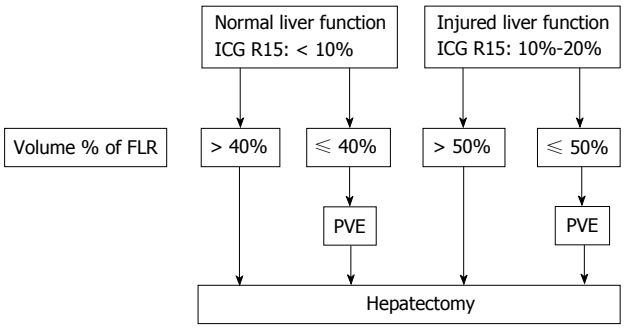

Figure 1 Indications of portal vein embolization for patients with hepatocellular carcinoma. PVE: Portal vein embolization; FLR: Future liver remnant; ICG R15: Indocyanine green retention ratio at 15 min.

advantageous from the standpoint of safety, as the portal branch of the resected segments is punctured. Currently, PTPE using the ipsilateral approach, although the most technically demanding, is the most popularly used approach; however, the optimal approach must be selected according to the tumor location and past history of laparotomy.

Segment 4 embolization

When a more extended hepatic resection, such as right trisegmentectomy, is needed, embolization of the segment 4 portal branch in addition to the right portal vein branch may yield additional beneficial effects[21]. Embolization of the segment 4 branch is easy when the ipsilateral PTPE approach or TIPE is used. Two previous reports have confirmed the additional beneficial effect of embolization of the segment 4 portal branch on segment 2 + 3 hypertrophy, however, both reports dealt with non-injured livers, and no data are available for patients with underlying liver cirrhosis[22,23].

Embolic material

A number of embolic materials have been used for PVE, including gelatin sponge, gelatin powder, thrombin, fibrin glue, polyvinyl alcohol particles, absolute ethanol, cyanoacrylate, absolute ethanol, small spherical particles, and metallic coils[19]. The ideal agent would be the one that would lead to rapid, reproducible, and substantial functional hypertrophy of the FLR in the majority of patients without producing significant toxicity or adverse events. Currently, a combination of absolute ethanol and microcoils is widely used for HCC patients, as these agents have been shown to induce a greater degree of hypertrophy of the FLR as compared with other embolic materials[24]. However, there have been no randomized controlled trials to compare the efficiency of the embolic materials.

BASIC ASPECTS OF PVE

Liver regeneration after PVE

The mechanism of liver hypertrophy/regeneration after PVE has been widely studied using animal models or in clinical settings. Several experimental results imply that the mechanism of liver regeneration after PVE/portal vein ligation (PVL) is different from that after hepatectomy, as indicated by the different response to follistatin[25]. The difference is fundamentally attributed to maintained or enhanced arterial blood flow to the embolized liver segments after PVE, or the presence *per se* of the embolized segments, and the atrophying embolized liver segments are supposed to retain their specific functions. In addition, negative regulators of hepatocytes proliferation (such as transforming growth factor-β and interleukin-1β) are strongly expressed in the embolized segments. These factors in the embolized segments may modify the whole process of regeneration after PVE, although no definitive conclusions have been made yet[26].

Enhancement of the effect of PVE

Various factors have been shown to influence the effect of PVE: Age, gender, body mass index, nutrition status, previous chemotherapy, diabetes mellitus, *etc*[26]. It has been shown that liver regeneration is impaired in chronically diseased livers[3]. Sugawara *et al*[14] have examined the clinical factors associated with liver hypertrophy after PVE in HCC patients, and have found that the hypertrophic effect was significantly enhanced when PVE was combined with TAE. Recently, Beppu *et al*[27] have shown a favorable effect of branched-chain amino acid supplementation on functional liver regeneration after PVE.

CLINICAL IMPLICATIONS OF PVE

Clinical outcomes after PVE and major hepatic resection

Clinically, the percent increase in the volume of the FLR in cirrhotic livers within the first 2-3 wk after PVE is reported to in the range of 5% to 10%[10-12], and the hypertrophy ratio of the FLR has also been reported to be approximately 1.3 to 1.5[10,11,13]. Others have reported a rate of hypertrophy in cirrhotic livers of 9 cm^2/d at 2 wk[14]. These figures are significantly smaller than those reported in non-cirrhotic livers[14-17]. Nevertheless, most previous reports have documented the safety of the PVE procedure and of subsequent major hepatic resection even in cases with a cirrhotic liver[28-32].

Previous reports have documented satisfactory long-term results after PVE and subsequent major hepatic resection for HCC (Table 1)[11-18]. The reported 5-year survival rates range from 44% to 72%, and the reported 5-year disease-free survival rates range from 21% to 56%. These figures are comparable to those after major hepatic resections for HCC without PVE. It may be deduced that PVE does not have any adverse effect on the risk of oncogenesis (*i.e.*, intrahepatic HCC recurrence or development of new primary lesions) in the FLR after hepatic resection.

PVE also has significance as a preoperative "tolerance test". Indeed, if the liver cannot tolerate PVE, sufficient hypertrophy of the FLR cannot be expected, and a subsequent major hepatic resection is precluded. In

Table 1 Clinical outcomes of portal vein embolization for hepatocellular carcinoma

Ref.	Year	Technique	No. of patients	Morbidity (%)	Mortality (%)	5-yr disease-free survival (%)	5-yr overall survival (%)
Azoulay *et al*[11]	2000	PVE	10	55	0	21	44
Tanaka *et al*[12]	2000	PVE	33	-	3	33	50
Wakabayashi *et al*[13]	2001	PVE	26	-	11.5	40	46
Sugawara *et al*[14]	2002	PVE	66	-	0	37.9	58.9
Aoki *et al*[15]	2004	TACE + PVE	24	24	0	47	56
Ogata *et al*[16]	2006	TACE + PVE	18	39	-	37	-
		PVE	18	56	-	19	-
Seo *et al*[17]	2007	PVE	32	19	0	37	72
Palavecino *et al*[18]	2009	PVE	21	24	0	56	72

PVE: Portal vein embolization; TACE: Transcatheter arterial chemoembolization.

addition to the volumetric increase of the FLR, the kinetic growth rate (speed of increase in the volume of the FLR) has also been shown to be a predictor of the morbidity and mortality after subsequent major hepatic resections[33].

Tumor growth after PVE

On the other hand, tumors in the nonembolized liver segments have been reported to grow more rapidly than tumors in the embolized segments. Alternatively, tumors in the nonembolized segments show an enhanced rate of progression as compared to their natural history. This possible underlying mechanisms for this observation are that: (1) the increased arterial blood supply to the nonembolized liver segments after PVE can promote tumor growth; and (2) the cytokines associated with the atrophy-hypertrophy complex can also promote the progression of tumors. Several previous reports have addressed this issue. Despite some conflicting results, accumulating evidence suggests an adverse effect of PVE on tumor growth[34-38], although most previous studies investigating the risk of tumor growth after PVE have dealt with patients having colorectal liver metastases.

Tumor growth after PVE, especially tumor growth in the nonembolized FLR and/or extrahepatic tumor progression, may preclude curative resection. Indeed, a recent meta-analysis reported that about 15% of patients could not undergo curative resection after PVE, and about a half of these patients showed severe tumor progression or extrahepatic tumor spread[19].

Sequential transcatheter arterial chemoembolization and PVE and two-staged hepatectomy

As mentioned above, the risk of tumor growth after PVE may counteract the beneficial effect of PVE. Therefore, measures to prevent tumor growth during the waiting period before hepatectomy should be considered.

Our group has employed combined transcatheter arterial chemoembolization (TACE) with PVE as a preoperative treatment in HCC patients. The antitumor effect of TACE in cases of HCC has been reported previously[39]. TACE is also useful for embolizing the arterio-portal shunts in the tumor. Thus, the combination of TACE plus PVE before planned major hepatic resection may strengthen the effect of PVE while simultaneously preventing tumor progression. Our study showed satisfactory short- and long-term outcomes after sequential preoperative TACE and PVE in 17 patients with HCC[15]. During the waiting period after PVE, tumor progression, as evaluated by measurements of the tumor volume, serum alpha-fetoprotein level, and plasma des-γ-carboxy prothrombin level, was significantly suppressed.

Another European group compared 18 patients who underwent sequential preoperative TACE and PVE with 18 patients who underwent PVE alone prior to hepatic resection[16]. All the patients underwent a right hepatectomy 4-8 wk after the PVE. They found that the degree of hypertrophy of the FLR was greater in the TACE + PVE group, and that the recurrence-free survival period was also significantly longer in the TACE + PVE group than that in the PVE alone group.

A potential concern of sequential TACE and PVE is infarction or necrosis of the non-cancerous liver parenchyma. Our previous results showed, however, that necrosis of the non-cancerous liver parenchyma in the resected specimens was minimal. Possibly, recanalization of the hepatic artery abrogates the possible adverse effect of dual embolization.

Two-stage hepatectomy with preoperative PVE can also be applied in patients with metastatic liver tumors[40]. The tumors in the FLR are removed by limited resections as the first step, PVE is performed as the second step, and finally, the major hepatic resection is carried out as the third and final step. This strategy is fascinating, but is rarely performed in HCC patients as the surgical indications for bilobar multiple HCC are extremely limited.

ALTERNATIVES TO PVE

PVE vs PVL vs ALPPS

In general, PVL at the right branch is believed to induce canalization of the intrahepatic communications of the peripheral portal branches within a few days, therefore, PVE is considered to be more efficient as compared to PVL. However, a meta-analysis has shown only a borderline difference in the increase of the FLR volume

after PVE and PVL. The morbidity and mortality of the two procedures are similar[41].

Recently, European groups have reported a novel approach to rapid liver regeneration in patients scheduled for extended right hepatectomy. This procedure, termed ALPPS, consists of right portal ligation and in situ splitting of the liver parenchyma on the right side of the umbilical portion of the portal vein. Schnitzbauer *et al*[5], who published the first report of this procedure, reported a marked and rapid hypertrophy of about 75% of the left lateral lobe within a median of 9 d. This growth rate has been reported to be 11 times higher as compared to that after PVE/PVL, and comparable to that in donors after living donor liver transplantation[42]. The mechanisms of the apparent profound hepatic growth of the FLR after ALPPS are unknown, although probably this noteworthy phenomenon may be attributable to an abruption of the arterial blood flow between the two parts of the liver. The same group and others also documented that ALPPS significantly improved the chance of curative resection for initially unresectable liver tumors as compared to conventional PVE/PVL[6,43].

The concern about this procedure, however, is the high morbidity and mortality rates associated with it[44,45]. The reported 90-d mortality after ALPPS is 15%, while that after PVE/PVL is 6%, and the odds ratio for perioperative death was 2.7-fold higher in the patients who underwent ALPPS[6]. In addition, a high recurrence rate within a short follow-up period has also been reported[46]. Based on these observations, Shindoh *et al*[47] concluded that PVE (right portal branch plus segment 4) and interval surgery remain the standard for patients with small FLRs.

Is ALPPS applicable to HCC patients with cirrhosis? The ALPPS series included some patients with HCC (about 10% of the patients), and some recent papers have documented that ALPPS can be safely performed in HCC patients with cirrhosis; however, no detailed data are available because of the small number of patients[5,6,48]. Currently, the indications of ALPPS for HCC patients are extremely limited and each patient should be carefully examined as to his/her suitability to undergo ALPPS.

Radioembolization

Our group has applied a combination of preoperative TACE and PVE to prevent tumor progression during the waiting period before surgery. An alternative to this strategy is radioembolization, which treats the tumor in the embolized lobe along with induction of contralateral hypertrophy. An increase in the size of the non-embolized lobe by 42% after radioembolization has been reported in cirrhotic livers[49]. A comparison of PVE and radioembolization in non-cirrhotic livers has shown that PVE induces a greater degree of hypertrophy of the FLR than that radioembolization[50]. Nevertheless, this novel procedure is promising, as it enables both embolization and treatment of the tumor(s) in a single step.

CONCLUSION

Much basic and clinical evidence associated with PVE has been accumulated, however, especially for cases of HCC with underlying liver cirrhosis or chronic hepatitis, the available clinical data are limited. Development of safe and reliable novel approaches that can be used in combination with PVE to induce rapid hypertrophy of FLR, which can be applied even to chronically diseased livers, is needed.

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MINIREVIEWS

Focal liver lesions found incidentally

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Abstract

Incidentally found focal liver lesions are a common finding and a reason for referral to hepatobiliary service. They are often discovered in patients with history of liver cirrhosis, colorectal cancer, incidentally during work up for abdominal pain or in a trauma setting. Specific points should considered during history taking such as risk factors of liver cirrhosis; hepatitis, alcohol consumption, substance exposure or use of oral contraceptive pills and metabolic syndromes. Full blood count, liver function test and tumor markers can act as a guide to minimize the differential diagnosis and to categorize the degree of liver disease. Imaging should start with B-mode ultrasound. If available, contrast enhanced ultrasound is a feasible, safe, cost effective option and increases the ability to reach a diagnosis. Contrast enhanced computed tomography should be considered next. It is more accurate in diagnosis and better to study anatomy for possible operation. Contrast enhanced magnetic resonance is the gold standard with the highest sensitivity. If doubt still remains, the options are biopsy or surgical excision.

Key words: Focal liver lesions; B-mode ultrasound; Ultrasound; Magnetic resonance; Fine needle biopsy; Computed tomography

Core tip: Focal liver lesions are being found more commonly, which may need further investigations. History and physical examination is essential part of work up. Blood work is an important adjunct in the patient's journey. There are different modalities of imaging (B-mode ultrasound, contrast enhanced ultrasound, contrast enhanced computed tomography and contrast enhanced magnetic resonance); each has advantages and disadvantages. The decision of biopsy or surgery is kept for the treating team.

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INTRODUCTION

Focal liver lesions (FLLs) are a common reason for consultation to a hepatobiliary service, they often need further work up, and investigations. They are often discovered in patients with a cirrhotic liver or colorectal cancer but can be found incidentally during work up for abdominal pain and sometimes in the trauma setting.

Incidental liver lesions are being found more commonly due to advancement in imaging modalities. In some reports, incidental FLLs were found in up to 33% of radiological studies. In autopsy cases, it reached more than 50%[1,2].

Unfortunately, there is no clear pathway for work up and with a wide differential diagnosis; these lesions may need multiple imaging modalities to characterize whether they are benign or malignant.

A cornerstone in evaluating these patients is history and physical examination. A deferential diagnosis of metastasis *vs* hepatocellular carcinoma (HCC) should be considered for patients with family history of previous malignancies or chronic liver diseases. However, in a healthy population without significant medical background, the differential diagnosis should include wider possibilities, both benign and malignant.

Different modalities are being used to reach a definitive diagnosis. These include: B-mode ultrasound (B-US), contrast enhanced ultrasound (C-US), elastography, contrast enhanced computed tomography (C-CT) scan and contrast enhanced magnetic resonance (C-MR) imaging. Due to the lack of guidelines, most institutions are using all available modalities to establish a diagnosis, which is time consuming, uncomfortable, and not cost effective.

HISTORY AND PHYSICAL EXAMINATION

Specific points should be taken in consideration as a part of history taking; risk factors for liver cirrhosis like hepatitis and alcohol consumption, exposure to substances known to cause liver lesions, use of the oral contraceptive pill should be elucidated especially in childbearing aged women. Obesity and metabolic syndromes and diabetes are know pathognomic factors for non alcoholic fatty liver disease which is know to increase hepatocellular cancer[3]. Patients with a previous cancer should raise the suspicion of a liver metastatic lesion. A family history of malignancy should also be clarified[4]. A history of fever and travel should raise the suspicion of infective process.

During physical examination of the patient-jaundice, cachexia, palpable masses, palpable lymph nodes and stigmata of liver disease - should be looked for (Table 1)[4].

The differential diagnosis of a liver lesion is wide, and can be benign requiring no treatment or an advanced malignant condition beyond cure. The list can be minimized with a careful clinical, chemical and radiological assessment (Table 2).

BLOOD WORKS

When requesting blood investigation for patients with FLL the results should answer three essential points.

The general condition of the patient; using a full blood count, renal profile, liver function test and albumin level.

The assessment of liver status using the above with the addition of a coagulation profile. These will help obtain a Childs-Pugh score and can be determinant in planning proper management plan.

Tumor markers such as carcinembryonic antigen (CEA), alpha-feto protein (AFP) and cancer antigen 19-9 (CA19-9) should be requested. A high-level of CEA should raise the possibilities of metastatic colorectal cancer. HCC and cholangiocarcinoma could have raised level of AFP and CA19-9 respectively. An elevated AFP (over 400 ng/mL) may confirm the diagnosis if combined with the addition of two confirmatory imaging techniques[5].

B-US

The limitation of any type of ultrasonography (USS) (B-mode or contrast enhanced) is the visualization of the whole liver. When the whole liver can be seen USS is a very useful screening test but in certain patients views of parts of the liver can be very limited which limits the usefulness of the investigation.

B-US is one of the most commonly used modalities to investigate the liver and can help to diagnose different pathology. In patients presenting with liver disease, abdominal pain and jaundice a B-US is usually requested. In the Focused Assessment with Sonography for Trauma examination, liver lesions are found in approximately 12 of every 1000 patients examined[6]. B-US is also recommended in the surveillance for patients at a high risk of developing HCC[7,8].

The role of B-US in the diagnosing FLLs in a healthy patient is limited to a few diagnoses, of which hemangioma is the most common. Haematomas, hydatid cysts, and abscesses can be conveniently identified using B-US alone. The diagnosis of other FLLs with B-US alone is more challenging and rarely possible.

The use of pulsed and color Doppler USS is limited to focal nodular hyperplasia (FNH) in which the central artery with radial distribution is a characteristic element present in approximately 80% of cases[9].

C-US

There are two main types of contrast used with ultrasound, micro-bubbles (MBs) and Sonazoid. MBs can be

Table 1 Clinical signs in-patients with liver disease

General	Compensated	Decompensated
Jaundice	Xanthelasmas	Disorientation
Fever	Parotid enlargement	Drowsiness
Loss of body hair	Spider naevi	Coma
	Gyanecomastia	Hepatic flap
	Large or small liver	Fetor hepaticus
	Splenomegaly	Ascites
	Clubbing	Dilated veins on abdominalwall
	Liver palms	Oedema
	Dupuytren's contracture	
	Xanthoma	
	Scratch marks	
	Testicular atrophy	
	Purpura	
	Pigmented ulcers	

defined within different vascular phases: Arterial, portal and the delayed venous phase and are very useful in the detection of malignancies. Sonazoid is approved only in Japan and has an extra post-vascular phase (also called the Kupffer phase), MBs become phagocytosed by Kupffer cells and hence there is no post vascular phase when MBs are used.

Malignancies are characterized by hypo enhancement in the portal and venous phases as well as in the post-vascular phase, making their detection with C-US possible. C-US has been shown to be a reliable imaging technique for follow-up of metastatic liver disease with an accuracy of 91% compared to CT scan and MR imaging[10].

In imaging of HCCs C-US is more complicated. Well-differentiated HCC lesions are iso enhancing in late phases in 51% of cases only, meaning that other imaging modalities are required[11].

The use of USS contrast agents has radically changed the approach to the characterization of FLLs. C-US allows the classification of the majority of FLLs with a high diagnostic accuracy. The typical pattern of FLLs has been well described in the European Federation of Societies for Ultrasound in Medicine and Biology guidelines for C-US, originally published in 2004, updated in 2008, and soon to be updated again[12,13].

Excluding simple cysts (without enhancement in all phases), benign FLLs are generally characterized by an iso echoic pattern in the portal and late phases; because of the persistence of USS contrast agents in the sinusoidal space. In contrast, the washout of these agents in late phases is characteristic of malignant lesions.

Hervé Trillaud confirmed the superior results of real-time C-US for FLLs characterization, compared to that of unenhanced ultrasound. Furthermore, it was demonstrated that the diagnostic accuracy of SonoVue®-enhanced ultrasound was better in comparison to C- CT and C-MR[14].

Hohmann *et al*[15] using MBs agents in C-US with a long-lasting late phase, showed no significant difference in lesion detection compared with C-MR imaging.

Table 2 Common differential diagnosis of focal liver lesions

Benign lesions	Malignant lesions
Cystic lesion (5%-14%)	Metastasis (14.4)
Simple, infectious, pre malignant	Cystic lesions (8%)
Hemangioma (2%-20%)	Hepatocellular carcinoma (2%-6%)
Hepatic adenoma (3%)	Cholangiocarcinoma (2%)
Biliary hamartoma (1.5%)	Lymphoma
Regenerative nodule (11%)	Sarcoma

ELASTOGRAPHY

Real-time (RT) elastography is a technique that can estimate the strain modules from radiofrequency signals in response to external compression and provide an estimation of tissue elasticity. This technique has been studied for the characterization of nodules in superficial structures such as the breast, thyroid, and prostate. Few studies are available concerning its application to the liver, particularly for the evaluation of liver fibrosis. Apart from its use for characterization, RT elastography has been studied for the detection of liver nodules in animal models and during surgery[16,17]. In the latter setting, it has been demonstrated to have a higher diagnostic accuracy than B-mode intraoperative USS in detecting lesions surrounded by a heterogeneous background or with an iso echoic pattern (96% *vs* 89%). Nevertheless, its role in the detection of FLLs is yet to be definitively assessed.

C-CT SCAN

C-CT scan is one of the essential imaging studies of FLL. The protocol and ability to acquire a multiphasic study is paramount in characterizing liver lesions. Triphasic images are the method of choice, which give a significant improvement in the result compared to single-phase studies[18]. The ability for three-dimensional reconstruction helps in assessing the vascular anatomy, the liver and tumor volumes. It also provides a good screening tool to the rest of the abdomen as well as to stage a malignant pathology. Differentiation between benign and malignant conditions is based on the degree of uptake of the contrast agent at different phases of the study. For example, hepatocellular cancer has an early uptake of contrast in the arterial phase with an early washout in the portal and delayed phases (Figure 1)[8]. One of the limitations of C-CT is the large dose of radiation given to the patient and the nephrotoxic effect of the iodine contrast that limit its use in patients with renal impairment.

C-MR SCAN

C-MR is the best modality for FLLs assessment, in both primary and metastatic malignancy. C-MR represents the current technique of choice in this setting since it is free of ionizing radiation as well as demonstrating a high contrast resolution using several sequences and different

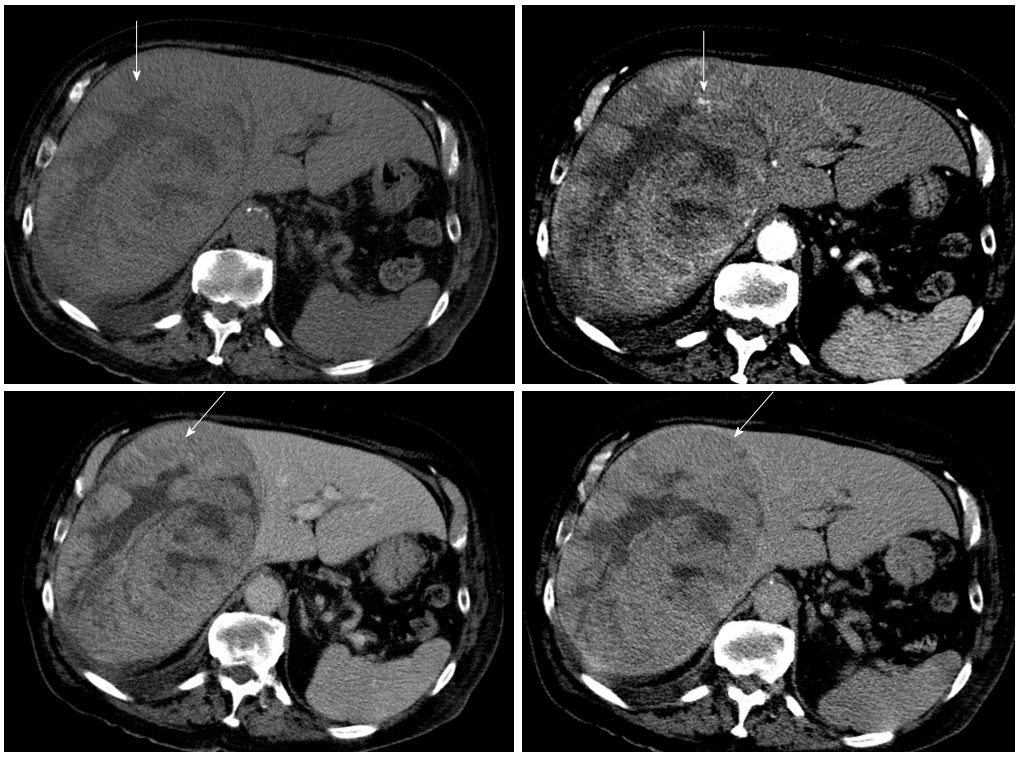

Figure 1 Contrast enhanced computed tomography images of hepatocellular carcinoma. A 55 years old male, diabetic, presented with upper abdominal pain (arrows shows the lesion in different phases with clear washout at the venous phase).

types of contrast media. The commonly used contrast media are gadolinium-chelates, which have an extracellular hepatic distribution which help in differentiating liver lesions and obtaining angiography. Other types of contrast agent have an intra-cellular distribution such as ferrumoxides and hence help to detect liver parenchymal lesions[19-21]. There is general agreement about the superiority of C-MR with extra-cellular contrast medium compared to the baseline study without contrast or with other types of contrast[22-26].

Primovist (Gd-EOB-DTPA) is a biphasic hepatobiliary magnetic resonance contrast agent. Dynamic C-MR imaging can be performed with the Gd-based extracellular contrast agents where the hemodynamic characteristics of the lesion can be studied. Following that, the hepatobiliary phase can be obtained when the contrast agents are excreted in both renal and biliary systems. Obtaining hepatobiliary phase can provide histological as well as functional information about lesions which might improve the diagnostic accuracy of FLLs[27]. Gd-EOB-DTPA-enhanced MR can provide useful information to help characterizing benign and malignant focal lesions and not only to detect them (Figure 2)[28].

Soussan *et al*[29] reported that using gadolinium-based C-MR gives a diagnostic accuracy of 52%-66% for incidentally found solid liver lesions compared to 52%-53% with C-US.

Chung *et al*[30] demonstrated that Gd-EOB-DTPA-enhanced MR is more accurate to differentiate between benign and malignant lesions and more specific to diagnosis FNH and focal eosinophilic infiltration. Both dynamic C-CT and Gd-EOB-DTPA-enhanced MR had similar high diagnostic accuracy for hemangiomas and HCCs, whereas other relatively uncommon lesions such as inflammatory myofibroblastic tumor, embryonal sarcoma or schwannoma are rarely diagnosed accurately on both modalities[30].

An advantage of C-MR is lack of ionizing radiation and the ability to use in renal impairment patients. It also provides a better characterization of liver lesions compared to other modalities. A drawback is the high cost and the longer procedure duration[30].

BIOPSY *VS* SURGERY

Radiological imaging, tumor markers and other information gathered through the assessment process are often diagnostic, and therefore biopsy is rarely needed. Biopsy increases risks of bleeding and needle-track seeding. Biopsy of hepatic adenomas, FNH, and hemangioma has an increased risk of bleeding[31]. It has been reported that biopsy of HCCs are associated with a significant risk of needle-track seeding (1.6%-5%)[4,32,33].

A group of investigators studied 160 patients with FLLs. Preoperative fine needle biopsy was not performed. After surgery, 98% of preoperative diagnosis was confirmed histologically[34].

In rare cases imaging might not be conclusive, and hence, a surgical resection for definitive diagnosis might be needed. Resection will confirm the diagnosis, prevent progression of premalignant conditions and will reduce the risk of bleeding or seeding if biopsy were done.

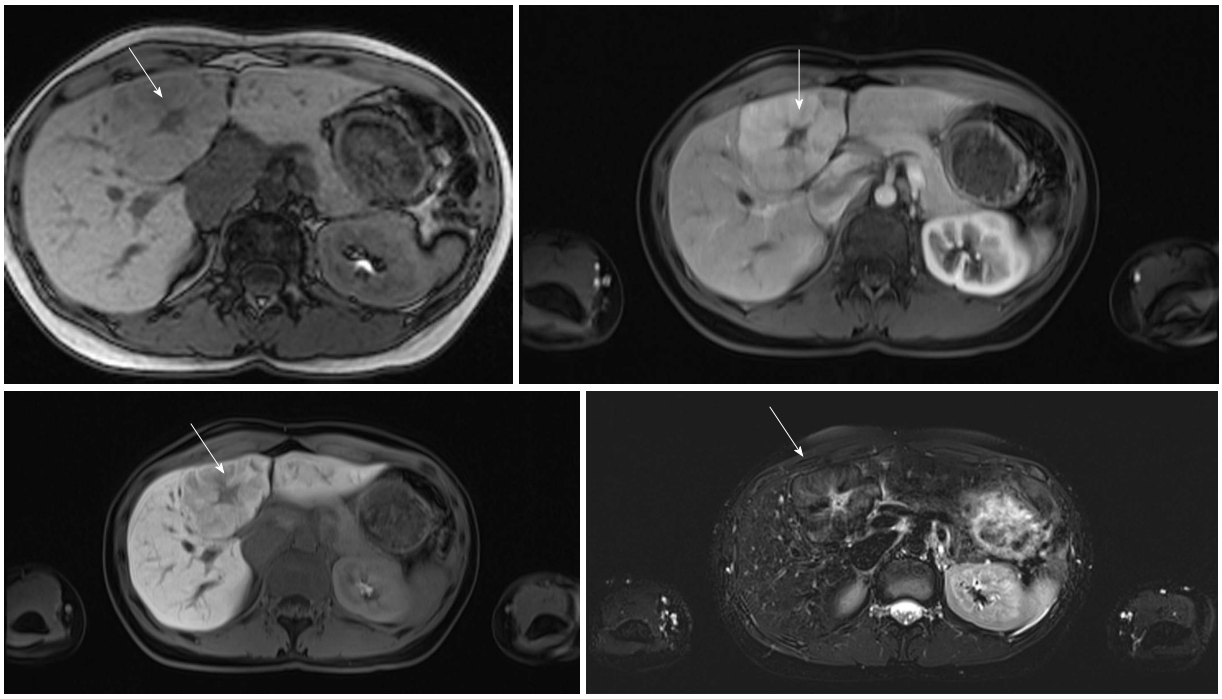

Figure 2 Contrast enhanced magnetic resonance images of focal nodular hyperplasia. A 30 years old female, medically free, had abdominal pain; ultrasonography showed gallstones and liver lesion (arrows shows the lesion with the characteristic central scar of FNH).

Other indication for surgery is resectable lesion, which has been characterized on imaging, and a diagnosis has been made.

Fine-needle liver biopsy of FLLs is generally reserved for patients who are not surgical candidates and can be done at the same time of non-surgical treatments such as radiofrequency ablation or trans arterial chemoembolization.

CONCLUSION

Incidentally found FLLs should be thoroughly assessed using history and physical examination in association with blood tests as the starting point to formulate a differential diagnosis. Imaging modalities should be used wisely to save cost but to get the highest sensitivity possible. Ultrasound is fast, feasible, safe, cost effective and if combined with contrast, has an increased sensitivity in reaching the diagnosis but C-CT has a greater accuracy in diagnosis, is more widely applicable (less influenced by body morphology) and is helpful to study liver anatomy. C-MR is the modality of choice with the highest sensitivity. Biopsy should be reserved for questionable lesions where surgery is not an option.

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Comprehensive review of telbivudine in pregnant women with chronic hepatitis B

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Abstract

AIM: To achieve an evidence-based conclusion regarding the safety and efficacy of telbivudine during pregnancy.

METHODS: A pooled analysis of data from a literature search reported 1739 pregnancy outcomes (1673 live births) from 1725 non-overlapping pregnant women treated with telbivudine. The prevalence of live birth defects (3.6/1000) was similar to that of the non-antiviral controls (3.0/1000) and not increased as compared with overall prevalence (14.5 to 60/1000). No target organ toxicity was identified. The prevalence of spontaneous abortion in pregnant women treated with telbivudine (4.2/1000) was not increased compared with the overall prevalence (16/1000). The mother-to-child transmission rate was significantly reduced in pregnant women treated with telbivudine (0.70%) compared to those treated with the non-antiviral controls (11.9%; $P < 0.0001$) or compared to the historical rates of hepatitis B virus (HBV)-infected population without antiviral treatment (10%-15%).

RESULTS: Cumulatively 489 pregnancy cases have been reported in the telbivudine pharmacovigilance database (with a cut-off date 31 August 2014), of those, 308 had known pregnancy outcomes with 249 cases of live births (239 cases of live birth without congenital anomaly and 10 cases of live birth with congenital anomaly). In the latest antiretroviral pregnancy registry report (1 January 1989 through 31 January 2015) of 27 patients exposed to telbivudine during pregnancy (18, 6 and 3 during first, second and third trimester, respectively) 19 live births were reported and there were no cases of birth defects reported.

CONCLUSION: Telbivudine treatment during pregnancy presents a favorable safety profile without increased rates of live birth defects, spontaneous abortion or elective termination, or fetal/neonatal toxicity. Exposure to telbivudine in the first, second and third trimester of pregnancy has been shown to significantly reduce the risk of HBV transmission from mother to child on the basis of standard immune prophylaxis procedure.

Key words: Telbivudine; Hepatitis B virus; Pregnancy; Mother-to-child transmission; Vertical transmission

Core tip: The data from literatures, pharmacovigilance reports on telbivudine exposure and antiretroviral pregnancy registry during pregnancy in women with hepatitis B virus (HBV) infection showed no increased rates of live birth defects, spontaneous abortion or elective termination. No fetal/neonatal toxicity was reported during telbivudine treatment. Telbivudine exposure in the second and/or third trimesters of pregnancy has been shown to reduce the risk of HBV transmission from mother to child if administered in addition to hepatitis B immunoglobulin and HBV vaccination with a favorable safety profile.

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INTRODUCTION

Chronic hepatitis B (CHB) infection is a major public health problem. Perinatal or childhood transmission of hepatitis B virus (HBV) commonly leads to chronic hepatitis which causes necroinflammation and progression of fibrosis resulting in higher risk of developing cirrhosis and hepatocellular carcinoma[1]. Over 50% of CHB carriers in endemic areas acquired their infection perinatally[2,3]. In the absence of prevention, infants born to hepatitis B e antigen (HBeAg) positive mothers have a 40%-90% risk of acquiring CHB *via* vertical transmission[4]. In addition, 15%-90% of infected infants develop chronic infection (according to the HBeAg status of the mother), compared with < 5% of patients who acquire infection during adulthood[5-7].

It was reported that 42.1% of infants born to HBsAg-positive mothers globally acquired HBV infection perinatally, because those infants did not receive any active or passive immunoprophylaxis for HBV. In contrast only 2.9% of infants who received immunoprophylaxis acquired HBV infection perinatally[8]. HBV perinatal transmission or mother-to-child transmission (MTCT) is considered to occur mainly at delivery. Therefore, standard immunoprophylaxis procedures to prevent perinatal transmission are recommended[9]. This standard procedure is based on the combination of passive and active immunization with hepatitis B immunoglobulin (HBIg) and HBV vaccination. However, immunoprophylaxis may not be effective in a proportion of newborns from highly viremic mothers (serum HBV DNA > 10^{6-7} IU/mL) who are mostly HBeAg positive, who carry a > 10% risk of vertical HBV transmission despite efficient HBIg and vaccination[10]. The vaccine failure cases were reported in previous studies[11-13]. There was an earlier report from Mayotte, a French territory in Africa, that newborns who had received complete and timely sero-vaccination had a low immunoprophylaxis failure rate (3%)[14].

Antiviral therapy administered to HBV carrier mothers during pregnancy plus appropriate immunoprophylaxis to newborns have been suggested to effectively prevent MTCT by reducing maternal HBV DNA levels and developing passive immunization in newborns. The European Association for the Study of the Liver (EASL) guidelines recommend the use of a nucleos(t)ide analogue to reduce viral loads in pregnant women who are hepatitis B surface antigen (HBsAg) positive and have high HBV DNA levels (> 10^{6-7} IU/mL) to enhance the effectiveness of HBIg and vaccination[15,16]. Pregnant women with cirrhosis have an increased risk of developing maternal complications, significant perinatal complications, and poor pregnancy outcomes[9]. Therefore, it is often recommended that woman of childbearing age with advanced fibrosis or cirrhosis should be treated with nucleos(t)ide analogues and that their treatment regimen must be maintained during a future pregnancy[13].

No anti-HBV therapies are currently approved for the prevention of MTCT in pregnancy. Each antiviral has been assigned by the Food and Drug Administration (FDA) to one pregnancy drug class based on preclinical evaluation of the potential teratogenicity. Of the seven antiviral drugs for CHB currently available, alpha interferons and pegylated alpha interferons have anti-proliferative actions and are contraindicated during pregnancy[15]. Of the currently approved five oral nucleos(t)ide analogues, tenofovir and telbivudine belong to pregnancy category B (animal reproduction studies have failed to demonstrate a risk to the fetus and studies in pregnant women failed to demonstrate a risk to the fetus), while the other three

Table 1 Food and drug administration pregnancy categories for hepatitis B virus antiviral therapy[15]

Pregnancy category	definition	HBV therapy categorization
A	Adequate and well controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)	None
B	Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women or animal studies that have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester	Telbivudine; Tenofovir
C	Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well controlled studies in humans, but potential benefits might warrant use of the drug in pregnant women despite potential risks	Lamivudine; Entecavir; Adefovir
D	There is positive evidence of human fetus risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits might warrant use of the drug in pregnant women despite potential risks	None
X	Studies in animals or humans have demonstrated fetus abnormalities, and/or there is positive evidence of human fetus risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits	Interferon

drugs, lamivudine, adefovir and entecavir, belong to pregnancy category C (animal reproduction studies have shown an adverse effect on the fetus and no adequate or well controlled studies in humans)[15] (Table 1). Of the aforementioned drugs, there are limited data on treating HBV infection during pregnancy. A prospective randomized controlled trial of tenofovir in HBV infected mothers have been reported[17]. Treatment with lamivudine in late pregnancy has shown reduced mother-to-infant transmission but drug resistance is a potential concern[15].

Telbivudine has shown no carcinogenicity, teratogenicity, mutagenicity or mitochondrial toxicity in preclinical studies. Telbivudine has demonstrated greater antiviral and clinical efficacy than lamivudine in CHB patients[18-20]. In a prospective cohort study, telbivudine showed better preventive effect in reducing perinatal transmission when used in early trimesters of pregnancy than latter in pregnancy. There were no complications or severe adverse events observed in telbivudine-treated mothers or infants[21]. Another study showed that telbivudine treatment in chronic HBV-infected mothers was effective in blocking the MTCT of HBV and growth and development of the children were normal[22]. As recommended by EASL and the Asian-Pacific Association for the Study of the Liver guidelines, telbivudine is listed as one of the preferred drugs to be used for the prevention of MTCT in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA > 10^{6-7} IU/mL)[15,23].

Here we present a summary of the information available on the safety and efficacy of telbivudine when used during pregnancy. This analysis was based on scientific literature, and analysis of a Novartis pharmacovigilance database and a public Antiretroviral Pregnancy Registry. The objective of this analysis was to achieve an evidence-based conclusion regarding the safety and efficacy of telbivudine use in HBV infected pregnant mothers and to confirm the observations from telbivudine preclinical studies.

MATERIALS AND METHODS

Preclinical studies

Several preclinical studies of reproductive and developmental toxicity have been conducted with telbivudine to assess its potential adverse effects on fertility, general reproductive performance, development of the conceptus, gestation, birth and post-natal performance (Novartis; data on file). An overview of these studies conducted is summarized in Table 2.

Clinical studies

Programmed searches were conducted in literature databases for an extensive literature review. The cut-off periods were set as no starting limit till May 2015. Databases included BIOSIS Previews, EBM Reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database), Embase, International Pharmaceutical Abstracts, MEDLINE (including in-process and other non-indexed citations, MEDLINE Daily Update, and OLDMEDLINE). The search strategy included the following keywords in all fields using different combinations with the Boolean operators OR and AND: "telbivudine" or equivalent names ("2′ deoxy beta thymidine", "beta thymidine", "epavudine", "LdT 600", "NV 02B", "NV02B", "Sebivo" or "Tyzeka"); pregnant or pregnancy; hepatitis. Another search was conducted in Chinese databases to review Chinese literatures in the following Chinese databases: Wanfang Med Online (med.wanfangdata.com) and China Knowledge Resource Integrated Database (www.cnki.net). Keywords for search in Chinese databases included "telbivudine", "gestation", "pregnancy", "intrauterine infection", "mother-to-child transmission" and "vertical transmission".

A consistent methodology was used when reviewing each paper. The main criterion for selecting a publication

Table 2 Reproductive and developmental toxicity with telbivudine

Study type	Route of administration	Species	No. of animals	Doses (mg/kg per day)	Treatment	Reference
Rat studies						
Fertility, reproduction, developmental	Oral gavage	Sprague Dawley rats	25 males 25 females	0, 100, 500, 1000	Males: -28 AC to DG 17 Females: -15 AC to DG 17	Study 1314-001
Fertility	Oral gavage	Sprague Dawley rats	25 males 25 females	0, 1000, 2000	Males: -28 AC to DG 13	Study 1314-005
Fertility	Oral gavage	Sprague Dawley rats	25 males 25 females	0, 2000	Females: -15 AC to DG 7	Study 1314-006
Peri/postnatal	Oral gavage	Sprague Dawley rats	25 females	0, 100, 250, 1000	Females: DG 7 to DL 20	Study 1314-003
Rabbit study						
Developmental	Oral gavage	New Zealand White rabbits	20 females	0, 50, 250, 1000	Females: DG 6-18	Study 1314-002

AC: Ante coitum; DG: Gestation day; DL: Lactation day.

was completeness of safety data ("adequate safety information" was defined as including both pregnancy and pregnancy/infant outcome to address the safety profile of telbivudine use in pregnancy) and non-overlapping cases. For articles reported more than once by the same author, the corresponding author was contacted for clarification of the case details. Systemic reviews or meta-analysis were not included in this analysis. Studies with non-overlapping data and safety information were selected and analyzed. All pregnant women who were treated with telbivudine during the period of pregnancy and were reported with a pregnancy outcome were included in the analysis of this review. All those pregnancies without a pregnancy outcome reported or lost to follow up were excluded from this review.

Pharmacovigilance database

Pregnancy cases from Novartis pharmacovigilance database were collected with a cut-off date of 31 August 2014. Data collected prospectively (acquired prior to the knowledge of the pregnancy outcome or prior to the detection of a congenital malformation at prenatal examination (*e.g.,* fetal ultrasound or serum markers) were separated from data collected retrospectively (acquired after the outcome of the pregnancy was known or after the detection of a congenital malformation on prenatal test). Only safety data were collected from the cases; data on perinatal and intrauterine information was not adequately collected.

Antiretroviral pregnancy registry

The Antiretroviral Pregnancy Registry (APR; www.APRegistry.com) is designed to collect and evaluate data on the outcomes of pregnancies exposed to antiretroviral products. It has been actively collecting relevant data since January 2003 and telbivudine has been included in the list of evaluated drugs. An interim analysis report is issued online semi-annually including data from 1 January 1989 through the latest period. The interim report contains analyses of voluntary prospective reports (*i.e.,* reports made to the Registry prior to the outcome of pregnancy being known) of prenatal exposures. Additionally, data from retrospective reports are collected, but the outcomes are reviewed and evaluated separately. The present analysis was based on the latest available APR Interim Report[24] (1 January 1989 through 31 January 2015)

Endpoints assessment and variables of analysis

The following endpoints were selected in pregnant women with HBV infection: Pregnancy outcome and efficacy of preventing MTCT.

According to the Committee for Medicinal Products for Human Use (CHMP) 2005 guidelines on the exposure to medicinal products during pregnancy, "pregnancy outcome" is defined as the end products of pregnancy, which include three main categories: (1) fetal death; (2) termination of pregnancy; and (3) live birth[25].

Fetal death (intrauterine death or *in utero* death) is defined as death prior to complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not show any evidence of life [World Health Organization (WHO) International Classification of Diseases (ICD) 10]. There are 2 types of fetal death: (1) early fetal death (before 22 completed weeks of gestation) comprises ectopic pregnancy (extrauterine pregnancy or early fetal death most often in the Fallopian tube) and miscarriage (spontaneous abortion or molar pregnancy); and (2) late fetal death (after 22 completed weeks of gestation) is known as stillbirth.

Termination of pregnancy (induced abortion or elective abortion) is artificial interruption of pregnancy.

Live birth is the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy, which breathes or shows any evidence of life after separation (WHO ICD 10).

The same guidelines also defined the variables used to measure prevalence of birth defects[25]: (1) live birth prevalence rate = (number of cases among live born infants/total number of live born infants) × 1000; (2) birth prevalence rate = [number of cases among live and stillborn infants/total number of (live + still) born infants] × 1000; and (3) Total prevalence rate = (number of cases among live births, stillborn and terminated pregnancies)/(number of live births, stillbirths and

Table 3 Non-overlapping literature references of telbivudine exposure during pregnancy

Ref.	Original language	Study design	LdT starting trimester during pregnancy	No. of pregnancy with exposure to LdT	Maternal HBV DNA (at inclusion)
Chen *et al*[46]	Chinese	Prospective	1st trimester	43	$\geqslant 1 \times 10^7$ copies/mL
Han *et al*[47]	English	Prospective	2nd and 3rd trimesters	362	$> 1.0 \times 10^6$ copies/mL
Jiang *et al*[53]	Chinese	Prospective	3rd trimesters	28	$> 10^3$ copies/mL (at inclusion)
Liu *et al*[38]	Chinese	Prospective	3rd trimester	5	$\geqslant 1 \times 10^7$ copies/mL (before treatment)
Liu *et al*[28]	English	Prospective	1st trimester	89	$> 1 \times 10^5$ copies/mL
Liu *et al*[21]	English	Prospective	1st, 2nd or 3rd trimesters	82	$\geqslant 10^6$ IU/mL
Mohan *et al*[54]	English	Prospective	1st trimester	1	4.0433×10^4 copies/mL
Peng *et al*[39]	Chinese	Prospective	3rd trimester	40	$\geqslant 1 \times 10^6$ copies/mL
Wu *et al*[27]	English	Prospective	2nd or 3rd trimester	279	$> 10^6$ IU/mL
Yu *et al*[44]	English	Prospective	1st, 2nd or 3rd trimester	233	$> 1.0 \times 10^6$ copies/mL
Zeng *et al*[40]	Chinese	Prospective	3rd trimester	22	$\geqslant 10^5$ copies/mL
Zeng *et al*[22]	English	Prospective	1st or 3rd trimester	54	Not reported
Zhao *et al*[55]	Chinese	Prospective	3rd trimester	30	Not reported
Zhang *et al*[41]	Chinese	Prospective	3rd trimester	31	$> 1 \times 10^7$ copies/mL
Zhang *et al*[42]	Chinese	Prospective	3rd trimester	60	$\geqslant 1 \times 10^6$ copies/mL
Zhang *et al*[26]	English	Prospective	3rd trimester	257	> 6 log10 copies/mL
Zhou *et al*[43]	Chinese	Prospective	3rd trimester	36	$\geqslant 1 \times 10^7$ copies/mL
Zhou *et al*[45]	Chinese	Prospective	1st trimester	73	$\geqslant 1 \times 10^7$ copies/mL

terminated pregnancies) × 1000.

The efficacy variable is the rate of MTCT, which is conservatively defined as evidence of HBV infection (detectable HBV DNA or detectable HBsAg) at the age of 6-12 mo or older in the source literature references.

RESULTS

Preclinical studies

Studies in pregnant rats (Study 7245-112) and rabbits (Study GVA00010) showed that telbivudine crosses the placenta. Developmental toxicity studies in rats (Study 1314-001) and rabbits (Study 1314-002) at doses up to 1000 mg/kg per day and with exposure levels 6- to 37-times higher indicated that telbivudine was not a developmental toxin in either species (Table 2). Similarly, the high doses (1000 mg/kg per day) given to rats during the peri- and post-natal developmental periods showed no evidence of post-natal developmental toxicity or change in behavior (Study 1314-003). Based on these findings, it is concluded that telbivudine is not teratogenic and has shown no adverse effects in developing embryos and fetuses, as well as in pre- and postnatal development. Telbivudine use is considered to pose a negligible risk to fetus during pregnancy.

Clinical studies from literature search

Characteristics of the selected cases: A total of 18 publications with non-overlapping data and safety information were identified through the literature search, in which 1725 mothers were treated with telbivudine during pregnancy period. These 1725 non-overlapping pregnancy cases were all prospective cases where mothers were exposed to telbivudine during different trimester of pregnancy. The 18 selected publications are listed in Table 3.

MTCT rate: Based on the literature review, MTCT rate of telbivudine treatment during pregnancy with the standard immunoprophylaxis procedure was reported to be 0.70% (11/1572; Table 4). Of the 11 infants with MTCT, 8 mothers started telbivudine treatment from 3rd trimester and 3 mothers started from 1st trimester. Of the 11 infants with MTCT, 6 mothers had > 6 log copies/mL HBV DNA prior to telbivudine treatment, 2 mothers had > 5 log copies/mL and 2 mothers had > 3 log copies/mL HBV DNA. There was no report on HBV DNA level for 1 mother.

Of the 18 selected literature references, 14 had a non-antiviral control group. The MTCT rate in the non-antiviral treatment group was 11.9% (124/1041; Table 4). The MTCT rate calculated in telbivudine treated patients (0.70%) was significantly lower *vs* MTCT rate calculated in patients from non-antiviral control group (11.9%) ($P < 0.0001$, Fisher's exact test).

Rates of birth defects: A total of 1739 pregnancy outcomes were reported from 1725 pregnancies (Figure 1). The safety outcomes of infants in terms of rates of birth defects were calculated according to the three definitions of the CHMP guidelines[25].

Of the 1673 live births, a total of 6 infants had birth defects (3 infants with ankyloglossia, cutaneous hemangioma, and vaginal canal leak[22]; 1 infant with unilateral cleft palate[26]; 2 infants with a congenital cleft lip, palate and ear accessories[27,28]). Of the 6 infants with birth defects, 4 were born to mothers starting telbivudine treatment in 1st trimester and 2 were born to a mother starting telbivudine treatment in 2nd or 3rd trimester. The "live birth prevalence rate" was 6/1673 = 3.6/1000 which was not significantly different from the non-antiviral control (3.0/1000) ($P = 1.0000$) (Table 4). Since no stillbirth was reported, the "birth prevalence rate" was same as the "live birth prevalence rate" 6/1673 = 3.6/1000, which was not significantly different from the non-antiviral control (3.0/1000) ($P = 1.0000$). The "total prevalence rate" of birth defects with telbivudine exposure was 7/1674 = 4.2/1000 (Table

Table 4 Summary of prevalence rates of birth defects, abortion and perinatal transmission rates with telbivudine exposure during pregnancy in literature studies

	Events (*n*)	Population (*N*)	Rate in telbivudine treated patients (*n*/*N*)	Non-antiviral treatment control in literature studies	Background rates in overall population (prevalence based on surveillance reports)
Birth defects: Live birth prevalence	6	1673	3.6/1000[a]	3.0/1000	14.5-60/1000[1]
Birth defects: Birth prevalence	6	1673	3.6/1000[a]	3.0/1000	NA
Birth defects: Total prevalence	7	1674	4.2/1000[b]	3.0/1000	NA
Spontaneous abortion	7	1682	4.2/1000	NA	16/1000[2]
Elective termination	1	1682	0.6/1000	NA	230/1000[3]
MTCT	11	1572	0.70% (11/1572)[d]	11.9% (124/1041)	10%-15%[4]

[1]EUROCAT data[48]; MACDP data[49]; Christianson *et al*[50] (2006); Dai *et al*[34] (2011); [2]US CDC data[51]; [3]WHO data[52]; [4]Historical data from HBV-infected population without antiviral treatment[10-12]. [a]P = 1.0000 *vs* non-antiviral treatment control in the same literature studies (Fisher's exact test); [b]P = 0.7502 *vs* non-antiviral treatment control in the same literature studies (Fisher's exact test); [d]P < 0.0001 *vs* non-antiviral treatment control in the same literature studies (Fisher's exact test). NA: Not available; MTCT: Mother-to-child transmission.

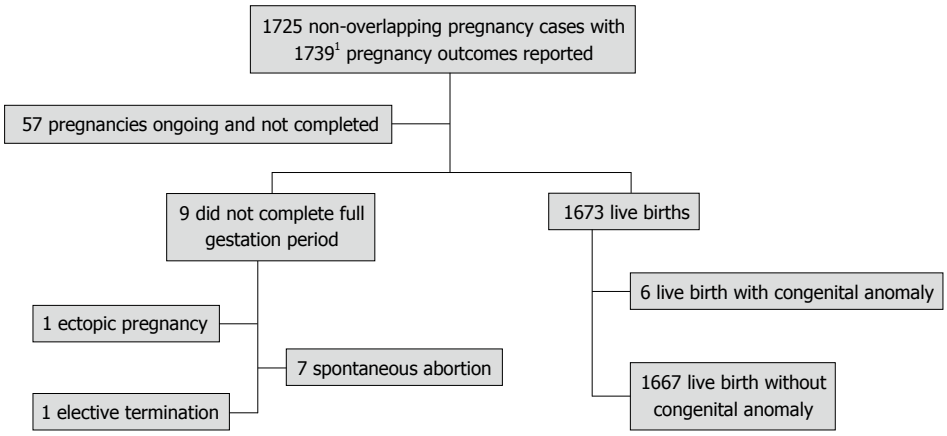

Figure 1 Analysis of the pregnancy outcomes from non-overlapping literature references. [1]1734 pregnancy outcomes from 1721 pregnancy mothers due to multiple births.

4), which was not significantly different from the non-antiviral control (3.0/1000) (P = 0.7502).

Pharmacovigilance database: A total of 489 cumulative pregnancy cases have been reported in the telbivudine pharmacovigilance database (with a cut-off date 31 August 2014). Of the 489 cases, 308 had known pregnancy outcomes with 249 cases of live births (239 cases of live birth without congenital anomaly and 10 cases of live birth with "congenital anomaly" including medical conditions that were not birth defects). Of these 10 cases, 6 cases were considered with congenital birth defects (one case each of hypertrophic pyloric stenosis, cryptorchism, atrial septal defect, syndactyly, hemangioma, and congenital heart disease). Of these 6 cases, 3 had telbivudine exposure during the first trimester.

Fifty-nine cases were reported with the following situations: Ectopic pregnancy (n = 2), spontaneous abortion (n = 11), intrauterine death (n = 3), neonatal death (n = 1), elective termination with fetal defects (n = 5) and elective termination without fetal defects or unknown (n = 37).

Antiretroviral pregnancy registry: Based on the cumulative current APR report (1 January 1989 through 31 January 2015), a total of 17332 evaluable prospective cases treated with anti-retroviral drugs during pregnancy period [most with human immunodeficiency virus (HIV) infection] were included in the primary analysis. Of the 8602 birth outcomes with a 1st trimester exposure to an antiretroviral drug, there were 219 reports of birth defects. Of the 9026 birth outcomes in the combined second and/or third trimester exposure to antiretroviral drugs, 249 were reported birth defects. Of 27 patients who were exposed to telbivudine during pregnancy (18, 6 and 3 during first, second and third trimester, respectively), 19 live births were reported and there were no cases of birth defects reported.

DISCUSSION

The prevention of vertical transmission of HBV from mothers to their infants, while limiting toxicity is the key for treating pregnant women with HBV infection and is a significant unmet medical need. Telbivudine, classified as a FDA pregnancy category B drug, is listed

as one of the preferred drugs and may be used for the prevention of MTCT in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA > 10^{6-7} IU/mL)[15,23]. Preclinical studies have demonstrated that telbivudine is not teratogenic and has not shown any adverse effects in developing embryos and fetuses, as well as in pre- and postnatal development. However, certain other antiviral drugs are associated with some potential teratogenic risks during fetal development. A French long-term perinatal cohort study in HIV-infected mothers reported the risks of lamivudine exposure during pregnancies as it causes birth defects in children[29]. In the present analysis, based on a systematic literature review of clinical studies, the total prevalence rate of live birth defects in telbivudine-treated pregnancies was not significantly different as compared to the non-antiviral controls in the same literature studies or did not increase as compared to overall prevalence. In the six cases that were reported with congenital anomalies, no particular organ toxicity emerged. Three infants were reported with ankyloglossia, cutaneous hemangioma, and vaginal canal leak; 1 infant with unilateral cleft palate; 2 infants with a congenital cleft lip, palate and ear accessories. The reported prevalence of accessory auricle (0.06%) in this study was not higher than in studies from China (0.3%)[30], Taiwan (0.2%)[31], or Turkey (0.47%-0.7%)[32,33]. The reported prevalence of cleft lip and palate (0.12%) in this study was similar to those rates reported in studies performed in China (0.13%)[34], in United States (cleftlip with or without palate 0.114% or cleft palate without cleft lip 0.109%)[35].

The present analysis provides evidence that telbivudine usage in pregnant women in all pregnancy trimesters is generally safe and efficacious, which is in accordance with the EASL guidelines[15]. Moreover, at least 297 mothers with telbivudine exposure during 1st trimester were included in our study. Of note, 4/6 infants with birth defects were born to mothers who were exposed to telbivudine in the 1st trimester; and 8/11 infants with MTCT were born to mothers who were exposed to telbivudine in the 3rd trimester of pregnancy. Accordingly, the starting trimester of telbivudine treatment should be a balanced decision considering the maternal HBV DNA load and the need of minimizing risk of birth defects to achieve a best efficacy and safety outcome.

The pharmacovigilance database setting is different from clinical trials in terms of nature, objective or data completeness. In a clinical trial setting, all pregnancy cases treated with telbivudine are required to be collected either prospectively or retrospectively according to a predefined protocol. In contrast, pharmacovigilance database is an observational setting which is targeted to collect adverse event cases reported from all sources and physicians (or consumers) are trained to report cases when any "adverse" event occurs. However, pregnancy is usually not regarded by physicians and consumer as an "adverse" event. As a result, a majority of pregnancy cases with normal outcomes are not reported to the pharmacovigilance database, but those with unfavorable pregnancy or infants' outcome are more likely to be regarded as "adverse" events and reported. In other words, pregnancy cases with normal outcomes are either under-reported by physicians or cannot be sufficiently collected in the current safety database settings. Therefore, in this review, data from the pharmacovigilance database was cited as another source of data, and it was not pooled with data from literature studies to calculate the prevalence rates of birth defects.

Several recent reviews on telbivudine use in pregnancy have reported results of pregnancy outcomes and prevention of HBV transmission, which were consistent with our results. A meta-analysis of telbivudine use in pregnancy (two randomized controlled trials and four non-randomized controlled trials) analyzed 306 mothers who received telbivudine treatment (*vs* no treatment, n = 270). After a follow-up of 6-12 mo after delivery, HBV DNA positive rates were 0.9% in the telbivudine group *vs* 14.6% in the control group[36].

In another review of 8 studies, a total of 663 infants born to telbivudine-treated mothers had significantly lower rates of HBsAg positivity and HBV DNA positivity measured post-partum at 6 mo (OR = 0.06, P < 0.00001; OR = 0.05, P = 0.0003) and 12 mo (OR = 0.13, P = 0.007; OR = 0.08, P = 0.001) *vs* the non-treatment control[37].

Although the mechanism of MTCT of HBV is not yet fully elucidated, there are three proposed mechanisms (intrauterine transmission, transmission during delivery and post-partum transmission)[9]. Maternal serum HBV DNA level has been identified as the most important independent risk factor for MTCT[15].

A majority of patients in our analysis had HBeAg-positive CHB and high HBV DNA levels prior to treatment with HBV DNA levels and HBeAg status being evenly matched between the telbivudine-treated patient and control groups. Telbivudine use during pregnancy resulted in a low rate of MTCT at 0.70% despite high HBV DNA levels at baseline. The MTCT rate in the non-antiviral control groups of the 14 literature references was 11.9%, which was similar to the rates reported in previous literature references (10%-15%)[10,11]. These results from 18 different studies with 1725 pregnancies indicate that the overall blocking of vertical transmission is 99.3% (MTCT 0.70%). Of the 18 literature studies, 15 studies did not report antiviral resistance associated with telbivudine treatment; 3 studies had reported a resistance rate of 1.2%, 2.3% or 6.5%.

A limitation of the analysis is the follow-up period in literature references which was a maximum of 12 mo for most of infants; therefore, long-term effects on such infants remain to be assessed.

In conclusion, the data from literatures, post-marketing pharmacovigilance reports on telbivudine exposure and APR during pregnancy in women with HBV infection showed no increased rates of live birth defects, spontaneous abortion or elective termination. No fetal/neonatal toxicity was reported during telbivudine treatment. The favorable safety profile observed from telbivudine reproductive and developmental preclinical

studies have been confirmed in various clinical settings. Importantly, based on the evidences from more than 1700 of HBV infected mothers reported from literature, telbivudine exposure in pregnancy has been shown to reduce the risk of HBV transmission from mother to child if administered in addition to HBIg and HBV vaccination with a favorable safety profile.

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COMMENTS

Background

Currently, no anti-hepatitis B virus (HBV) therapies are approved for the prevention of mother-to-child transmission (MTCT) of HBV during pregnancy. In this comprehensive review, data were collected from the published literature, a pharmacovigilance database and an ongoing public registry antiretroviral pregnancy registry (APR).

Research frontiers

Here the authors present a summary of the information available on the safety and efficacy of telbivudine when used during pregnancy. This analysis was based on scientific literature, and analysis of a Novartis pharmacovigilance database and a public APR.

Innovations and breakthroughs

The favorable safety profile observed from telbivudine reproductive and developmental preclinical studies have been confirmed in various clinical settings. Importantly, based on the evidences from more than 1700 of HBV infected mothers reported from literature, telbivudine exposure in pregnancy has been shown to reduce the risk of HBV transmission from mother to child if administered in addition to hepatitis B immunoglobulin and HBV vaccination with a favorable safety profile.

Peer-review

This is a very interesting study on the safety of telbivudine administration in pregnancy and its efficacy in preventing MTCT of HBV infection. The data are well analysed and written and the conclusions are useful particularly for the hepatitis B e antigen positive mothers with high viral loads.

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