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Contents

Three issues per month Volume 9 Number 13 May 8, 2017

REVIEW

- 613 Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease
Tran-Minh ML, Sousa P, Maillet M, Allez M, Gornet JM

MINIREVIEWS

- 627 Management of centrally located hepatocellular carcinoma: Update 2016
Yu WB, Rao A, Vu V, Xu L, Rao JY, Wu JX

ORIGINAL ARTICLE

Retrospective Study

- 635 Importance of surgical margin in the outcomes of hepatocholangiocarcinoma
Ma KW, Chok KSH

LETTERS TO THE EDITOR

- 642 Bi-directional hepatic hydrothorax
Nellaiyappan M, Kapetanios A

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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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Hepatic complications induced by immunosuppressants and biologics in inflammatory bowel disease

My-Linh Tran-Minh, Paula Sousa, Marianne Maillet, Matthieu Allez, Jean-Marc Gornet

My-Linh Tran-Minh, Paula Sousa, Marianne Maillet, Matthieu Allez, Jean-Marc Gornet, Department of Gastroenterology, AP-HP, Saint Louis Hospital, 75010 Paris, France

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Correspondence to: Dr. Jean-Marc Gornet, Department of Gastroenterology, AP-HP, Saint Louis Hospital, 1 Avenue Claude Vellefaux, 75010 Paris, France. jean-marc.gornet@aphp.fr
Telephone: +33-1-42499575
Fax: +33-1-42499168

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Abstract

The incidence of inflammatory bowel diseases (IBD) is

rising worldwide. The therapeutic options for IBD are expanding, and the number of drugs with new targets will rapidly increase in coming years. A rapid step-up approach with close monitoring of intestinal inflammation is extensively used. The fear of side effects represents one the most limiting factor of their use. Despite a widespread use for years, drug induced liver injury (DILI) management remains a challenging situation with Azathioprine and Methotrexate. DILI seems less frequent with anti-tumor necrosis factor agents and new biologic therapies. The aim of this review is to report incidence, physiopathology and practical guidelines in case of DILI occurrence with the armamentarium of old and new drugs in the field of IBD.

Key words: Drug induced liver toxicity; Inflammatory bowel disease; Crohn's disease; Ulcerative colitis

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Core tip: The therapeutic options for inflammatory bowel disease (IBD) are expanding, and the number of drugs will rapidly increase in coming years. The fear of side effects represents one the most limiting factor of their use. Despite a widespread use for years, drug induced liver injury (DILI) management remains a challenging situation with Azathioprine and Methotrexate. DILI seems less frequent with anti-tumor necrosis factor agents and new biologic therapies. The aim of this review is to report incidence, physiopathology and practical guidelines in case of DILI occurrence with the armamentarium of old and new drugs in the field of IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) mainly involve the intestinal tract. They may be associated with many extra intestinal manifestations^[1]. Among them, hepatobiliary manifestations are frequent and often linked with immune disorders (primary sclerosing cholangitis, auto immune hepatitis, overlap syndrome and IgG4 associated cholangiopathy) or drug induced liver injury (DILI)^[2]. Approximately 30% of IBD patients will present abnormalities of liver function tests (LFT) during the course of the disease^[3]. Over the decades, immunosuppressants (thiopurines, methotrexate, calcineurine inhibitors) and anti-tumor necrosis factor (TNF) agents, took an increasing part in the armamentarium of IBD^[4]. More recently, integrin antagonists and interleukine 12/23 inhibitors have emerged in patients refractory or intolerant to anti-TNF therapy^[5]. The safety profile of these drugs is an important issue that may limit their use. Acute and/or chronic hepatic injuries directly induced by the treatment or consequently to occurrence or reactivation of an infection have been described with almost all of these treatments. This article reviews the literature regarding hepatic complications of immunosuppressants and biologics in IBD.

Thiopurines

Thiopurines including azathioprine (AZA) and 6-mercaptopurine (6-MP) have been shown to be effective for induction and maintenance of remission in IBD^[6,7]. Combination therapy with infliximab plus azathioprine is more likely to induce clinical remission than those receiving azathioprine or infliximab alone in both CD and UC^[8,9]. Addition of AZA/6-MP can eliminate antibodies to infliximab in serum and restores clinical response of infliximab in IBD patients^[10]. Some studies have also suggested that thioguanine (TG) could be used as an alternative for patient's refractory or intolerant to AZA or 6-MP^[11]. AZA and 6-MP have frequent side effects which usually occur within four to six weeks after introduction and concern up to 25% of patients with an annual risk of 7% per patient-year of treatment^[12,13]. Depending on its definition, thiopurines hepatotoxicity frequency can vary between 0% and 17%^[14,15]. In a large study of 786 patients, LFT elevation was observed in 4% of the population^[16]. In a systematic review of 34 studies including a total of 3485 patients, the mean prevalence of AZA/6-MP induced liver disorders was estimated at 3.4% with no difference between both drugs^[17]. It has been suggested that the risk of hepatotoxicity was lower in females and higher in CD and active smokers^[13,18]. Nonalcoholic fatty liver disease (NAFLD) is increased in IBD patients and has been shown to be an independent risk factor for hepatotoxicity in patients exposed to AZA/6-MP^[19]. In a prospective study, use of corticosteroids was associated with an increased risk of AZA/6-MP induced hepatotoxicity whereas anti-TNF had a protective effect^[20]. Thus, according to this relatively

high frequency, LFT monitoring is mandatory in exposed patients. Adverse reactions to thiopurines can be divided in two groups: Dose independent and dose dependent. The most frequently reported dose-independent events are rash, fever and arthralgia, pancreatitis and hepatitis. It is thought to be immunological mediated and frequently observed in the first weeks of treatment^[20]. Dose dependent effects appear later, after months to years, and are correlated with elevated concentration of 6-MMP. Various endothelial cell injuries with resultant raised portal pressures can also developed.

Physiopathology: Purine analogues act as a DNA synthesis inhibitor by incorporation of thiopurine nucleotide metabolite into DNA, leading to both cytotoxicity and immunosuppression^[21]. Thiopurines metabolism go through a complex enzymatic pathway. AZA and 6-MP are prodrugs of 6-thioguanine metabolite (6-TGN), the final effective metabolite. AZA is first absorbed and metabolized in the liver to 6-MP which is metabolized by 3 enzymes including thiopurine S-methyltransferase (TPMT) leading to 6-methylmercaptopurine (6-MMP) formation. 6-MMP is a non-effective metabolite but is involved in thiopurine toxicity, particularly hepatotoxicity. Up to 20% of IBD patients preferentially metabolize thiopurines to 6-MMP. Indeed, high 6-MMP level (up to 5700 pmol/8 × 10⁸ erythrocytes) is correlated with a 3-fold increased risk of LFT elevation (18% vs 6%)^[14]. Various polymorphisms of TPMT gene has been described, leading to different level of enzyme activity: 0.3% of individuals have low or absent TPMT activity, 11% have intermediate activity and 89% have normal activity^[22]. TPMT polymorphisms has been mainly associated with hematotoxicity especially neutropenia^[23,24]. It was suggested that high TPMT activity could facilitate hepatotoxicity by the accumulation of 6-MMP. However, in a recent meta-analysis of 10 studies including 1875 patients, TPMT polymorphisms were not associated with hepatotoxicity^[25]. The mechanisms by which thiopurines cause hepatotoxicity are not well established. A recent study with a proteomic approach suggests that induction of oxidative stress in T-lymphocytes by thiopurines could play an important role^[26].

Acute hepatotoxicity: Half of thiopurine DILI occur within the first 3 mo usually prematurely after AZA/6MP introduction^[20]. This acute dose independent toxicity is linked to hypersensitivity and idiosyncratic cholestatic reaction non-mediated by IgE reaction. These effects are unrelated to 6-MMP. Clinical symptoms such as fever, rash or lymphadenopathy, hepatomegaly and other biological abnormalities (atypical lymphocytosis, eosinophilia) may be observed concomitantly with elevated LFT. Most of hypersensitive reactions are hepatitis-like picture with moderate elevation of aspartate aminotransferase and alanine aminotransferase (ALT). More rarely, severe cholestatic hepatitis with jaundice

have also been reported with AZA^[27,28].

Long term hepatic injury: Nodular regenerative hyperplasia (NRH) is defined by hepatocytes hyperplasia and nodules formation, without fibrosis proliferation separating nodules consecutive to vascular flow variation within liver. It frequently results in portal hypertension (PHT) with its potential complications^[29]. NRH may be asymptomatic with normal liver tests for many years^[30]. The diagnosis of NRH remains challenging and mainly depends on histological report. However, the interobserver agreement on the histopathologic diagnosis of NRH is flawed, even when assessed by well-experienced liver pathologists^[31]. The pathogenesis of NRH in IBD patients is poorly understood but is likely to be multifactorial.

The largest series describing NRH in IBD under thiopurines reported 37 cases in 11 French tertiary centers of the GETAID group. The cumulative risk of NRH was estimated to 0.5% at five years and 1.25% at 10 years. The diagnosis was made after a median time of 48 mo after AZA introduction (range: 6 to 187 mo) and 14 patients (38%) developed PHT during follow-up. Identified risks factors were male sex and stricturing behavior^[28]. Another study has shown that the high-risk patient group was males with small bowel resection \geq 50 cm either prior to or after AZA initiation^[32]. However, IBD in itself can be associated with NRH, and was incidentally found in 6% of thiopurine naive IBD patients undergoing bowel resection^[33]. It has been hypothesized that intestinal surgery might promote obliterative portal venopathy by causing malabsorption of vitamins B12, B6 and folic acid, with resultant hyperhomocysteinemia^[34]. Some studies have demonstrated that TG treatment (Lanvis[®]) induced more NRH than AZA or 6-MP^[35,36]. In the study by Dubinsky *et al.*^[35], 33% of the patients treated with TG had NRH at liver biopsy. No association was found with duration of TG treatment, cumulative dose, or TG nucleotide levels. Geller *et al.*^[37] reported systematic liver biopsies in 37 patients exposed to TG during 1 to 3 years. NRH of varying degree was seen in 20 patients (53%). Another study has suggested that low-dose TG maintenance therapy may be safer^[38]. In 28 patients treated at least 30 mo with TG, they observed no histological sign of HNR in 93% of the cases. This finding is reinforced by a recent study which nicely shows in a murine model that sinusoidal obstructive syndrome induced by TG may be avoided by either inhibition of endothelial activation or simple changes to dosing regimens of TG^[39]. Nevertheless, regarding the extensive use of newer alternative drugs to thiopurines, TG has been abandoned in clinical practice because of its hepatotoxicity. Natural history of HNR after thiopurines discontinuation remains unclear and either persistent aggravation or improvement have been reported^[11,40].

Other vascular disorders associated with thiopurines such as peliosis hepatitis, veno-occlusive disease, hepatoportal sclerosis, sinusoidal dilatation and perisinusoidal fibrosis were also described initially in patients treated for acute leukemia but have been occasionally reported in

IBD patients^[41-44]. *In vitro* studies with murine sinusoidal endothelial cells and hepatocytes exposed to azathioprine have suggested that the mechanism of hepatotoxicity is sinusoidal endothelial damage associated with glutathione depletion^[45].

Management: Most of LFT abnormalities resolve spontaneously or after dose reduction. In a large study with long term follow-up, only 3.6% of patients required treatment cessation for hepatotoxicity^[16]. In another study, 90% of patients normalized their liver test after decreasing dose or treatment withdrawal^[46]. One of the main questions concerning AZA toxicity management is whether substitution of AZA by 6-MP might affect or decrease hepatotoxicity. In a study of 135 patients with AZA intolerance, 6-MP was well tolerated in almost three quarters of the patients who presented hepatotoxicity (12/17 patients; 71%) suggesting that this option deserves to be tested^[47]. Some authors have suggested that routine thiopurines metabolite (especially 6-MMP) monitoring may identify subjects at high risk of hepatotoxicity. Administration of 6-MP twice daily instead of once daily has even been proposed to decreased 6-MMP levels to reduce the risk of hepatotoxicity^[46]. Furthermore, twice daily administration decreases 6-MMP levels without affecting 6-TGN levels may lead to equivalent efficacy^[48]. Another tool to adapt 6-MMP dosage is coadministration of allopurinol. This drug is a xanthine oxidase inhibitor, an enzyme which metabolizes 6-MP. Xanthine oxidase inhibition leads to increase 6-TGN level by improving drug availability. Since more 6-MP is available for conversion to 6-TGN, a lower dose of thiopurines is sufficient and may avoid toxicity. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in IBD patients has been proven whatever the initial adverse event with increased 6-TGN and decreased 6-MMP concentrations^[49,50]. In a pilot study of 11 patients with acute thiopurine hepatotoxicity secondarily treated with allopurinol co-therapy with low-dose AZA or MP, 82% of the patients remained in long-term remission with normal liver tests^[51]. A larger study in 25 patients showed similar results with normalization of LFT in 80% of the cases after switch to a combination treatment^[52]. It has been shown that 5-ASA daily use results in increased 6-TGN levels and reduced 6-MMP levels with a dose-dependent effect suggesting that salicylates may reduce the risk for hepatotoxic adverse reactions related to AZA/6-MP^[53,54]. However, there is a lack of prospective data supporting the therapeutic impact of 5-ASA on AZA/6-MP hepatotoxicity prevention. Recently, in a small cohort of 12 patients, no pharmacokinetic interaction was found between adalimumab and thiopurines with comparable concentrations of 6-TGN and 6-MMP before anti-TNF introduction and throughout 12 wk of follow-up^[55].

Methotrexate

Methotrexate (MTX) is an antimetabolite with both anti-proliferative and immunosuppressive activities impairing DNA synthesis *via* inhibition of dihydrofolate reductase,

decreased the production of proinflammatory cytokines and lymphocytes apoptosis^[56]. Regimens containing MTX are classified as high-dose, intermediate or low dose, determined as dose per unit of body surface area. The management of CD utilized only low dose MTX (< 50 mg/m²), usually over a long period of time. In this last group the association between MTX and hepatic dysfunction has been extensively studied. In CD, MTX given intramuscularly once weekly at a dose of 25 mg is effective at inducing and maintaining remission in thiopurine-naïve patients^[57,58]. Small labelled studies have also suggested efficacy in patients who failed or are intolerant to thiopurines^[59,60]. Data are more limited and conflicting in UC^[61,62]. In addition, MTX is widely prescribed in combination with biological therapy to reduce immunogenicity and to maintain clinical response^[63]. The most common adverse effects involve the gastrointestinal tract such as nausea, vomiting and diarrhea. More serious toxicities such as myelosuppression and abnormal LFT are dose-dependent. Liver toxicity was firstly reported with the use of MTX in psoriasis and inflammatory rheumatic disorders with high initial rate over 25% of the patients. Obesity, alcoholism, diabetes mellitus, previous abnormalities in LFT and a high accumulated dose of MTX were considered as risk factors of liver toxicity in those diseases^[64,65]. There is a paucity of studies evaluating liver toxicity as a complication of MTX therapy in the setting of IBD, and no gastroenterology societal recommendations on monitoring for hepatic toxicity have been formulated.

Profile and mechanism of liver injury: Most of understanding of the hepatotoxic potential of MTX came from its use in non-malignant disease such as rheumatoid arthritis (RA) and psoriasis.

The mechanism by which MTX adversely affect the liver remains unclear. Liver response to inflammation is fibrosis *via* stellate cell, mediated by metabolite accumulation in liver cell and inhibition of folate metabolite leading to a decreased nucleotid synthesis.

Several polymorphisms in enzymes involved in the metabolism of folic acid are related to the toxicity of MTX. The C677T and A1298C polymorphisms in the MTHFR gene were the most reported, however studies have reported conflicting results. Two meta analyses have been performed. One described an association of the C677T polymorphism with increased toxicity whereas the second found no association between either the C677T or the A1298C polymorphisms of MTHFR and toxicity of MTX in RA^[66,67].

Methotrexate can induce a variety of non-specific histologic changes including macrovesicular steatosis, stellate cell hypertrophy, portal and lobular inflammation and hepatic fibrosis.

Histological toxicity is assessed according to the Roenigk's classification, a subjective and semi quantitative grading liver injury in four 4 groups^[68].

Grade findings: (1) Normal; (2) mild fatty infiltration, nuclear variability, or portal inflammation; (3) moderate

to severe fatty infiltration, nuclear variability, or portal inflammation and mild fibrosis; (4) moderate to severe fibrosis; and (5) cirrhosis.

DILI frequency: The first case of MTX liver toxicity was described in 1955 in children treated for leukemia. NAFLD syndrome seems to be an independant risk factor associated with DILI under long term low dose methotrexate use^[69].

Administration schedule seem to be associated for high, daily dose to liver fibrosis comparing to weekly low dose of MTX. Supplementation with folic acid or folinic acid is associated with reduced incidence of serum transaminase elevation however a relationship between folate depletion and hepatic toxicity has not been fully established^[70,71]. The reported incidence of liver enzyme abnormalities in subjects with IBD receiving MTX is variable.

The pooled incidence rate of abnormal hepatic aminotransferase levels (defined as more than 2-fold increase over the upper limit of the normal range) in patients treated with methotrexate for IBD was 1.4 per 100 person-months, while the rate of hepatotoxicity (defined as greater than a 2-fold over the upper limit of the normal range) was 0.9 per 100 person-months. The rate of withdrawal from treatment due to these abnormalities was 0.8 per 100 person-months^[72].

It is estimated that 15% to 50% of patients receiving a chronic low dose of MTX therapy will develop elevated LFT, usually mild and limited. In most recent studies, incidence seems lower varying from 5%-10% probably due to co-founding risk factors in initial studies such as alcohol intake, obesity, diabetes mellitus, daily dosing and concomitant use of hepatotoxic drugs increasing^[72-74].

In a retrospective study by Fournier on 87 IBD patients with a mean duration of 81 wk and a cumulative dose of 1813 mg, 76% of the population kept normal LFT throughout MTX therapy. Among the patients who developed abnormal LFT, underlying risk factors were found in nearly half of the cases. In 11 patients who have received a cumulative dose exceeding 15000 mg, a liver biopsy found no case of moderate or severe fibrosis (Roenigk IIIb or IV) despite abnormal LFT in nine of them. In twenty patients (23%) with abnormal LFT at baseline, spontaneous normalization under MTX was observed in 45% of the cases. Eventually, only 5% of the whole population, needed treatment discontinuation for MTX hepatotoxicity^[74].

Another study reporting 20 liver biopsies in patients treated with a cumulative MTX dose of 2633 mg with abnormal LFT in 30% of the cases confirmed the low incidence of severe fibrosis (Roenigk IIIb in 5%)^[75]. These data suggest that abnormal LFT are poorly correlated with liver histology and confirm the low incidence of severe hepatotoxicity and its uncertain relation with cumulated MTX dose.

End stage liver disease is rare under MTX treatment. In a large retrospective study identifying patient who were listed for liver transplantation over 24 years in the United States, only 117 (0.07%) had MTX related

liver disease with characteristic closed to alcoholic liver disease and NAFLD^[76].

Management: Patients who undergo MTX therapy should have a careful initial evaluation of historic and physical examination emphasis in alcohol intake, exposure to viral hepatitis, NAFLD risk factors and family history of liver disease.

Regular liver laboratory studies are recommended in patients treated with MTX. Liver biopsy is not recommended routinely during MTX treatment whatever the cumulative dose. However, it should be performed in cases of persistent alteration of transaminases (especially if they do not decrease after reducing the drug dose) and in patients with high accumulated doses, together with other risk factors.

According to RA and psoriasis guidelines^[64,65]: Laboratory tests for monitoring hepatotoxicity are recommended, every 2 wk initially for 6 wk to 2 mo and then every 2-3 mo; liver biopsy should be performed in selected cases, in case of sustained liver abnormality (especially in case of persistent abnormal LFT despite dose reduction) or high accumulated doses in patients with others risk factors of hepatotoxicity. Treatment needs to be discontinued in cases of severe fibrosis or cirrhosis; adjusting MTX dose could be proposed in case of liver blood elevation and control in 2 and 4 wk.

Transient elastography (Fibroscan) and non-invasive biochemical methods are emerging as new diagnostic tools to evaluate liver fibrosis in various situations^[77]. In a prospective study in CD patients, the median fibroscan values were similar in 33 treated with cumulative dose of more than 1500 mg and 21 patients naïve of Methotrexate^[78]. However, this tool could be useful to select patient who should undergo liver biopsy. In a retrospective study of 46 patients treated with MTX for IBD, transient elastography detected six cases of significant fibrosis in patients with normal liver function tests^[79]. In a case-control study of 518 patients treated with MTX for various inflammatory diseases, 44 patients (8.5%) had FibroScan and/or FibroTest results suggesting severe liver fibrosis. In a multivariate analysis, the 2 factors associated with abnormal markers of liver fibrosis were high body mass index > 28 kg/m² and high alcohol consumption. Neither long MTX duration nor cumulative doses were associated with elevated FibroScan or FibroTest results^[78]. These data suggest that transient elastography should be useful mainly in heavy drinkers or patients with NAFLD risk factors treated with MTX.

Anti-TNF

TNF- α is a cytokine produced mainly by macrophages that participates in the regulation of inflammation, cell death and proliferation. This cytokine has proinflammatory and immunoregulatory functions and plays a central role in IBD. TNF- α has also effects in the liver, as a mediator of hepatotoxicity and promotor of hepatocyte proliferation and liver regeneration^[80,81]. There are several anti-TNF agents currently approved for the induction and main-

tenance treatment of IBD, namely infliximab (IFX), adalimumab (ADA), golimumab and certolizumab pegol. Several adverse events have been reported with the use of these agents, such as acute infusion and injection-site reactions, cardiopulmonary and neurologic events, among others^[80]. The greatest emphasis has been given to the risk of infections and malignancies, but with an increasing use, other side effects are being uncovered, such as immune-mediated diseases^[82,83].

DILI frequency: In the earlier controlled trials of IFX in RA and CD minor elevation of liver enzymes were reported, but extreme elevations were rare, and there were no cases of jaundice or liver failure^[84,85]. In a Food and Drug Administration (FDA) post-marketing surveillance program more than 130 cases of liver injury associated with either IFX or etanercept were reported, some of which were fatal or necessitating liver transplantation. This led FDA to issue a safety warning in December 2004 stating that severe hepatic reactions, including acute liver failure, autoimmune hepatitis (AIH) and cholestasis could be caused by IFX^[86]. In contrast, ADA hepatotoxic potential appears to be low, usually manifesting as an asymptomatic and transient elevation of liver enzymes^[87]. During ADA controlled Phase 3 trials for CD the rate of liver enzymes elevation was similar to the control-treated patients^[88]. In a study from Iceland that included patients with IBD, rheumatologic and dermatologic disorders, the absolute risk of DILI associated with IFX was 1 in 120, and with ADA was 1 in 270, but only 11 patients with liver injury were identified in a 5-year period^[89]. Even though the numbers were small, no statistically significant differences were found between the rates of DILI of the anti-TNF agents studied. Similar rates had been found in a population-based group from the same group, with a 1 in 148 risk of DILI associated with IFX^[90]. However, as data on the propensity of the anti-TNF to cause drug-induced liver disease comes mainly from case reports and small series it is difficult to estimate the absolute and relative risk of hepatic injury associated with these drugs^[91,92]. In a retrospective study by Shelton *et al*^[93] 1753 IBD patients who initiated anti-TNF therapy (1170 IFX, 575 ADA, 8 certolizumab pegol) were analyzed for new onset ALT elevation. One hundred and two patients (6%) had at least one elevated ALT after initiation of the anti-TNF but in 54 of these patients an alternate cause for liver enzymes elevations was found. Of the 48 patients left (45 due to IFX and 3 to ADA), 4 were considered as highly probable of being caused by anti-TNF. There were no differences in the frequency of concomitant immunomodulator use, either thiopurines or methotrexate. In respect to the newest anti-TNF agents, certolizumab and golimumab, to our knowledge there aren't literature reports of DILI. Nevertheless, FDA label for both of them mentions the risk of hepatitis B virus reactivation and elevation on liver enzymes.

Profile of liver toxicity: In addition to the risk of reactivation of hepatitis B virus (HBV) infection, anti-

TNF are associated with specific patterns of liver injury. The most common presentation is a hepatocellular injury, found in about 75% of the cases^[89,92,94,95]. Other presentations are also described, such as a mixed injury pattern with lower peak ALT levels and, more rarely, a cholestatic injury pattern, reported with both IFX and ADA^[94,96-98]. Overt liver failure sometimes requiring transplantation has rarely been reported^[98-100]. Immunoallergic features such as eosinophilia and rash don't seem to occur frequently in anti-TNF DILI^[89,98]. The median latency time to liver enzyme elevation is reported between 13 and 18 wk^[89,93,98]. Most patients treated with IFX develop liver injury within the fourth infusion, but, rarely, it can occur after several years of treatment^[89,91]. Histologically, a review by Colina *et al.*^[92] found necroinflammation in the biopsied cases of DILI caused by IFX reported in the literature, but with uneven characteristics between reports. Bridging and massive necrosis were described in the most severe cases. There were also features normally described in AIH such as piecemeal necrosis in the periportal interface and prominent plasma cells. In two cases ductal damage was reported, one of which was diagnosed as overlap syndrome. Rarely, features associated with toxicity such as eosinophils and neutrophils infiltration and ceroid containing Kupffer cells were seen. One of the features of DILI associated with anti-TNF is the presence of autoimmunity markers in some patients, such as positivity for antinuclear (ANA - often with a homogeneous pattern), anti-double-stranded DNA (anti-DsDNA) and anti-smooth muscle antibodies and/or classic histologic features of AIH, already described for IFX^[83,91-94,101-104], etanercept and ADA^[105-107]. One of the largest series of 34 patients with DILI, have included 26 cases associated with IFX, 6 with ADA and 4 with etanercept^[94]. Twenty-two of 33 subjects who underwent serologic analysis (67%) were tested positive for anti-nuclear and/or smooth muscle antibodies and presented both later and higher peak levels of alanine aminotransferase than seronegative patients. Of these 22, 17 underwent liver biopsy and 15 subjects had clear features of autoimmunity. The prognosis was good after drug discontinuation, although some patients had benefit from a course of corticosteroids. It is a challenge to distinguish between AIH and drug-induced-AIH as these entities may have similar clinical, biochemical, serological and histological manifestations, with no pathognomonic features^[108]. In a Weiler-Norman and Schramm editorial a specific nomenclature for immune-mediated DILI in 3 categories was proposed^[109]. Furthermore, the diseases for which anti-TNF are used may have simultaneous autoimmune disorders and increased autoimmune markers at baseline as part of their immune dysregulation. Lastly, anti-TNF agents can also induce autoantibodies positivity in some patients without the development of liver abnormalities^[110-113]. In several of the mentioned studies and case series, a proportion of the patients presenting with autoimmune features were treated with corticosteroids. In some of these patients, there was a decrease or disappearance of

autoantibodies with no need of further treatment which suggests an immune-mediated DILI rather than a drug-induced AIH^[89,91,92,94]. Of note, there are also cases of malignancies described in patients treated with anti-TNF agents, notably case reports of hepatocellular carcinoma in non-cirrhotic patients^[114-116] and of hepatosplenic T cell lymphoma^[117-121]. All these patients were in combination treatment with an anti-TNF and a thiopurine, making it difficult to establish the specific role of the anti-TNF agent.

Hepatotoxicity as a class-effect? Even though IFX, etanercept and ADA are all anti-TNF agents that directly bind soluble and membrane-bound TNF- α , they are structurally different. IFX is a chimeric IgG1 monoclonal antibody, ADA a fully humanized IgG1 monoclonal antibody and etanercept (not used in IBD but frequently used in rheumatology) is a soluble TNF- α receptor fusion protein^[122]. This might partially explain why patients with a lack of response to one anti-TNF agent benefit from a switch to another anti-TNF. Also, in the past years, polymorphisms in genes encoding proteins related to TNF- α were identified, explaining to some extent the differences in treatment efficacy and toxicity profile^[123]. So, even though these drugs were all associated with the development of features of autoimmunity, the capacity in doing so is different for each molecule. In some studies, IFX generated a much higher rate of ANA seroconversion and ANA titer increase than etanercept and ADA^[90]. Development of autoantibodies has also been described for certolizumab pegol and golimumab^[124,125]. There are already several cases of successful treatment with another anti-TNF after a prior DILI episode^[90,93-95,126,127]. This suggests a lack of cross-toxicity within this class of drugs. Etanercept is not a treatment option for IBD, but ADA seems to be a safe alternative in patients who developed liver injury due to IFX and vice-versa.

Mechanism of liver injury: The mechanism by which anti-TNF agents induce DILI is still unknown. Even more puzzling is the fact that some patients develop autoimmune diseases for which anti-TNF are a therapeutic option, such as AIH^[109]. As liver injury can occur after only one infusion and is not related to the dose it seems more likely that the hepatotoxicity of anti-TNF agents is idiosyncratic as opposed to dose-dependent^[93]. But the complexity of TNF- α role in the liver makes it difficult to draw firm conclusions and several explanations were suggested to date. Genetically predisposed individuals may develop autoimmune diseases triggered by environmental factors. Another possibility is that anti-TNF agents unmask an already existing autoimmune disorder^[83]. A third explanation relates to the anti-TNF potential in the generation of autoantibodies. The binding of IFX to the transmembrane TNF- α may lead to apoptosis of monocytes and T-lymphocytes with exposition of nucleosomal autoantigens and formation of autoantibodies^[128,129]. The reduced clearance of nuclear debris due to the downregulation of C-reactive protein may also play a role

by prolonged immune system exposure to intracellular material^[130]. The structural differences of anti-TNF agents with different binding affinities do membrane TNF- α and different abilities of complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity may explain the different potentials on the induction of autoimmunity^[113,128,129,131]. Another hypothesis is that anti-TNF agents inhibit the induction of cytotoxic lymphocytes that would suppress auto reactive B cells, therefore promoting humoral autoimmunity^[132]. All these proposed mechanisms try to explain the immune-mediated DILI caused by anti-TNF agents. However, there are several cases without evidence of autoimmunity, in which direct liver damage may be involved^[133,134].

Management of DILI associated with anti-TNF:

The optimal management of liver injury induced by anti-TNF therapy is still not consensual. The prognosis is generally good, with most patients presenting with mild elevation in liver enzymes resolving spontaneously with continuation of anti-TNF therapy^[93]. A consensus statement proposes more restrictive criteria, with avoidance or discontinuation of treatment in patients with transaminases superior to 3 times the upper limit of normal^[135]. Many authors have since suggested different management algorithms^[91,101,136]. Ideally, before initiation of treatment, a baseline panel of liver enzymes should be obtained, together with a determination of HBV and HCV status^[137]. After initiation of treatment, liver enzymes should be monitored periodically, especially during the first three months. When faced with an elevation of liver enzymes, other causes should be excluded, as in any case of suspected DILI. In case of minor elevations of ALT (< 3 times the upper limit of normal), anti-TNF may be continued with close monitoring until resolution. If the enzymes are persistently elevated, superior to 3 times the upper limit of normal or in case of alarm signals such as jaundice, a multidisciplinary approach with refer to an hepatologist and consideration for corticosteroid treatment is advised. A liver biopsy may be useful in this context. If a DILI is documented, anti-TNF withdrawal remains controversial^[91,136]. Even though advocated by some authors the interest of routine assessment of autoimmune markers prior to the introduction of an anti-TNF agent is not established^[83,91,113,136,138]. Several studies show that this approach doesn't predict the risk of developing subsequent liver injury or autoimmune events and treatment with anti-TNF can be continued in the presence of an asymptomatic ANA seroconversion^[89,110,112]. Therefore, routine testing for autoantibodies can't be recommended until further evidence of the clinical implications of these autoantibodies is obtained.

New biologic treatments

Natalizumab and vedolizumab are two integrin antagonists approved for the treatment of IBD. Natalizumab is a humanized recombinant monoclonal antibody that blocks $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrin-mediated interactions, preventing migration of leukocytes into the gut and brain^[139].

Even though its efficacy in the treatment of CD was demonstrated, natalizumab association with a number of cases of progressive multifocal leukoencephalopathy has limited its use^[140,141]. Vedolizumab is a humanized monoclonal antibody with specificity to the gut $\alpha 4\beta 7$ integrin with proven efficacy in the treatment of CD and UC^[142,143]. Both drugs appeared to have good safety profiles during initial trials. However, on post-marketing surveillance, 6 cases of clinically significant DILI related to natalizumab were reported to FDA, leading to an alteration of its label^[144]. In all cases, natalizumab was used for the treatment of multiple sclerosis, and liver injury occurred as early as 6 d after the first administration of the drug. Five of the cases had a hepatocellular pattern of injury, and 3 patients had autoimmune features. One patient had recurrence of the increase of liver enzymes upon readministration of natalizumab, providing evidence that natalizumab was responsible for the injury. There were no deaths nor was a liver transplantation needed. Since then, a case of acute liver failure possibly due to drug-induced AIH and a case of fatal fulminant liver failure due to acute HBV infection in patients treated with natalizumab for multiple sclerosis were reported^[145,146]. There were also cases of elevation of transaminases and/or bilirubin in vedolizumab trials for IBD. Ustekinumab is a fully human monoclonal antibody that blocks the activity of interleukin 12/23 shared p40 subunit. This drug has shown efficacy in the treatment of CD, particularly in patients previously treated with IFX^[147]. The majority of safety data of ustekinumab comes from dermatologic studies. In PHOENIX 1 and 2^[148,149], two studies that evaluated efficacy and safety of ustekinumab in patients with psoriasis, the proportion of patients with liver enzymes abnormalities was low and similar between ustekinumab and control groups. In a small retrospective study including 44 patients with psoriasis treated with ustekinumab, elevation of liver enzymes was mild and uncommon, with no cases of severe DILI^[150]. Interleukin-12 is involved in the clearance of HBV by suppressing viral replication, which may explain why patients treated with ustekinumab might be at increased risk of HBV reactivation^[151]. Most pivotal studies of ustekinumab excluded patients infected with HBV and HCV; for this reason its safety in this context is not known. In a retrospective study in patients with psoriasis and concurrent HBV infection treated with ustekinumab, 4 patients infected with HBV received antiviral prophylaxis during treatment, without evidence of virus reactivation^[152]. Of the 10 patients who didn't receive prophylaxis, 2 fulfilled the criteria for HBV reactivation. In another retrospective study, 3 patients with HCV and 1 patient with HBV under prophylaxis with entecavir were treated with ustekinumab and didn't have an aggravation of the hepatitis^[153]. Cases of acute HBV infection/HBV reactivation during ustekinumab treatment and, on the other hand, cases where ustekinumab was safely administered despite HBV or HCV infection were reported recently^[154-157]. Even though a real frequency of hepatic adverse events is not yet known for these drugs, this evidence suggests that all patients considered

for biologic treatment should be screened for hepatitis B and C infection prior to introduction of the drug, and liver function should be monitored periodically for the duration of the treatment.

Calcineurine inhibitors

Cyclosporine is a potent immunosuppressive drug effective in the treatment of acute severe UC refractory to corticosteroids^[158,159]. Tacrolimus is a potential alternative to cyclosporine^[160,161]. One of the main limitations to cyclosporine use in clinical practice is its safety profile, namely nephrotoxicity, neurotoxicity and infections, with a need of frequent monitoring^[158]. The hepatotoxicity associated with cyclosporine was mainly described in transplant patients. It's generally characterized by a cholestatic pattern due to an impairment of bile formation, probably caused by an interference in the bile secretory apparatus. Liver injury caused by cyclosporine is dose-dependent and can be reduced by a diminution of the dose. Even though the prevalence of liver injury due to cyclosporine was initially estimated to be superior to 50%, this phenomenon was probably due to the use of the drug without blood monitoring, leading to toxic levels of cyclosporine^[162]. Studies in IBD patients show a much lower prevalence of hepatotoxicity, between 1% to 4%, generally translated by an elevation in liver enzymes^[158,163,164]. In one study, 19% of patients (21/111) developed abnormal liver function tests, but they were only significantly high in one patient^[165]. Tacrolimus hepatotoxicity is rare with a similar clinical and biochemical profile to those of cyclosporine. In some cases, there is a lack of cross-reactivity between these two drugs, and one can be used after hepatotoxicity to the other^[162]. Nonetheless, hepatotoxicity is generally considered as a rare and minor adverse event with these drugs.

Thalidomide

Thalidomide was initially used to treat morning-sickness associated with pregnancy, until being withdrawn from the market due to its teratogenic effects. Since that, in view of its anti-inflammatory and immunomodulatory properties, it has been reintroduced for the treatment of various diseases including IBD^[166,167]. Hepatotoxicity with thalidomide is reported as a rare but serious adverse event. In a review of adverse events reported in the first 18 mo of postmarketing surveillance after thalidomide reintroduction in the market, one case of fatal hepatic failure possibly directly related to thalidomide was identified^[168]. In the latest years, other cases with different degrees of severity were reported, mostly in older females treated with thalidomide for multiple myeloma, some of them with an underlying hepatic disease^[169-172]. The mechanism of hepatotoxicity of thalidomide remains unclear. The main route of elimination of thalidomide is through non-enzymatic hydrolysis into multiple products in biological fluids and it doesn't seem to undergo significant hepatic metabolism^[173].

New investigational treatments

More recently several molecules have shown promising results in IBD and should obtain medical agreement within the next few years. Mongersen, a new oral SMAD 7 antisense oligonucleotide was superior to placebo for inducing clinical remission at day fifteen and maintained for at least two weeks in CD^[174]. Increased aminotransferase levels were observed at the dose of 40 mg per day in 5% of the patients but no case was reported at the dose of 10 mg and 160 mg per day.

Tofacitinib, a selective oral inhibitor of the Janus kinase, a family of kinases that mediates signal-transduction activity involving the common gamma chain of the surface receptors for multiple cytokines was superior to placebo for inducing clinical response at week eight in UC^[175]. At week twelve, adverse events occurring in $\geq 5\%$ of patients in any tofacitinib group did not include liver toxicity.

Ozanimod, an oral agonist of the sphingosine-1-phosphate receptor subtypes 1 and 5 that induces peripheral lymphocyte sequestration was superior to placebo at a dose of 1 mg per day for inducing clinical remission at eight weeks^[176]. After exposure to up of 32 wk, aspartate aminotransferase increasing was noted in 2% and 1% of patients treated with 0.5 and 1 mg of Ozanimod respectively. These preliminary data suggest that new therapeutic approaches in IBD induce minor hepatotoxicity.

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Management of centrally located hepatocellular carcinoma: Update 2016

Wei-Bo Yu, Andrew Rao, Victor Vu, Lily Xu, Jian-Yu Rao, Jian-Xiong Wu

Wei-Bo Yu, Victor Vu, Jian-Yu Rao, Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095, United States

Andrew Rao, the College of Letters and Science, University of California at Davis, Davis, CA 95616, United States

Lily Xu, Chemistry Department, Wellesley College, Wellesley, MA 02481, United States

Jian-Xiong Wu, Department of Hepatobiliary Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Author contributions: Yu WB and Wu JX designed the aim of this review; Yu WB, Rao A and Rao JY prepared the manuscript; Vu V and Xu L critically reviewed the manuscript.

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Correspondence to: Jian-Xiong Wu, MD, Professor, Chief, Department of Hepatobiliary Surgery, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Panjiayuan Nanli, Beijing 100021, China. dr.wujx@hotmail.com
Telephone: +86-10-87787100

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Abstract

Centrally located hepatocellular carcinoma (HCC) is sited in the central part of the liver and adjacent to main hepatic vascular structures. This special location is associated with an increase in the difficulty of surgery, aggregation of the recurrence disease, and greater challenge in disease management. This review summarizes the evolution of our understanding for centrally located HCC and discusses the development of treatment strategies, surgical approaches and recurrence prevention methods. To improve patient survival, a multi-disciplinary modality is greatly needed throughout the whole treatment period.

Key words: Centrally located hepatocellular carcinoma; Hepatectomy; Combined treatment; Hepatic vascular occlusion

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Core tip: Centrally located hepatocellular carcinoma (HCC) is situated in the deeper portions of the liver and adjoins main vascular structures. Due to this special location, the management of this group of patients is challenging. Low resection rates and high recurrence rates are two major problems that urgently need to be resolved. This review summarizes the evolution of our understanding for centrally located HCC and the development of disease management, and explores the possible strategies to improve overall patient survival.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide^[1]. Traditionally, we describe centrally located HCC as being sited in Couinaud hepatic segments IV, V or VIII^[2]. These tumors are often adjacent to main hepatic vascular structures and accept a dual blood supply from the right and left hepatic artery branches. Due to this special location, the management of this group of patients is still challenging. Low resection rates and high recurrence rates are two major problems that urgently need to be resolved. In this review, we focus on recently developed centrally located HCC classification, evaluation, surgical techniques and adjuvant treatments, and we explore the possible management strategies to improve overall patient survival.

DEFINITION AND CLASSIFICATION OF CENTRALLY LOCATED HCC

The traditional definition of centrally located HCC is based on Couinaud's segmental anatomy of the liver. In this system, the liver is divided into eight functionally independent segments. Each segment has separating vascular inflow, outflow and biliary drainage. Segments IV, V and VIII lie in the medial and make up the middle part of the liver. Tumors located in this area are called centrally located HCC. However, in clinical settings, the factor that determines the degree of surgical difficulty is not only the segment location of the tumor but also the proximity of the tumor to major vascular structures. To reflect upon its key clinical characteristics, we previously proposed a clinical definition of centrally located HCC based on the relationship between the tumor and vascular structures. This definition defines centrally located HCC as "carcinoma adjoined hepatic portals, less than 1 cm from major vascular structures (including the main portal branches, the main trunks of the hepatic veins as well as the inferior vena cava) which are usually located in Couinaud segments I, IV, V, VIII, or at the junction of the central segments"^[3].

More recently, a new classification system for centrally located HCC was proposed. Focusing on the involvement of resected areas and the anatomical location of tumors relative to the main vascular structures of the liver, this system divided centrally located HCC into four subtypes^[4]. The first subtype is the tumors that are located in liver segment V or/and IVb. The second subtype is the tumors that are located in liver segment IVa or/and VIII. The tumors that are located in the connection of liver segment V/IVb and liver segment IVa/VIII are categorized in the third subtype. This subtype can be further divided

into those that are superficially located and those that are deeply located. The latter is often closely adjacent to the inferior vena cava. The last subtype specifically describes the large tumors that are located in the middle of two hepatic portals. This classification system may help to plan the extent of resection or assess surgical risk, but its practical significance still needs to be further evaluated. The definition and classification of centrally located HCC, which not only rely on anatomic structures but also tumor behavior and treatment strategies, continue to evolve. We reported a single-center experience of the treatment of centrally located HCC in 2013^[5]. Since then, many novel retrospective and prospective studies have been performed in this field. With a deeper understanding, the evaluation and management of the disease have also been changed greatly.

THREE-DEMONSTRAL IMAGING RECONSTRUCTION IN PREOPERATIVE EVALUATION

Centrally located HCC has complex adjacent structures. Consequently, the detailed preoperative evaluation of resectability is necessary. Besides liver function status, a clear image including tumors, blood vessels and bile ducts are essential. This preoperative evaluation is commonly obtained by multiphase contrast-enhanced computed tomography (CT), magnetic resonance imaging or ultrasound. However, because hepatectomy procedures need to be completed in a three-dimensional (3D) setting, planning anatomic resections may be difficult when relying on 2D images. In 1995, van Leeuwen *et al*^[6] reported depiction of the relationship between tumor and individual segmental anatomy in a 3D format. In 2005, Numminen *et al*^[7] reported a 3D imaging technique, which was based on the data of multi-detector row CT scanning. So far the clinical value of 3D imaging systems in preoperative evaluations has been confirmed by a series of studies^[8-12].

Currently, the 3D morphometric analysis system not only can precisely visualize tumors and adjacent vascular structures such as portal veins, hepatic veins and bile ducts from different directions in a screen but also can calculate the volume of the tumor and its surrounding areas and perform a virtual hepatectomy. Tian *et al*^[13] reported a 3D morphometric analysis model of liver tumor image reconstruction with customized software for individual patients. This study included 39 patients with centrally located HCC. They all accepted a 3D image reconstruction and morphometric analysis before operation. The results demonstrated that the 3D model provides a quantitative morphometry of tumor masses. The predicted values were also confirmed by intraoperative conditions^[13]. In clinical practice, 3D image morphometric analysis is often combined with liver function measurements such as Indocyanine Green (ICG) clearance test to determine the appropriate resection area. With the development of imaging techniques,

the usage of 3D imaging reconstruction systems in the surgical evaluation for centrally located HCC will be more and more promising.

INTRAOPERATIVE VASCULAR OCCLUSION TECHNIQUES

Centrally located HCC is situated in the deeper portions of the liver and adjoins main vascular structures, making hepatectomy difficult and time-consuming. Controlling intraoperative bleeding without excessive hepatic warm ischemia is a critical problem that has long perplexed liver surgeons. In 1908, James Hogarth Pringle described that occlusion of hepatic pedicle could help hemorrhage control^[14]. Pringle's maneuver was then proposed to minimize blood loss during hepatic surgery. However, clamping of hepatic pedicle means occluding the total inflow of hepatic artery and portal vein. Clamping of hepatic pedicle carries potential hazards for liver function due to hepatic ischemia, while also contributing to intestinal congestion^[15,16]. In addition, there has been a study that showed that Pringle's maneuver induces hepatic metastasis by stimulating tumor vasculature^[17]. Especially in some HCC high incidence regions, where most patients have liver cirrhosis, long durations of hepatic pedicle occlusion should be treated with even greater care^[18].

To resolve this problem, several selective hepatic vascular approaches have been described, represented by a hemihepatic vascular occlusion technique, which divides hepatic inflow into total right and total left Glisson sheaths^[19]. In 2012, we proposed a concept named selective and dynamic region-specific vascular occlusion^[20,21]. Before resecting liver tumors, a careful hepatic pedicle dissection was performed. The left or right hepatic artery and portal vein were dissected, exposed, and encircled with occlusion tapes. If caudate resection was needed, all short hepatic veins were ligated and dissected to free the caudate lobe from the inferior vena cava. For tumors involving the second hepatic portal or the trunk of the hepatic vein, the hepatocaval ligament was divided to make the root of the right hepatic vein stand out. If necessary, the common trunk formed by the middle and left hepatic veins also needed to be isolated to avoid fatal hemorrhage and air embolism. When liver parenchyma was dissected, we dynamically selected different regions for inflow or outflow blood occlusion according to tumor location. We have explored usage of this technique in the hepatectomy of complex centrally located HCC. Our study and other groups' studies showed that selective interruption of the arterial and venous flow to specified regions of the liver can satisfactorily control intraoperative bleeding, while also reducing ischemia-reperfusion injury of the whole liver. Most importantly, selective occlusion can maintain a fluent portal vein blood flow, which potentially avoids intraoperative gastrointestinal congestion and may accelerate postoperative recovery^[20,22-24].

Given the complexity of centrally located HCC, there has been an upcoming consensus that the application of hepatic vascular occlusion needs to be more flexible in the hepatectomy. We believe the occlusion techniques not only include dissecting hepatic pedicle, hepatic veins or IVC, but also are embodied in each step of surgical procedure. For example, there is no need to occlude vascular structures when we dissect surface liver parenchyma. In some circumstances, the traditional sutures around the resection area of the liver, or even a simple hand pinching, could be effective to control bleeding. Appropriate occlusion methods can minimize intraoperative bleeding and maximize the protection of liver function. These methods allow surgeons to complete more complicated surgical procedures.

SURGICAL DETERMINATION AND RESECTION MARGIN

As a special type of HCC, the treatment choice of centrally located HCC is often challenging. Transcatheter arterial chemoembolization (TACE) is often recommended as the primary palliative treatment for unresectable HCC. This treatment is based on the fact that highly vascularized HCCs are mainly supplied by hepatic arteries, while normal liver parenchyma accepts blood supplies from both hepatic arteries and portal veins^[25]. TACE was frequently performed in patients with centrally located HCC as a combined approach, but the efficacy of the treatment is still controversial. Mostly for unresectable centrally located HCCs, which are often associated with portal vein thrombosis (PVT), TACE in combination with radiotherapy has been reported to be therapeutically beneficial^[26]. Chen *et al.*^[27] reported preoperative TACE in 89 patients with large centrally located HCC and compared their recurrence patterns and long-term outcomes. The results showed that preoperative TACE potentially improved resection rate and extended overall patient survival, but preoperative TACE also increased chronic inflammation, perihepatic adhesion and the likelihood of postoperative complications. Radiofrequency ablation (RFA) is another treatment choice for selected patients. Guo *et al.*^[28] reported 196 patients with centrally located small HCC (diameter < 5 cm), in which 94 patients accepted percutaneous RFA and 102 patients received partial hepatectomy. The results showed that RFA could get similar treatment efficacy as that of partial hepatectomy but with fewer complications in patients with small centrally located HCC. In this study, centrally located HCCs were defined as tumors located at Couinaud's segments IV, V and VIII. For the patient group that we discussed above, the tumor control rate of RFA is often disappointing due to potential injuries to adjacent main vasculatures and risks of bile leakage^[29]. RFA can also be used to assist liver resection, which showed efficacy of reducing operation time and blood loss^[30,31]. In addition, tumor ablation can be completed simultaneously in the operation. This new modality is worthy of being

Table 1 Surgical treatment of centrally located hepatocellular carcinoma

Years	Patients' number	Surgical approaches	Operative variables and outcomes
1993	19	Extended major hepatectomy or irregular hepatectomy (large tumor)	Mean operative blood loss: 1186.6 mL Mean operative time: 7.5 h One year overall survival rate: 84.2% One year recurrence-free survival rate: 73.7% ^[65]
1999	15	Mesohepatectomy	Mean operative blood loss: 2450 mL Hospital stay: 14.9 d Six year overall survival rate: 30% Six year recurrence-free survival rate: 21% ^[2]
2000	18	Mesohepatectomy	Mean operative time: 238 min Mean operative blood loss: 914 mL Hospital stay: 9 d ^[66]
2003	52	Central hepatectomy	Blood transfusion was needed: 1030 ± 1320 mL Bile leak occurred in 4 patients The median overall survival: 51 mo ^[35]
2007	246	Mesohepatectomy (larger tumor)	Mean operative blood loss (without pre-TACE): 420 mL Overall hospital mortality (without pre-TACE): 0.6% Five year overall survival rate (without pre-TACE): 31.7% ^[27]
2008	27	Central bisectionectomy	Median operative time: 330 min Twelve patients had postoperative complications and two died Bile duct injury was the most common complication ^[36]
2012	104	Hemi-/extended hepatectomy and central hepatectomy	Mean blood loss of hemi-/extended hepatectomy and central hepatectomy: 750 mL and 500 mL Five year overall survival rate for hemi-/extended hepatectomy and central hepatectomy: 66.2% and 53.1% Five year recurrence-free survival rate for hemi-/extended hepatectomy and central hepatectomy: 38.9% and 15% ^[67]
2013	292	Mesohepatectomy	Mean operative time: 259 min Mean operative blood loss: 634 mL Hospital stay: 10 d ^[68]
2014	350	Mesohepatectomy	Mean blood loss for large tumor: 950.7 mL Ascites was the most common complication Five year overall survival rate for larger tumor: 30% ^[69]
2014	24	Mesohepatectomy	Mean operative time: 238 min Mean operative blood loss: 480 mL Three year overall survival rate: 46% ^[70]
2014	198	Extended hepatectomy and mesohepatectomy	The biliary leakage incidence after mesohepatectomy: 10.2% Five year overall survival rate for mesohepatectomy: 28.9% Five year recurrence free survival rate for mesohepatectomy: 16.9% ^[71]
2014	119	Hepatectomy with narrow margin	Bile leak occurred in 4 patients Five year overall survival rate: 48.3% Five year recurrence-free survival rate: 27.8% ^[3]
2015	69	Hemi-/extended hepatectomy and central hepatectomy	Mean blood loss of hemi-/extended hepatectomy and central hepatectomy: 522.2 mL and 447.8 mL Hospital stay for hemi-/extended hepatectomy and central hepatectomy: 21.3 and 14.9 d Three year overall survival rate for hemi-/extended hepatectomy and central hepatectomy: 64% and 61% ^[72]
2016	353	Mesohepatectomy	Five year overall survival rate: 40.2% Five year recurrence-free survival rate: 30.7% ^[4]

TACE: Transcatheter arterial chemoembolization.

explored in centrally located HCC treatment. Liver transplantation is an ideal option, but the shortage of liver donors limits its applicability. Only a few patients can fulfill the strict selection criteria of liver transplantation.

Under these circumstances, surgical resection aimed at a total removal of the tumor mass remains the optimal treatment choice for selected patients with centrally located HCC. In early reports, extended major hepatectomy and mesohepatectomy were often recommended (Table 1). The reported overall survival of patients after surgery was much greater than the natural history of the disease^[32,33]. However, the surgical procedures for centrally located

HCC are still more technically demanding. As is shown in Table 1, the operation time was relatively long and the operative blood loss could be a severe problem, especially before 2000. In recent years, due to the fact that extensive hepatectomy removing the major part of live parenchyma was often difficult to achieve in clinical practice, several non-anatomic approaches of central hepatectomy have been proposed. Surgeons need to weigh the dangers of postoperative liver dysfunction against the radical major resection, especially in patients with chronic hepatic diseases. A surgical group from Japan reported a no-margin resection in HCC patients.

These tumors closely adhered to main hepatic vascular structures and were resected along the surfaces of tumors and vascular structures. There existed no significant differences in patient recurrence free survival and overall survival between this group and those who underwent regular hepatectomy^[34]. Our group reported 118 patients with centrally located HCC, where the tumor is adherent to major hepatic vessels. These patients underwent comprehensive preoperative assessment. Unfortunately, most of them, especially patients with chronic liver diseases, would not have enough liver functional reserve to accept major hepatectomy based on ICG clearance test and 3D image reconstruction. To completely remove the tumor and preserve remnant liver function, we carefully exposed and resected the tumor from the vascular surface. This surgical approach increased the resection rate for patients with a special type of centrally located HCC. In combination with comprehensive adjuvant therapies, a five-year overall survival rate of 44.9% was reported, which is clearly superior to previously reported palliative strategies^[35-38].

For a long time, the safe resection margin is one of the major disputes in the practice of HCC surgery. Several previous studies indicated that a resection margin of more than 1cm is an independent factor of improved recurrence-free survival^[39-42]. But whether it can benefit all HCC patients is still controversial^[43-47]. The clinical definition of centrally located HCC emphasizes the vicinity of liver tumor with major vascular structures. It is not easy to obtain a safe (> 1 cm) resection margin for this group of patients. More in-depth studies are needed to explore the possible ways to reduce postoperative recurrence and increase patient survival. It should be noted that HCC is a systematic disease; it would be impractical to prevent recurrence only by extending the resection region. We believe that the individualized surgical approaches, which are based on the patients' condition, liver function, and tumor location, are optimal for patients with centrally located HCC.

ADJUVANT THERAPIES FOR RECURRENT PREVENTION

Recurrence disease is one of the main causes of long-term treatment failure for HCC patients. It was reported that the five-year risk of recurrence of HCC after hepatectomy could be as high as 70%^[48]. Many factors are associated with tumor recurrence, such as tumor size, number, grade, vascular invasion, positive margin, cirrhosis and preoperative treatment^[49-54]. Surgeons have long been searching for improved adjuvant therapies to reduce recurrence. TACE was investigated most in early studies and showed limited efficacy in preventing recurrence for selected HCC patients. Peng *et al.*^[55] reported that postoperative TACE enhances the effect of liver resection combined with PVT removal for HCC patients. Another study reported 115 Stage IIIA HCC patients who underwent hepatectomy with adjuvant

TACE or hepatectomy alone. The results indicated that hepatectomy with adjuvant TACE improved patients' recurrence-free and overall survival^[56]. But for most HCC patients, the primary role of postoperative TACE is to detect and treat early metastasis, rather than extend patient survival^[57]. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of HCC also has been reported in recurrence prevention. However, the clinical value of this particular treatment is still uncertain^[58-60].

As addressed above, the limited resection margin is a major concern for centrally located HCC. In clinical practice, we observed a higher recurrence rate for this group of patients^[20]. In 2014, a randomized controlled study explored the safety and efficacy of adjuvant radiotherapy (RT) for centrally located HCC after a narrow margin (< 1 cm) resection^[3]. The results showed that adjuvant RT for centrally located HCCs after narrow margin hepatectomy was technically feasible and relatively safe. The subgroup analysis demonstrated that postoperative region-specific RT remarkably increased patient recurrence-free survival. Patients with centrally located HCC are often at high risk of recurrence after hepatectomy. It is necessary to pay more attention to postoperative management. Regular follow-up, liver function monitoring, appropriate nutrition support and treatment of chronic liver disease (anti-virus) are important for improving patient survival^[61]. Some recent studies have shown that integrative strategies, such as herbal medicine, could be effective in maintaining inner environment homeostasis and inhibiting tumor growth^[62-64]. Integrative medicine focuses on restoring and maintaining a state of complete physical, mental and social well-being and not merely on the eliminating disease or infirmity. It will be interesting to explore these strategies in recurrence prevention. Currently, the development of novel treatment strategies, which incorporate molecular and immunological mechanisms, are underway and hold promise to be used for recurrence control in the future.

CONCLUSION

Over the past two decades, the management of centrally located HCC has evolved profoundly. Surgical indications, approaches, and techniques are greatly shifting. However, due to the complex procedure of centrally located HCC resection, obtaining high-level clinical evidence of surgical approaches on a large scale is still challenging. Dedicated clinical trials for this population with standardized classification are warranted. Currently, novel treatment options for HCC are constantly emerging. To elucidate which specific therapies or therapeutic combinations may be most beneficial for individual patients, a multi-disciplinary work team involving specialists in surgery, oncology, hepatology, radiology and integrative medicine is greatly needed during the whole treatment period. With more studies being involved, a general guideline for this special type of HCC can be expected and can further contribute to improving patient survival.

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Retrospective Study

Importance of surgical margin in the outcomes of hepatocholangiocarcinoma

Ka Wing Ma, Kenneth Siu Ho Chok

Ka Wing Ma, Department of Surgery, Queen Mary Hospital, Hong Kong, China

Kenneth Siu Ho Chok, Department of Surgery and State Key Laboratory for Liver Research, the University of Hong Kong, Hong Kong, China

Author contributions: Ma KW designed and performed the research, conducted the statistical analysis, and wrote the manuscript; Chok KSH designed and supervised the research and provided clinical advice.

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Correspondence to: Kenneth Siu Ho Chok, MS, Associate Professor, Department of Surgery, the University of Hong Kong, 102 Pok Fu Lam Road, Hong Kong, China. kennethchok@gmail.com
Telephone: +852-22553025

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Abstract

AIM

To evaluate the significance of resection margin width in the management of hepatocholangiocarcinoma (HCC-CC).

METHODS

Data of consecutive patients who underwent hepatectomy for hepatic malignancies in the period from 1995 to 2014 were reviewed. Patients with pathologically confirmed HCC-CC were included for analysis. Demographic, biochemical, operative and pathological data were analyzed against survival outcomes.

RESULTS

Forty-two patients were included for analysis. The median age was 53.5 years. There were 29 males. Hepatitis B virus was identified in 73.8% of the patients. Most patients had preserved liver function. The median preoperative indocyanine green retention rate at 15 min was 10.2%. The median tumor size was 6.5 cm. Major hepatectomy was required in over 70% of the patients. Hepaticojunctionostomy was performed in 6 patients. No hospital death occurred. The median hospital stay was 13 d. The median follow-up period was 32 mo. The 5-year disease-free survival and overall survival were 23.6% and 35.4% respectively. Multifocality was the only independent factor associated with disease-free survival [$P < 0.001$, odds ratio 4, 95% confidence interval (CI): 1.9-8.0]. In patients with multifocal tumor ($n = 20$), resection margin of ≥ 1 cm was associated with improved 1-year disease-free survival (40% vs 0%; log-rank, $P = 0.012$).

CONCLUSION

HCC-CC is a rare disease with poor prognosis. Resection margin of 1 cm or above was associated with improved survival outcome in patients with multifocal HCC-CC.

Key words: Hepatocholangiocarcinoma; Hepatocellular cholangiocarcinoma; Survival; Hepatectomy; Resection margin

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Core tip: A retrospective review of all patients who had undergone curative resection for hepatocholangiocarcinoma in the last 20 years was performed in a university center. The 5-year disease-free and overall survival were 23.6% and 35.4% respectively. Various patient and disease factors were investigated with respect to their effect to disease free and overall survival using cox regression analysis. Multifocality was the only independent factor associated with disease-free survival ($P < 0.001$). In a subgroup of patient ($n = 20$) who had multifocal tumor, resection margin of ≥ 1 cm was associated with improved 1-year disease-free survival (40% vs 0%, $P = 0.012$).

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INTRODUCTION

Hepatocholangiocarcinoma (HCC-CC) is a rare disease entity contributing to 1%-3% of primary hepatic malignancies^[1-4]. Histologically, tumor cells of hepatocyte and bile ductal epithelial origins are identified in HCC-CC^[5]. While "pseudoglandular" structures can as well be observed in other hepatocellular carcinoma (HCC) variants^[6], genuine HCC-CC should demonstrate true glandular structures with mucin production^[7]. Since the first description of HCC-CC in 1949 by Allen and Lisa^[8], 3 subtypes of the disease were established: Type 1, double separate tumors - HCC and intrahepatic cholangiocarcinoma (ICC) - in the same liver; type 2, the presence of HCC and ICC in a continuum; type 3, intermingling of HCC and ICC cells^[8]. In 1985, Goodman *et al*^[9] revised the classification with new descriptions of 3 types of HCC-CC: The collision type, the transitional type, and fibrolamellar HCC with mucin-producing pseudoglands. Later, the World Health Organization redefined HCC-CC as a distinct tumor with intimate and unequivocal fusion of HCC and ICC cells^[10]. The disease's clinical outcomes and prognostic factors have barely been studied. The median survival after HCC-CC resection varied from study to study, from 12 to 48 mo^[11-15]. This disparity may be partially explained by the heterogeneity in diagnostic criteria for

HCC-CC in the studies. The inclusion of HCC variants (which do not contain genuine ICC components) and the collision type of HCC-CC (which is no longer regarded as HCC-CC according to the World Health Organization) probably led to data contamination and resulted in difference in prognosis^[16].

The width of resection margin had been shown to affect the oncological outcomes of hepatectomy for HCC^[17-19] and ICC^[20,21]. In a prospective randomized trial involving 169 patients by Shi *et al*^[19], patients who were randomized to the narrow margin group (1 cm) had significantly inferior 5-year overall survival when compared with patients who had HCC resection with wide margin (2 cm) (49.1% vs 74.9%). For the role of resection margin in ICC, Farges *et al*^[21] demonstrated a significant correlation between resection margin and median survival in a subgroup of node-negative patients (≤ 1 mm: 15 mo, 2-4 mm: 36 mo, 5-9 mm: 57 mo, ≥ 10 mm: 64 mo; $P < 0.001$). In a recent article by our center, patients with early ICC were shown to benefit from resection margin of over 1 cm^[20]. Nonetheless, the role of resection margin in management of HCC-CC remains to be defined. This retrospective study aimed to elucidate the clinical features of HCC-CC and the impact of resection margin width on patient survival.

MATERIALS AND METHODS

Data of consecutive patients who underwent hepatectomy for hepatic malignancies in the period from 1995 to 2014 were reviewed. Patients included for analysis were those who: (1) had pathologically confirmed HCC-CC; (2) were not younger than 18 years; and (3) did not receive re-resection for recurrent HCC-CC. Diagnosis of HCC-CC was made by a combination of histological and immunohistochemical staining^[22,23], supplemented by electron microscopy examination when necessary^[11]. Demographic, biochemical, operative and pathological data were analyzed against survival outcomes. Categorical parameters were analyzed with Pearson's χ^2 test and continuous data were analyzed with the Mann-Whitney U test. Univariate analysis with bivariate correlation and multivariate analysis with the Cox regression model were performed. In this study, survival outcomes of HCC-CC were compared with the HCC and ICC patients of the same period. The Kaplan-Meier method was used for survival analysis and the log-rank test was used for survival comparison. P -values of ≤ 0.05 were considered statistically significant. The computer software Statistical Product and Service Solutions for Windows (SPSS, Chicago, Illinois, United States) was used for statistical analyses.

Perioperative care and follow-up protocol

Before hepatectomy, a basic biochemistry test was performed to assess complete blood picture, clotting profile, and liver and renal functions. Levels of tumor markers such as alpha-fetoprotein, carcinoembryonic antigen and cancer antigen 19-9 were recorded. Major

Table 1 Demographic characteristics and baseline biochemistry of the study population

	No. of patients = 42
Male:female	29:13
Age (yr)	52.5 (26-72)
Hepatitis B virus carrier	31 (73.8%)
Hepatitis C virus carrier	0
Hemoglobin (g/dL)	13.4 (8.6-16.7)
White cell count ($10 \times 6/L$)	5.8 (3.5-10.1)
Platelet count ($10 \times 9/L$)	185 (89-499)
Creatinine (mmol/L)	84 (61-131)
Total bilirubin (mmol/L)	10 (2-61)
Albumin (g/L)	40 (29-49)
Aspartate transaminase (umol/L)	44 (14-270)
Alkaline phosphatase (umol/L)	92 (26-516)
Prothrombin time (s)	13.5 (10.9-13.5)
Alpha-fetoprotein (u/L)	75.5 (2-219020)
Carcinoembryonic antigen (u/L)	2.3 (0.4-5.9)

Data are presented as median (range) unless otherwise stated.

hepatectomy was defined as resection of more than 3 Couinaud segments. Indocyanine green retention rate at 15 min after injection (ICG-R15) was used to evaluate the sufficiency of liver function for hepatectomy. For major hepatectomy, ICG-R15 of $\leq 18\%$ was required. For minor hepatectomy, ICG-R15 of $\leq 22\%$ was required. Patients having planned major hepatectomy were required to undergo computed tomographic volumetric study. The minimum ratio of future liver remnant to standard liver volume was 25% for non-cirrhotic livers^[24,25]. Our technique of liver resection has been described elsewhere^[24]. For follow-up, patients were seen at our out-patient clinic every 3 mo in the first 2 years and every 6 mo afterwards. Tumor markers were checked in every visit. Computed tomographic scan was performed 1-3 mo after discharge and then every 6 mo. Adjuvant therapy was not a routine and was offered at the discretion of the surgeon. Recurrence was defined as the presence of radiological or histological evidence of intrahepatic or extrahepatic HCC-CC.

RESULTS

From 1995 to 2014, 1696 patients underwent hepatectomy for primary liver malignancy. Among them, 50 adult patients had pathologically confirmed HCC-CC (3%). Eight of these 50 patients were excluded because of re-resection. As a result, 42 patients were included for analysis. Their demographic characteristics and baseline biochemistry are shown in Table 1.

Operative and pathological results

Most of the patients required major hepatectomy, and right hepatectomy was the most commonly performed procedure. Hepaticojejunostomy was performed in 6 patients (Table 2). The median operation time was 414 min (range, 177-1149 min) and the median blood loss volume was 800 mL (range, 5-2400 mL). There was no hospital death. The median length of hospital stay was 13 d

Table 2 Types of operative procedure performed

	No. of patients (%)
Right/extended right hepatectomy	17 (40.5)
Left/extended left hepatectomy	5 (11.9)
Right trisectonectomy	6 (14.3)
Left trisectonectomy	1 (2.4)
Central bisectonectomy	2 (4.8)
Left lateral sectionectomy	3 (7.1)
Other minor hepatectomy	8 (19.0)

(range, 3-50 d). Three patients developed postoperative complications of Clavien-Dindo grade 3a or above (grade 3a in 1 patient and grade 4 in 2 patients).

Histological examination was performed for all patients. The median tumor size was 6.5 cm (range, 2-23 cm). Twenty patients (47.6%) had multiple (more than 1) tumor nodules. Moderate tumor differentiation (new Edmondson grading) was found in 40% of the patients and 33.3% of the patients had poor tumor differentiation. R0 resection was achieved in 90% of the patients. The median resection margin width was 1 cm (range, 0-6 cm).

Survival outcomes and related factors

The median follow-up period was 110 mo. Adjuvant treatment was given to 13 patients in the form of transarterial chemo- or radio-embolization, systemic chemotherapy, external radiotherapy, molecular targeted therapy, or a combination of any of these. When it comes to survival outcomes, HCC-CC patients compared unfavorably with HCC patients. The median overall survival was 32 mo in HCC-CC patients and 70 mo in HCC patients (Figure 1A), and the median disease-free survival was 9 mo in the former and 28 mo in the latter (Figure 1B). On the other hand, HCC-CC patients and ICC patients had comparable overall survival (a median of 27 mo in ICC patients) (Figure 1C) while the latter had better disease-free survival (median, 20 mo) (Figure 1D). Recurrence developed in 33 HCC-CC patients (78.6%) (14 had intrahepatic recurrence, 3 had extrahepatic recurrence, and 16 had both).

In Cox regression analysis, tumor multiplicity was the only independent factor associated with overall survival [$P < 0.001$, odds ratio (OR) 5.26, 95%CI: 2.254-12.290] and disease-free survival ($P = 0.001$, OR 4.00, 95%CI: 1.897-8.434) (Table 3). Patients with solitary tumor nodule had a median overall survival of 106 mo whereas those with multiple tumor nodules had a median overall survival of 16 mo ($P < 0.001$) (Figure 2A). The median disease-free survival was 19.2 mo in patients with solitary tumor nodule and 3.1 mo in patients with multiple tumor nodules ($P < 0.001$) (Figure 2B).

Further analyses of the subgroup of patients ($n = 20$) who had multiple tumor nodules were performed. In univariate analysis, disease-free survival had an association with preoperative albumin level ($P = 0.022$) and resection margin width ($P = 0.013$). Multivariate analysis showed

Table 3 Cox regression analysis for factors affecting overall and disease-free survival

Factor	Overall survival (<i>P</i> -value)		Disease-free survival (<i>P</i> -value)	
	Univariate	Multivariate	Univariate	Multivariate
Age	0.269	NS	0.501	NS
Sex	0.513	NS	0.868	NS
HBV status	0.507	NS	0.441	NS
Platelet count	0.389	NS	0.331	NS
Total bilirubin	0.471	NS	0.176	NS
Albumin	0.811	NS	0.663	NS
ICG-R15	0.955	NS	0.749	NS
AFP	0.937	NS	0.308	NS
CEA	0.832	NS	0.716	NS
Operation time	0.239	NS	0.682	NS
Blood loss	0.138	NS	0.037	NS
Resection extent ¹	0.152	NS	0.108	NS
Tumor size	0.845	NS	0.975	NS
Multifocality	< 0.0001	< 0.001	< 0.0001	0.001
Margin width	0.523	NS	0.9	NS
Wide margin (≥ 1 cm)	0.491	NS	0.096	NS
Microvascular invasion	0.373	NS	0.170	NS
Nodal metastasis	0.314	NS	0.229	NS
Adjuvant treatment	0.162	NS	0.052	NS

¹Major *vs* minor. NS: Not significant; HBV: Hepatitis B virus; ICG-R15: Indocyanine green retention rate at 15 min after injection; AFP: Alpha-fetoprotein; CEA: Carcinoembryonic antigen.

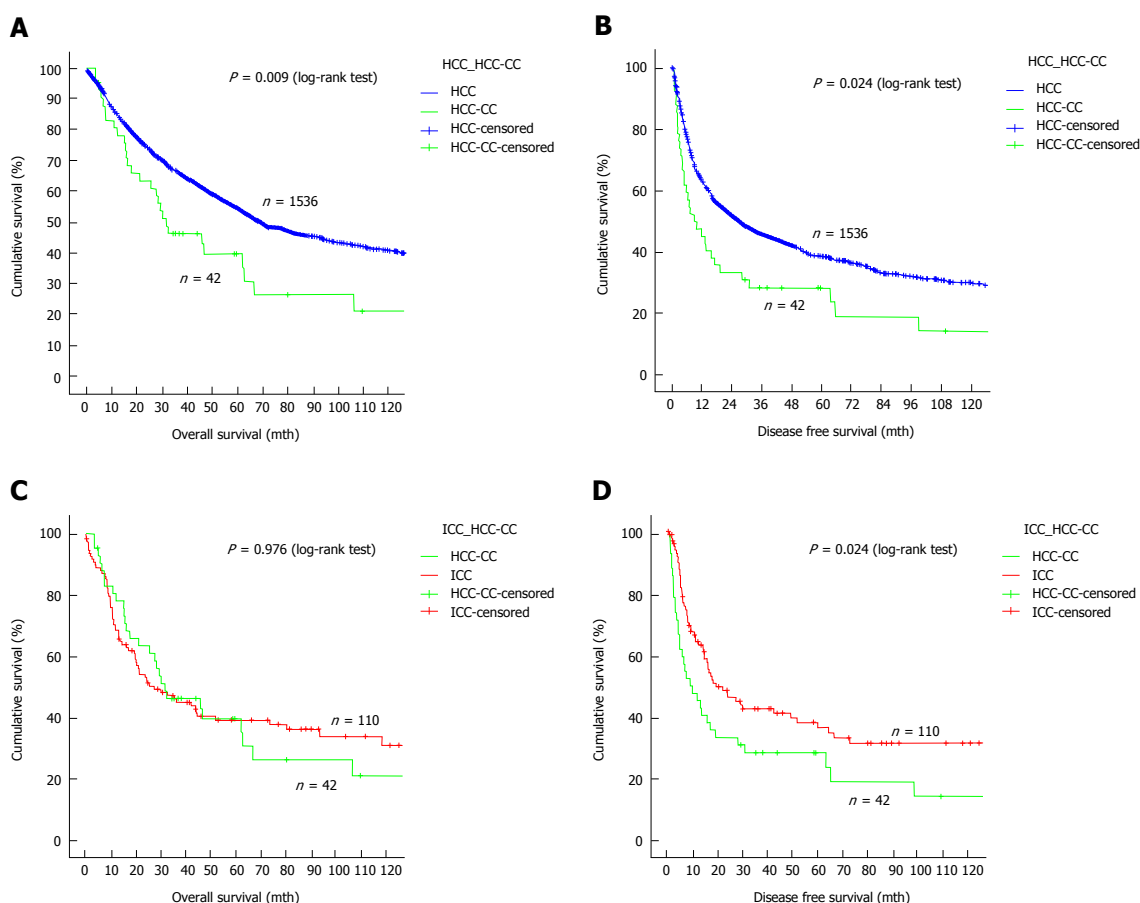


Figure 1 Survival comparisons between different groups of patients. A: Overall survival of HCC-CC patients and HCC patients; B: Disease-free survival of HCC-CC patients and HCC patients; C: Overall survival of HCC-CC patients and ICC patients; D: Disease-free survival of HCC-CC patients and ICC patients. HCC-CC: Hepatocolangiocarcinoma; ICC: Intrahepatic cholangiocarcinoma.

that resection margin width was the only independent factor affecting disease-free survival. A clear resection

margin of ≥ 1 cm could improve 1-year disease-free survival from 0% to 40% ($P = 0.012$) (Figure 3).

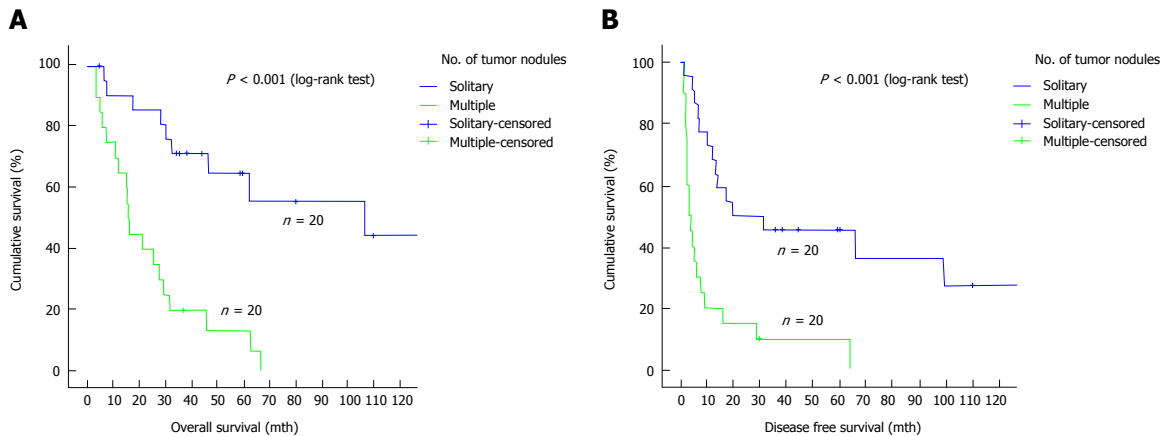


Figure 2 Survival of hepatocholangiocarcinoma patients with solitary vs multiple tumor nodules. A: Overall survival of HCC-CC patients with solitary tumor nodule and with multiple tumor nodules; B: Disease-free survival of HCC-CC patients with solitary tumor nodule and with multiple tumor nodules. HCC-CC: Hepatocholangiocarcinoma.

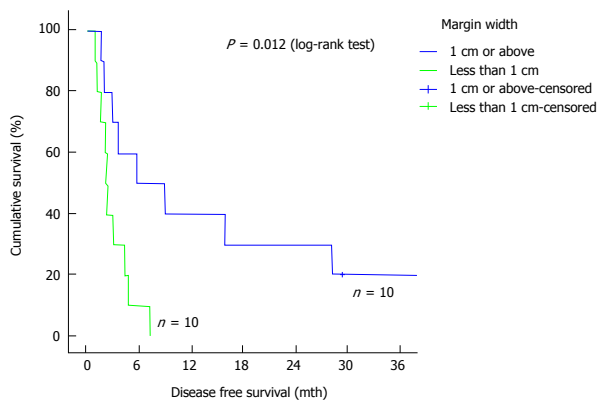


Figure 3 Effect of wide resection margin on disease-free survival of patients with multifocal hepatocholangiocarcinoma.

DISCUSSION

This retrospective study has further illustrated that HCC-CC is a rare and sinister primary hepatic malignancy. The reported incidences of HCC-CC vary greatly. This is probably due to the difference in the pathological definition of the disease. HCC-CC shares the clinicopathological features of HCC and ICC. Male predominance, the existence of background cirrhosis and elevation of alpha-fetoprotein level are hallmarks of HCC. These features are also often seen in HCC-CC. Tumor hypovascularity, involvement of regional lymphadenopathy and poor survival outcomes are common in HCC-CC as well as ICC. This study found that HCC-CC patients had significantly worse overall survival and disease-free survival when compared with HCC patients, which concurs with other reports^[26-29]. When compared with ICC patients, HCC-CC patients had inferior disease-free survival but were comparable in overall survival. This explains why HCC-CC should be included in the section of carcinoma of the intrahepatic duct in the 7th edition of the AJCC cancer staging manual^[30]. The worse survival outcomes were attributable to its propensity for vascular invasion and

lymph node metastasis^[1,9,31].

Despite the availability of the various classification systems for HCC-CC^[8,9,32], its prognosis remains difficult. Chantajitr *et al.*^[33] reported that a cancer antigen 19-9 level of ≥ 80 u/mL and the presence of intrahepatic ductal dilatation were independent factors for poor survival. Other studies found that lymphovascular permeation, large tumor size and the presence of tumor satellites were poor prognostic factors^[4,34-37]. In the current study, tumor multiplicity was the only independent factor associated with inferior disease-free survival and overall survival. This echoes the emphasis on the significance of tumor multiplicity in the staging of ICC in the 7th edition of the AJCC Staging^[30]. The role of adjuvant therapy in HCC-CC management is still unclear. One fourth of the patients in the current study received some form of adjuvant treatment (transarterial chemoembolization, radiotherapy, systemic therapy, *etc.*) at the discretion of the surgeon. Standardization of adjuvant treatment protocol is necessary before the role of adjuvant therapy can be established.

The current study could not demonstrate any benefit of R0 resection for patients with resectable HCC-CC, probably because of the small number of patients with R1 or R2 resection. Since HCC-CC is intrinsically associated with poorer prognostic outcomes when compared with HCC and ICC, small survival advantage conferred by wide resection margin (1 cm or above) could only be shown with a larger study population. However, this survival benefit was demonstrated in the subgroup of patients who had multifocal disease (40% vs 0% disease-free survival at 1 year). Since HCC-CC inherits the tumor biology of HCC and ICC, it has the ability of portal vein invasion and lymphovascular permeation. We therefore postulate that wide resection or even routine anatomical resection would eliminate residual satellite tumor cells or microtumor residing in the same vasculobiliary territory, thereby improving disease-free survival. The retrospective nature of the current study has posed a couple of limitations.

Firstly, missing data on carbohydrate antigen 19-9 made adequate analysis of its influence on survival outcomes impossible. In most of the cases, HCC-CC was diagnosed as HCC and routine blood check for carbohydrate antigen 19-9 was clinically irrelevant. Secondly, the small cohort size predisposed the study to type-II error; some potentially significant factors related to survival outcomes might not be identified by the analysis. However, the study period spanned two decades (1995-2014), which is relatively long. Furthermore, survival comparison between the study cohort and two much larger groups of patients (1536 HCC patients and 110 ICC patients) was performed, which should provide important data reference for future research.

HCC-CC is a rare and sinister primary hepatic malignancy. Patients with solitary tumor had better survival. A resection margin of at least 1 cm improved the disease-free survival of patients with multiple tumor nodules.

COMMENTS

Background

Hepatocolangiocarcinoma (HCC-CC) is an uncommon primary hepatic malignancy, contributing to about 1%-3% of all primary liver cancers. Its prognosis is worse than hepatocellular carcinoma (HCC) and similar to that of the intrahepatic cholangiocarcinoma. While resection margin was found to be an important factor associated with long-term oncological outcomes, its role in the management of this rare entity has not been reported.

Research frontiers

The role of resection margin has been extensively investigated in many cancers, such as oesophageal and colorectal cancers. In HCC and intrahepatic cholangiocarcinoma, wide resection margin was shown to be an independent factor leading to improved survival outcomes. In the context of HCC-CC, previous reports focused mainly on the epidemiology, diagnosis and disease nature, yet, the role of resection margin remained an unexplored area of the disease.

Innovations and breakthroughs

The rarity of the disease has always been a hurdle for statistical analysis. With the use of a well-maintained patient database in a university surgical center, a HCC-CC population of relatively large sample size were retrieved for analysis.

Applications

The results of this study showed that HCC-CC is associated with significantly worse overall survival when compared to HCC (9 mo vs 28 mo). Multifocality was found to be the only independent factor associated with inferior disease free survival. Early and regular postoperative surveillance should be offered to this group of patients for early detection of recurrence. In patients with multifocal HCC-CC, attempt should be made to achieve a clear resection margin of 1cm so as to improve the recurrence free survival.

Terminology

HCC-CC is a rare disease condition and histologically, the features of HCC and cholangiocarcinoma should both be demonstrated in the same tumour mass according to World Health Organization criteria.

Peer-review

This article is important for clinical management of HCC-CC, with well-designed analysis and trustable conclusions.

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Bi-directional hepatic hydrothorax

Madhan Nellaiyappan, Anastasios Kapetanios

Madhan Nellaiyappan, Anastasios Kapetanios, Department of Medicine, Allegheny Health Network, Pittsburgh, PA 15212, United States

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Correspondence to: Madhan Nellaiyappan, Resident, Department of Medicine, Allegheny Health Network, 7th Floor South Tower, 320 East North Ave, Pittsburgh, PA 15212, United States. drnmadhan@gmail.com
Telephone: +1-412-3302400

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Abstract

A 59-year-old male with alcoholic cirrhosis presented to our hospital with an acutely painful umbilical hernia, and 4 mo of exertional dyspnea. He was noted to be tachypneic and hypoxic. He had a massive right sided pleural effusion with leftward mediastinal shift and gross ascites, with a tense, fluid-filled, umbilical hernia.

Emergent paracentesis with drain placement and a large volume thoracentesis were performed. Despite improvement in dyspnea and drainage of 15 L of ascitic fluid, the massive transudative pleural effusion remained largely unchanged. He underwent a repeat large volume thoracentesis on hospital day 4. The patient subsequently developed a tension pneumothorax, which resulted in a dramatic reduction in the effusion. A chest tube was placed and serial radiographs demonstrated resolution of the pneumothorax but recurrence of the effusion. The radiographs illustrate the movement of fluid between the peritoneal and pleural cavities. In this case, the mechanism of pleural effusion was confirmed to be a hepatic hydrothorax *via* an unintended tension pneumothorax. Methods to elucidate a hepatic hydrothorax include Tc99m or indocyanine green injection into the ascitic fluid followed by its demonstration above the diaphragm. The unintended tension pneumothorax in this case additionally demonstrates bi-directional flow across the diaphragm.

Key words: Hepatic hydrothorax; Bidirectional flow; Iatrogenic pneumothorax

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Core tip: Hepatic hydrothorax is usually a clinical diagnosis in patients with cirrhosis and portal hypertension who present with a transudative pleural effusion. The authors herein report an interesting case of radiological confirmation of hepatic hydrothorax through a series of chest radiographs that depict the movement of ascitic fluid between the pleural and peritoneal cavities due to a iatrogenic pneumothorax.

Nellaiyappan M, Kapetanios A. Bi-directional hepatic hydrothorax. *World J Hepatol* 2017; 9(13): 642-644 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i13/642.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i13.642>

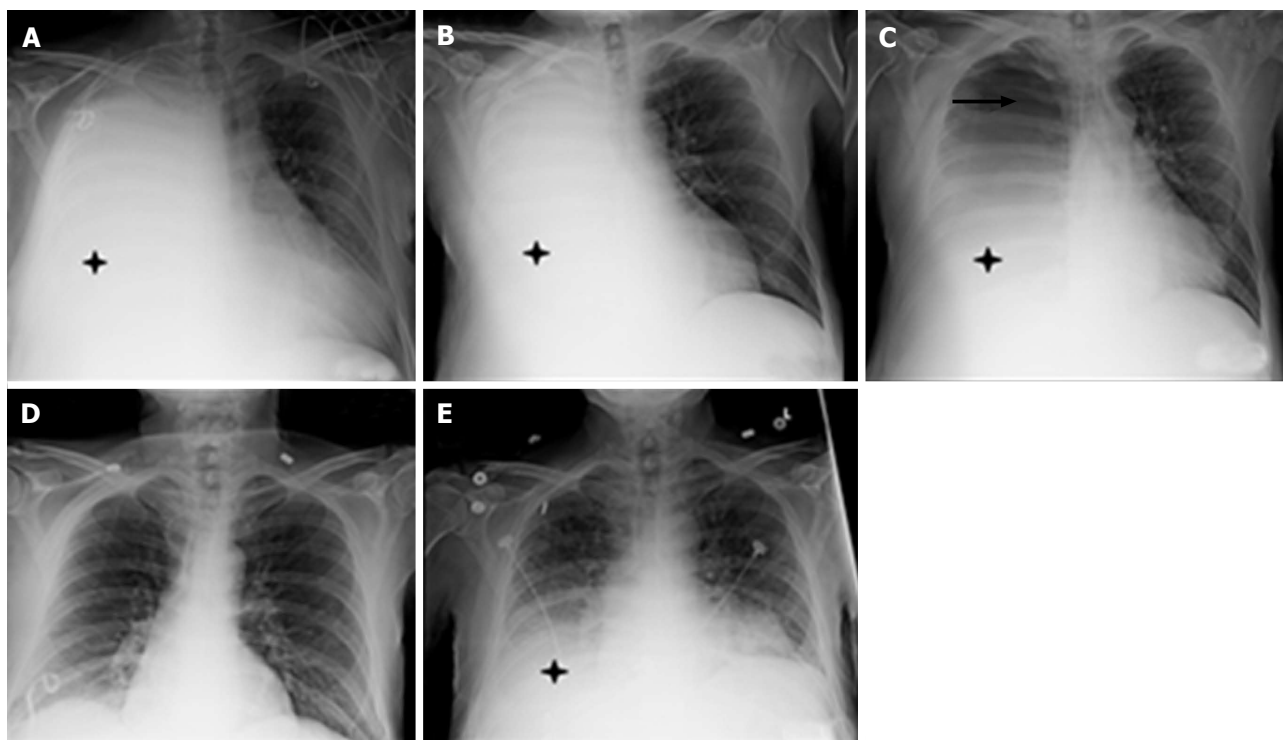


Figure 1 Serial chest radiographs. A: Day 0; B: Day 3; C: Day 4; D: Day 7; E: Day 26. A-C, E: Effusion (asterisks); C: Pneumothorax (arrow).

TO THE EDITOR

We read with great interest the article titled "A fascinating presentation of hepatic hydrothorax" by Gaduputi *et al*^[1]. We would like to thank the authors for sharing the clinical images and case details which illustrate the rapid shifts in the hydrothorax in a patient who was on invasive positive pressure ventilatory support. We would like to report an interesting case of hepatic hydrothorax that we encountered in our clinical practice which also demonstrates the mechanics of hepatic hydrothorax. We believe that the images of this common, yet incompletely understood phenomenon will be of interest to your readers at large.

The patient was a 59-year-old male with Child C cirrhosis in the setting of alcohol abuse and chronic hepatitis C who presented to our hospital with an acutely painful umbilical hernia, and 4 mo of exertional dyspnea. He was noted to be tachypneic and hypoxic. He had a massive right sided pleural effusion with leftward mediastinal shift (Figure 1A, day 0, asterisk) and gross ascites with a tense, fluid-filled, umbilical hernia. Emergent paracentesis with drain placement and a large volume thoracentesis were performed. Despite improvement in dyspnea and 15 L of ascitic fluid drainage, the massive transudative effusion remained largely unchanged (Figure 1B, day 3, asterisk). He underwent a repeat large volume thoracentesis on hospital day 4. The patient subsequently developed a tension pneumothorax, with a dramatic reduction in effusion size (Figure 1C, day 4, asterisk, arrow). A chest tube was placed, after which serial radiographs demonstrated resolution of the pneumothorax and recurrence of the effusion (Figure

1D). The radiographs demonstrate the movement of fluid between the peritoneal and pleural cavities (Figure 1C and E). In this case, the mechanism of pleural effusion was confirmed to be a hepatic hydrothorax *via* an unintended tension pneumothorax.

The diagnosis of hepatic hydrothorax should be considered for any patient with unilateral pleural effusion without an obvious cardio pulmonary cause. For cases in which the diagnosis is not obvious based on the clinical picture, methods to elucidate a hepatic hydrothorax include Tc99m labelled sulfur/albumin or indocyanine green injection into the ascitic fluid, followed by its demonstration above the diaphragm^[2,3].

The unintended tension pneumothorax in this case also demonstrates bi-directional flow across the diaphragm. As mentioned by Gaduputi *et al*^[1], fluid dynamics in hepatic hydrothorax are driven by pressure changes and pressure differences between the pleural, peritoneal cavities. In their patient, mechanical ventilation imparted positive pressure that was transmitted to the intrapleural space thereby causing the hydrothorax to track back to the peritoneal cavity which was relatively less pressurized^[1]. Similarly, in our patient, a tension pneumothorax imparted positive pressure in the pleural cavity, forcing pleural fluid back into the peritoneal cavity. In both patients, after the source of positive intrapleural pressure was eliminated, the hydrothorax recurred, highlighting bi-directional flow.

While rapid, bi-directional, hepatic hydrothoraces may represent a subset of larger diaphragmatic defects, this phenomenon may be more common than judged by the scant available literature. It is in these cases that an opportunity exists to better delineate the pathophysiology

of hepatic hydrothoraces, and begin to conceive more robust therapeutic options than those currently available to patients. As it stands, hepatic hydrothorax is often a harbinger of further suffering.

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