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EDITORIAL

# Synchronous resections of primary colorectal tumor and liver metastasis by laparoscopic approach

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## Abstract

Liver metastasis of colorectal cancer is common. Resection of solitary tumors of primary and metastatic colorectal cancer can have a favorable outcome. Open resection of primary colorectal tumor and liver metastasis in one operation or in separate operations is currently common practice. Reports have shown that synchronous resections do not jeopardize short or long-term surgical outcomes and that this is a safe and effective approach in open surgery. The development of laparoscopic colorectal surgery and laparoscopic hepatectomy has made a minimally invasive surgical approach to treating colorectal cancer with liver metastasis feasible. Synchronous resections of primary colorectal tumor and liver metastasis by laparoscopy have recently been reported. The efficacy and safety of laparoscopic colorectal resection and laparoscopic hepatectomy have been proven separately but synchronous resections by laparoscopy are in hot debate. As it has been shown that open resection of primary colorectal tumor and liver metastasis in one operation results in an equally good short-term outcome when compared with that done in separate operations, laparoscopic resection of the same in one single operation seems to be a good option. Recent evidence has shown that this new approach is a safe alternative with a shorter hospital stay. Large scale randomized controlled trials are needed to demonstrate the effectiveness of this minimally invasive approach.



**Key words:** Colorectal cancer; Hepatectomy; Laparoscopic; Liver resection; Simultaneous; Synchronous

**Core tip:** Open resection of primary colorectal tumor and liver metastasis in one operation or in separate operations is currently common practice but synchronous resections of the same by laparoscopy are controversial. Since open resection of primary colorectal tumor and liver metastasis in one operation results in an equally good short-term outcome when compared with that done in separate operations, laparoscopic resection of the same in one single operation seems to be a good option. Recent evidence has shown that this new approach is a safe alternative with a shorter hospital stay. Large scale randomized controlled trials are needed to demonstrate its effectiveness.

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## OVERVIEW

Colorectal cancer (CRC) is the third commonest cancer and the fourth leading cause of cancer deaths in the world. In 2008, there were around 50000 deaths related to CRC in the United States alone. Around 25% of CRC patients have stage Ⅳ disease upon presentation[1]. CRC metastasizing to the liver is common. Evidence has

shown that resection of solitary metastatic tumors of CRC can have a favorable outcome[2]. With the use of sophisticated imaging systems, such as high resolution contrast computed tomography and positron emission tomography, the sensitivity of detection of liver metastases larger than 2 cm is as high as 90%[3,4]. Open resection of primary colorectal tumor and liver metastasis in one operation or in separate operations is currently common practice[5,6]. Improved chemotherapies and biological agents have made many previously unresectable tumors resectable[7]. Reports have shown that synchronous resections do not jeopardize short or long-term surgical outcomes and that this is a safe and effective approach in open surgery[8-11].

Like laparoscopic hepatectomy, laparoscopic colorectal surgery has become popular in recent years because of its absolute advantage of allowing fast return of bowel motion and a shorter hospital stay[12-15]. More recently, synchronous resections of primary colorectal tumor and liver metastasis by laparoscopy have been reported[16-19]. Since the complication rate of synchronous resections is generally higher, as documented by Slesser *et al*[20], careful patient selection is important. Contrast computed tomography and positron emission tomography can provide accurate disease staging. Laparoscopy is not suitable for very bulky tumors. Although major resection by laparoscopy is feasible, the patient would not benefit from a small incision as a relatively large wound must be created for retrieval of the resected tumor.

Approximately 25% of CRC patients have concurrent liver metastasis on presentation. Liver is the most common site of hematogenous dissemination. Contemporary management of CRC calls for multidisciplinary involvement. Positron emission tomography using $^{18}$F-fluorodeoxyglucose can provide very accurate staging of disease, enabling surgeons to achieve an R0 resection with curative intention[21]. Novel chemotherapeutic agents used in target therapy are effective in causing remarkable tumor response[22,23]. Nonetheless, viable cancer cells can still be present after chemotherapy despite extensive tumor necrosis[5] and hence, chemotherapy should not replace resection. After all, resection of primary and metastatic tumors is the best way to maximize patient survival.

## TECHNIQUES

Laparoscopic synchronous resections of primary colorectal tumor and liver metastasis are normally carried out under general anesthesia. The patient is placed in a supine position with Trendelenburg adjustment. A 12 mm port is created using the open method. Pneumoperitoneum is introduced by insufflation of $CO_2$ and the intra-abdominal pressure is maintained at 12 cm $H_2O$. Another two 12 mm ports and two 5 mm ports are made under direct vision. Standard diagnostic and staging laparoscopy is then conducted. The liver is examined with laparoscopic ultrasound to confirm the extension of the tumor and its relationship to the hepatic vasculature[12-14]. It is preferred that resection of the colorectal tumor is conducted first to make sure that the primary tumor is resectable before any metastatic tumor is to be resected. Moreover, conducting colorectal resection before hepatic resection can avoid bowel edema, a condition that makes anastomosis difficult, caused by the Pringle maneuver. The colon or rectum is mobilized with an ultrasonic dissector and the mesenteric artery and vein are controlled with clips. For a rectal tumor, the rectum is transected with an endoscopic linear stapler[24]. Intracorporeal colorectal anastomosis is performed with a circular stapler. A laparoscopic anterior resection usually takes 2 h or so[15]. For hepatic resection, the no-touch technique can be used. The area to be transected is marked by diathermy. Transection of the liver parenchyma can be done with a Cavitron ultrasonic surgical aspirator and a Harmonic scalpel. The margin from the lesion is ideally 1 cm and is marked by intraoperative ultrasound. Both the primary and metastatic tumors are retrieved with protection through an incision with size similar to the largest diameter of the tumors[13]. Routine hepatic inflow control may not be necessary. A laparoscopic minor hepatectomy usually takes 2-3 h and a major one usually takes 6-8 h[14].

## CONSIDERATIONS

Short-term benefits of laparoscopic surgery for CRC have been proven by randomized controlled trials[25-29]. Emerging evidence also shows that the laparoscopic approach does not compromise patient survival[30,31]. As it has been shown that open resection of primary colorectal tumor and liver metastasis in one operation results in an equally good short-term outcome when compared with that done in separate operations[20], laparoscopic resection of the same in one single operation seems to be a good option. The obvious advantage of laparoscopic surgery is small surgical incisions. With improvements of laparoscopic equipment, the present high definition feature of most monitoring units provides magnificent magnification of the operation field. The margin of resection is thus not compromised even although the operation is conducted through a very small opening[32-34].

The risk of hemorrhage is an important concern when conducting hepatic resection on patients who have received chemotherapy treating their primary cancer and the location of liver metastasis can be a challenge in laparoscopic hepatic resection. Careful interpretation of the liver anatomy displayed by preoperative high-resolution imaging and intraoperative ultrasonography helps to avoid injury to the major hepatic vein, enabling safety of laparoscopic hepatic resection in difficult locations[35]. Careful use of the Cavitron ultrasonic surgical aspirator followed by application of clips helps to reduce blood loss. Strict control of the central venous pressure with careful administration of intravenous fluid and an intra-abdominal pressure of 12 to 15 mmHg contributes to minimal oozing of blood during liver transection[14]. The Pringle maneuver can be easily applied to the liver

hilum in the laparoscopic approach but a routine Pringle maneuver is not encouraged as it tends to cause venous congestion and thus leakage of anastomoses.

Both colorectal resection and hepatic resection are complicated operations. Whether combining these two complicated procedures in one laparoscopic surgery will do patients more harm or good is in hot debate. However, synchronous resections of primary colorectal tumor and liver metastasis by laparoscopy are not only feasible but also safe. Therefore, this approach is an alternative to open resection in one or separate operations for selected patients, especially when minimally invasive surgery is desired. Large-scale randomized controlled trials are needed to demonstrate the effectiveness of this minimally invasive approach.

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REVIEW

# Management of hepatocellular carcinoma: Enlightening the gray zones

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## Abstract

Management of hepatocellular carcinoma (HCC) has been continuously evolving during recent years. HCC is a worldwide clinical and social issue and typically a complicates cirrhosis. The incidence of HCC is increasing, not only in the general population of patients with cirrhosis, but particularly in some subgroups of patients, like those with human immunodeficiency virus infection or thalassemia. Since a 3% annual HCC incidence has been estimated in cirrhosis, a bi-annual screening is generally suggested. The diagnostic criteria of HCC has recently had a dramatic evolution during recent years. HCC diagnosis is now made only on radiological criteria in the majority of the cases. In the context of cirrhosis, the universally accepted criteria for HCC diagnosis is contrast enhancement in arterial phase and washout in venous/late phase at imaging, the so called "typical pattern". However, recently updated guidelines slightly differ in diagnostic criteria. Apart from liver transplantation, the only cure of both HCC and underlying liver cirrhosis, all the other treatments have to match with higher rate of HCC recurrence. The latter can be classified into curative (resection and percutaneous ablation) and palliative treatments. The aim of this paper was to review the current knowledge on management of HCC and to enlighten the areas of uncertainty.



**Key words:** Hepatocellular carcinoma; Management; Trans-arterial chemoembolization; Orthotopic liver transplantation; Surgery; Management

**Core tip:** Management of hepatocellular carcinoma (HCC) has been continuously evolving during recent years. The aim of this paper was to review the current knowledge on management of HCC and to enlighten the areas of uncertainty.

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## INTRODUCTION

Management of hepatocellular carcinoma (HCC) has been continuously evolving during recent years. However, albeit overall similar, the main Societies of Hepatology differently defined their own guidelines. In fact, despite an evident agreement in the general lines of HCC management, some gray zones still persist[1-4]. The aim of this paper was to review the current knowledge on management of HCC and to enlighten the areas of uncertainty.

### *Epidemiology*

HCC is a worldwide clinical and social issue. Actually, it is the sixth most common cancer and the third cause of cancer-related death. Incidence increases with advancing age, with a median age at onset of about 70 year-old in developed countries and there is a male preponderance, with a male to female ratio of about 2.4[5,6].

HCC is typically a complication of cirrhosis, although it can rarely develop in the absence of cirrhosis[1-4]. Known underlying diseases at risk for HCC development are chronic viral hepatitis C and B, alcoholic hepatitis, non- alcoholic fatty liver disease, autoimmune hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency, Wilson' s disease, Budd-Chiari syndrome (BCS). Diagnostic algorithm follows the same radiological criteria for HCC (see above) despite the different aetiologies of underlying liver disease. However, an exception is HCC developing in BCS. In fact, the radiological pattern of regenerative nodules in BCS is similar to that of HCC[7]. Moreover, as a consequence of the hindered hepatic venous outflow, radiological criteria for HCC can be altered[8,9]. Finally, although the risk of procedure-related bleeding is probably increased[10], generally diagnosis of HCC in BCS still needs histological confirmation[8,9].

Overall, the incidence of HCC is increasing, not only in the general population of patients with cirrhosis[11,12], but particularly in some subgroups of patients, like those with human immunodeficiency virus (HIV) infection or thalassemia. In fact, in both HIV and thalassemia, a recent significant outcome improvement due to, respectively, iron chelating drugs in the latter and highly active antiretroviral therapy in the former, has allowed the appearance of the complication of the underlying hepatic disease[13-18].

### Screening and recall policy

Surveillance of HCC is important simply because as little is HCC size at diagnosis as high is the probability of curative treatment. Since a 3% annual HCC incidence has been estimated in cirrhosis[19], a bi-annual screening is generally suggested[1-4]. Although less stringent, there is a risk of HCC development also in non-cirrhotic chronic hepatitis and treated viral hepatitis, for which an annual screening is generally performed[1-4]. Ultrasound (US) is the test of choice for surveillance. In fact, US is a cheap and safe test, due to the absence of contrast medium and radioactivity[20-23]. Moreover, differently from computed tomography (CT) and magnetic resonance (MR), US does not expose to the risk of false positive results. However, CT or MR should be preferred for surveillance of patients for which US is not adequate because of technical reasons or in liver transplantation (LT) waiting list[1-4].

Once hepatic nodules are discovered at US screening, the further work-up depends on the size[1-4]. Nodules < 1 cm should prompt a strict US surveillance every 3 or 4 mo for the first year and, in the absence of size increase, every six months after one year, like patients with cirrhosis without liver nodules. In fact, hepatic nodules < 1 cm rarely are HCC. Moreover, for such little size nodules, diagnostic value of either CT and MR is inadequate.

Nodules between 1 and 2 cm in size should be studied with CT and MR and, in case of non diagnostic imaging, undergo nodule biopsy. Moreover, a second biopsy should be contemplated in case of inconclusive findings at histology, nodule growth or change in enhancement pattern.

Nodules > 2 cm should undergo CT and MR and, in case of atypical imaging findings, nodule biopsy[1-4].

### HCC diagnosis update

The diagnostic criteria of HCC has recently had a dramatic evolution during recent years[1-4,24]. In fact, till the first half of the past decade, the Golden Standard for HCC diagnosis was histology. Then, since radiological diagnostic criteria have been shaped and established[1], HCC diagnosis is now made only on radiological criteria in the majority of the cases[1-4]. In the context of cirrhosis, the universally accepted criteria for HCC diagnosis is contrast enhancement in arterial phase and washout in venous/late phase at imaging, the so called "typical pattern" (Figures 1-3). However, recently updated guidelines slightly differ in diagnostic criteria[2-4].

Hepatic lesions > 1 cm with typical pattern at one imaging (CT or MR) have diagnosis of HCC in both the American Association for the Study of Liver Disease (AASLD) 2011 and European Association for the Study of the Liver (EASL) 2012 guidelines[2,4]. However, EASL 2012 guidelines specify that for lesions between 1 and 2 cm the concordance of typical pattern at two imaging (CT and MR) should be advices in suboptimal settings (technology, local skills)[4]. Both AASLD 2011 and EASL 2012 guidelines suggest lesion biopsy in the absence of typical pattern. Finally, both AASLD 2011 and EASL 2012 guidelines exclude from diagnostic criteria contrast-enhanced US (CEUS) and alpha-fetoprotein value[2,4].

Japanese Society of Hepatology (JSH) 2012 guidelines agree with the diagnostic value of typical pattern at one imaging (CT, MR, CEUS) regardless of the size, and maintains the diagnostic value of CEUS and biochemistry (AFP > 200 ng/dL, PIVKA-Ⅱ > 40, AFP L3 > 15%)[3]. However, the main difference between JSH 2012 and both AASLD 2011 and EASL 2012 guidelines is that the former consider a diagnostic criteria the lesion hypointensity in hepatic image of Gd-EOB-MR[2-4].

### HCC treatment

Apart from LT, the only cure of both HCC and underlying liver cirrhosis, all the other treatments have to match with higher rate of HCC recurrence. The latter can be classified into curative (resection and percutaneous ablation) and palliative treatments[2-4].

Resection is considered the First-Line treatment for patients with solitary tumours and preserved liver function (normal bilirubin and, either HVPG ⩽ 10 mmHg, PLT > 100000 or no varices at endoscopy). Resection can also be performed for multi-focal HCC inside Milan criteria or in case of mild portal hypertension when patients are not suitable for orthotopic LT (OLT), although it is debated if such patients could benefit from other locoregional therapies, avoiding the risk of surgery and of liver de-compensation after surgery. In fact, perioperative mortality in cirrhotics after HCC resection is about 2%-3%. Moreover, there is a risk of tumor recurrence af-

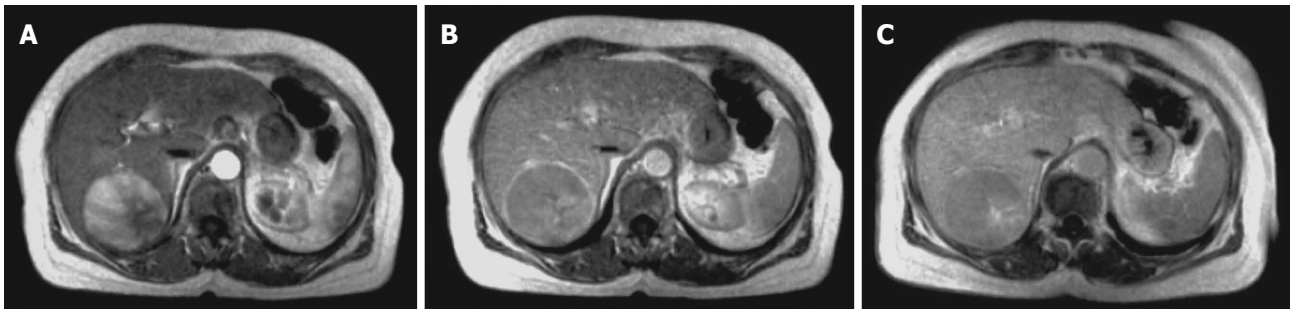


**Figure 1 Typical hepatocellular carcinoma at magnetic resonance imaging: contrast enhancement in arterial phase (A) and washout in venous (B)/late (C) phase.**

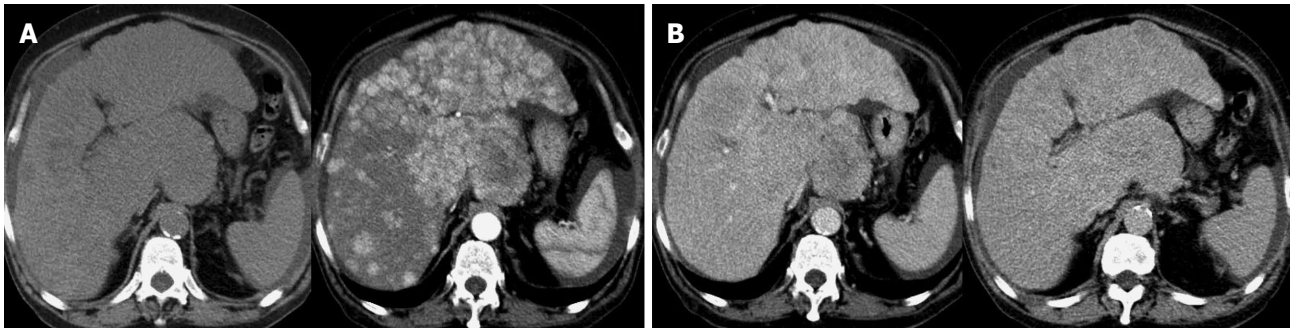


**Figure 2 Multi-nodular hepatocellular carcinoma.** A: Basal and arterial computed tomography (CT) phase; B: Venous and late CT phase.

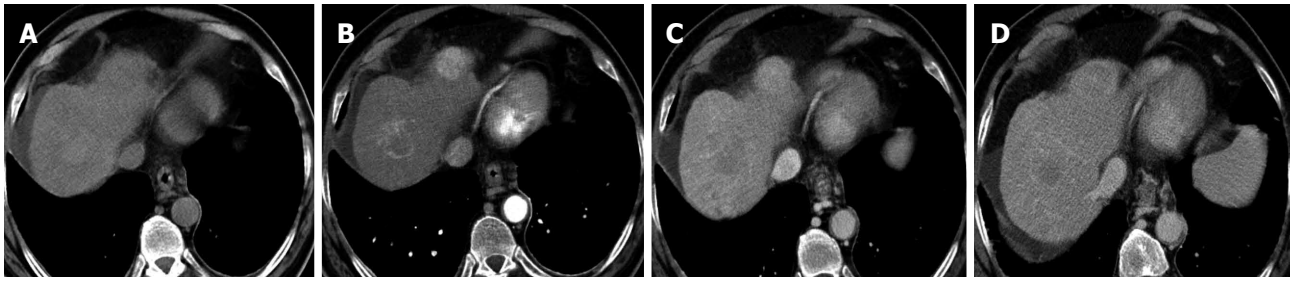


**Figure 3 A new typical hepatocellular carcinoma found at computed tomography during follow up another hepatocellular carcinoma treated with radiofrequency ablation (central lesion).** Note that also in the treated lesion there is a marginal area of vital hepatocellular carcinoma.

ter surgery of about 70% at 5 years, enclosing both true recurrence and the novo tumours[25-39].

Percutaneous local ablation, namely radiofrequency ablation (RFA) and ethanol injection (EI) are the standard of care for BCLC O-A not suitable for surgery. Although RFA is recommended in most instances as the main ablative therapy in tumors less than 5 cm, the probability of complete necrosis is very high for little tumors (< 2 cm) and progressively decreases with the increase of tumor size. In tumours ≤ 2 cm both RF and EI achieve complete responses in more than 90%, making percutaneous local ablation competitive with resection. EI is better indicated when RFA in not technically feasible. This is the case of tumors overflowing the liver margin or near organs, just like gallbladder or bowel, because of the risk of thermal injury and perforation, or when tumor is adjacent to a main vessel, because of the concern of thermal dispersion and inefficacy of RFA[40-64].

Trans-arterial chemoembolization (TACE) is the recommended treatment for BCLC stage B multinodular asymptomatic tumors without vascular invasion or extrahepatic spread. Drug-eluting beads have similar efficacy to gealfoam-lipiodol with probably less adverse events. Both should be discouraged in decompensated liver disease and in case of macroscopic vascular invasion or extrahepatic spread[65-80]. An alternative to TACE is radioembolization. However, radioembolization , although promising and with advantage of being indicated also in the case of portal vein neoplastic thrombosis, is expensive and further data are needed. In fact, to our knowledge there are not well designed studies comparing radioembolization with neither TACE nor sorafenib[81-84].

LT is actually a consolidated therapeutic option for HCC because it cures both tumor and underlying cirrhosis[1-4]. However, the indication of LT for HCC treatment has evolved over recent years[85-109]. Moreover, initial expe-

riences tended to offer LT as the last therapeutic chance when resection was not feasible. In fact, till the first half of nineties, the discouraging results of some experiences had questioned the possibility of LT efficacy as HCC treatment. In 1996, the publication of a pivotal prospective study on less than 50 patients, transplanted for HCC under predefined criteria (single HCC ≤ 5 cm or 3 HCC ≤ 3 cm each), the so called "Milan criteria", showed a 4-year survival of 75%[85]. Subsequent experiences of LT for HCC inside the Milan criteria, confirmed a survival rate exceeding 70% at 5 years, with a recurrence in less than 15%. Due to these data, LT is now the first-line treatment for one HCC ≤ 5 cm or 3 HCC ≤ 3 cm each[1-4].

Although all published guidelines go on considering the Milan criteria as the only fence inside which LT should be considered as treatment of HCC[2-4], the possibility of an extension of Milan criteria as indication for LT is already a debated issue. In fact, while it is universally recognized that LT for HCC inside Milan criteria guaranties an acceptable outcome, numerous heterogeneous experiences explore the possibility of extending the Milan criteria.

A line of experiences studies the applicability of the University of California San Francisco (UCSF) criteria, that is single nodule ≤ 6.5 cm or 2-3 nodules ≤ 4.5 cm and total diameter ≤ 8 cm. In fact, UCSF criteria on explant identified retrospectively a cohort of patients whose survival was not significantly different from those of patient transplanted for HCC inside the Milan criteria[93]. The same results had other retrospective experiences by other groups using UCSF criteria. Moreover, a recent prospective study showed a 5-year survival not significantly different in patients transplanted for HCC inside Milan and UCSF criteria[103].

A recent multicenter restrospective study on over 1700 found that HCC inside the "up-to-seven" criteria at explant (those HCCs having the number 7 as the sum of the size of the larger tumor and the number of tumors) and without microvascular invasion had a 5-year survival not significantly different from those inside the Milan criteria, while survival was significantly worst in case of HCC inside the "up-to-seven" criteria and with microvascular invasion[104].

Another line of studies suggest that down-staging for HCC exceeding conventional criteria could be effective for extending LT without worsening survival. These studies are heterogeneous in design, inclusion criteria and philosophy. In fact, while some suggests to offer LT to those patients who achieve an effective downstaging, so selecting patients with a less aggressive HCC and likely reducing the probability of HCC recurrence after LT, others indicate LT for those HCC without an effective downstaging, as a rescue treatment[107-109].

Despite all the above studies, guidelines still give indication to LT only to HCC inside Milan criteria[2-4]. However, as published experiences show, many center actually perform LT outside the Milan criteria, using criteria different from centre to centre[85-109].

Whatever the criteria adopted, a significant problem of HCC candidates for LT is the drop out, that is patients who do not reach the goal of LT because of progression of HCC or of causes unrelated to HCC. Many studies have investigated the risk of drop out that remains difficult to define, although some factors, like tumor multinodularity, neoadjuvant treatment failures, elevated AFP or model for end-stage liver disease score, have been correlated with a higher probability of drop out. From an opposite point of view, given the organ shortage, some patients with single HCC < 2 cm may benefit from alternative treatments and avoid LT at least until recurrence occours, highlighting the possibility of salvage transplantation in low risk population. Moreover, it is still uncertain which is the role of LT after surgery and high risk of recurrence at pathology[2-4].

Living donor LT (LDLT) is an alternative option if waiting list is long and offers the possibility of a LT after a short time. However, there is a donor risk of death of about 0.3% and of life threatening complications of about 2%. In fact, LDLT should be restricted to centers of excellence[110-120].

The mainstay of palliative therapy for advanced HCC is Sorafenib, which is indicated in advanced HCC (BCLC C) or HCC progressing upon loco-regional therapies in patients with well preserved liver function and good performance status. Registrative studies have shown a 3-mo increase in median overall survival of sorafenib compared to placebo. Moreover, adverse events are frequent a can be severe (Diarrea, Hand-foot skin-reaction)[121-125].

The role of Sorafenib in some subgroup of patients is debated. In fact, while some experiences report encouraging results of sorafenib therapy after HCC recurrence post OLT, others suggests that adverse events could affect sorafenib efficacy[126-135]. Moreover, our preliminary experience on HCC in HIV positive patient report a high incidence of hepatotoxicity. In both the subgroup the possibility of drug interections should be investigated.

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REVIEW

# Non-viral factors contributing to hepatocellular carcinoma

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## Abstract

Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide, accounting for over half a million deaths per year. The geographic pattern of HCC incidence is parallel to exposure to viral etiologic factors. Its incidence is increasing, ranging between 3% and 9% annually depending on the geographical location, and variability in the incidence rates correspond closely to the prevalence and pattern of the primary etiologic factors. Chronic infections with hepatitis B viruses or hepatitis C viruses have both been recognized as human liver carcinogens with a combined attributable fraction of at least 75% of all HCC cases. Multiple non-viral factors have been implicated in the development of HCC. Increased body mass index and diabetes with subsequent development of non-alcoholic steatohepatitis represent significant risk factors for HCC. Other non-viral causes of HCC include iron overload syndromes, alcohol use, tobacco, oral contraceptive, aflatoxin, pesticides exposure and betel quid chewing, a prevalent habit in the developing world. Wilson disease, α-1 antitrypsin deficiency, Porphyrias, autoimmune hepatitis, *Schistosoma japonicum* associated with positive hepatitis B surface antigen, and thorotrast-ray are also contributing hepatocellualar carcinoma. In addition, primary biliary cirrhosis, congestive liver disease and family history of liver cancer increase the risk of HCC incident. In conclusion, clarification of relevant non-viral causes of HCC will help to focus clinicians on those risk factors that are modifiable. The multilevel preventative approach will hopefully lead to a reduction in incidence of non-viral HCC, and a decrease in the patient morbidity and mortality as well as the societal economic burden associated with HCC.



**Key words:** Hepatocellular carcinoma; Viral etiologic factors; Non viral factors

**Core tip:** Hepatocellular carcinoma (HCC) is one of the most common and deadly cancers worldwide, there are multiple non-viral factors have been implicated in the development of HCC, hemochromatosis, obesity, diabetes, alcohol and tobacco have consistently been shown to dramatically increase the rate of HCC. Oral contraceptive, aflatoxin, pesticides exposure and betel quid chewing also increase HCC risk, in addition, Wilson disease, α-1 antitrypsin deficiency, porphyries, autoimmune hepatitis, *Schistosoma japonicum* infection associated with positive hepatitis B surface antigen, and thorotrast-ray are contributing in the prevalence of the disease. Moreover, primary biliary cirrhosis, congestive liver disease and family history of liver cancer play a significant role of disease progression.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) represents an international public health concern as one of the most common and deadly cancers worldwide[1]. It is the fifth most common cancers[2] and the third cancer-related death worldwide[1]. It is rarely to be detected early and usually fatal within a few

months of diagnosis[3]. HCC is represented by 85%-90% of primary liver cancers[4] accounting for 3.5% and 7.5% of all cancers among women and men, respectively[5] and accounts for half a million deaths per year[6].

Although this disease typically affects elderly males, in recent years there has been a shift towards relatively younger age groups[7]. In patients who are not transplant candidates, HCC is particularly lethal, with a 5-year survival of less than 5%[8]. HCC has a high incidence rate in sub-Saharan Africa and Southeast Asia, but a low incidence rate in the United States and Europe[9]. In Middle Eastern countries, liver cancer is a major concern among men, especially in certain countries such as Egypt and Saudi Arabia, and to a lesser extent in other countries of this region[5]. In Egypt, several attempts were made to establish cancer registries[10]. Among these attempts in 1998, the Egyptian Ministry of Health and Population in collaboration with the National Cancer Institute of Cairo University established a population-based Cancer Registry (NCR).

The NCR data confirmed the high incidence of HCC in Egypt and the change in the trends during the last decade. HCC was reported to account for about 4.7% of chronic liver disease patients[11]. It formed 11.75% of the malignancies of all digestive organs and 1.68% of total malignancies. Liver tumors were mostly HCC (70.48%), while hepatoblastoma constituted 10.24%, non-Hodgkin's lymphoma 4.21% of hepatic malignancies and adenocarcinoma unspecified 9.03%[10].

## VIRAL FACTORS CONTRIBUTING TO HCC

HCC has been increasing in worldwide with a doubling in the incidence rate in the past 10 years due to several biological and environmental factors[10]. A significant proportion of this increase is accounted by the growing prevalence of hepatitis C and B viruses (HCV and HBV) infection[8,12].

## NON-VIRAL FACTORS CONTRIBUTING TO HCC

Other potential causes of HCC are garnering close attention. Increased body mass index and diabetes with subsequent development of non-alcoholic steatohepatitis (NASH) represent significant risk factors for HCC[13-15]. This is especially concerning in light of the growing epidemic of obesity in adults and children over the past 25 years[16,17]. Other no viral causes of HCC include iron overload syndromes, alcohol use, tobacco, oral contraceptive, aflatoxin, pesticides exposure and betel quid chewing, a prevalent habit in the developing world[10,18]. Wilson disease, α-1 antitrypsin deficiency, Porphyries, autoimmune hepatitis, *Schist soma jabonium*, and thorotrastray are also contributing hepatocellualar carcinoma[19-22]. Primary biliary cirrhosis, congestive liver disease and family history of liver cancer increase the risk of HCC incident[9]. These factors are clearly illustrated in Table 1.

**Table 1 Non-viral factors associated with hepatocellular carcinoma**

| Non-viral factors contributing hepatocellular carcinoma | Ref. |
|---|---|
| Hereditary hemochromatosis | Powell *et al*[23] |
| Non-alcoholic fatty liver disease | Caldwell *et al*[14] |
| Obesity | Wolk *et al*[36] |
| Diabetes | El-Serag *et al*[15] |
| Diet | Polesel *et al*[44] |
| N-nitroso compounds | Sauvaget *et al*[47] |
| Alcohol | Donato *et al*[52] |
| Smoking | Marrero *et al*[55] |
| Oral contraceptives | Rosenberg[63] |
| Betel quid | Tsai *et al*[70] |
| Aflatoxin | Qian *et al*[77] |
| Coffee | La Vecchia *et al*[81] |
| Schistosomiasis | Ezzat *et al*[87] |
| Pesticides | Anwar *et al*[10] |
| Thorotrast | Bull *et al*[89] |
| Alpha-1 antitrypsin deficiency | Van Thiel *et al*[90] |
| Autoimmune hepatitis | Wong *et al*[92] |
| Porphyrias | Mogl *et al*[96] |
| Wilson disease | Reyes[98] |
| Primary biliary cirrhosis | Liang *et al*[100] |
| Congestive liver disease | Muguti *et al*[102] |
| Family history of liver cancer | Turati *et al*[103] |

Emerging evidence suggests that the etiology of many cases of HCC is in fact multifactorial, including both viral infections and non-viral environmental and dietary exposures[18].

### *Hereditary hemochromatosis (iron overload syndromes)*

Hereditary hemochromatosis, a condition characterized by excess iron absorption, is caused by mutations in the *HFE* gene and/or other mutations in the iron metabolism machinery. This condition represents one of the most common autosomal recessive genetic disorders, affecting as many as 1 in 200 people of Northern European descent[23]. The *HFE* gene is required for efficient *in vivo* iron metabolism and two mutations within the *HFE* gene product, C282Y and H63D, have been well described in patients with hereditary hemochromatosis[24]. The C282Y mutation, which results in a base pair substitution in which tyrosine is substituted for cysteine at amino acid 282, is found in the homozygous state in up to 83% of patients with hereditary hemochromatosis[24].

The H63D mutation, characterized by substitution of histidine with aspartic acid at codon 63, is present in a minority of cases of hereditary hemochromatosis either in a homozygous state or with one copy of the C282Y mutation, a state referred to as a compound heterozygote[24]. The clinical significance of this latter mutation within the *HFE* gene, however, continues to be controversial. The altered iron metabolism seen in hereditary hemochromatosis leads to excess iron storage in the liver and the subsequent development of liver dysfunction.

Although other organs systems are also susceptible to iron overload, the liver bears the majority of malignant disease, with those patients with hereditary hemochromatosis being 20 times more likely to develop liver cancer

than all other cancers combined[25]. Several population-based and case-control studies have shown that the diagnosis of hereditary hemochromatosis confers a consistent and markedly elevated risk for the development of HCC[25-27].

In addition, the relationship between hereditary hemochromatosis and HCC is modified by diabetes, sex and genetics. Subjects with liver cancer and concomitant diabetes mellitus were 82 times more likely to have a diagnosis of hemochromatosis[26]. Furthermore, a population-based study from Scandinavia found that men with hemochromatosis had a 29-fold increase in risk of liver cancer, whereas women with hemochromatosis had a sevenfold increase in risk[25].

In fact, those patients with excess total body iron secondary to other etiologies have been shown to have a higher risk of HCC in the absence of genetic hemochromatosis[28]. Studies have suggested that conditions such as β thalassemia or iron overload in people of African descent might be associated with an increased risk of HCC[28,29]. Mandishona *et al*[28] found that African iron loaded subjects had a 10-fold increase in the risk of developing HCC after adjusting for viral hepatitis, alcohol use and environmental exposures, such as aflatoxin. Regardless of etiology, iron overload is not a benign condition and when recognized, surveillance for HCC should be undertaken[30].

### Non-alcoholic fatty liver disease

Several case reports and subsequent observational studies have proposed that non-alcoholic fatty liver disease (NALFD), and more specifically, NASH, confers an elevated risk of developing HCC[14]. NAFLD is a spectrum of clinical disease that ranges from benign or bland steatosis to NASH. The latter stage of this disease, through a process of chronic inflammation and subsequent hepatic fibrosis, can lead to cirrhosis[31]. The presence of cirrhosis itself is an independent risk factor for the development of HCC[32].

To characterize the natural history of NAFLD, 420 patients identified in Olmstead County, United States with liver disorder were followed for an average of 7 years to determine overall mortality. In this population based study, NAFLD was associated with a 34% increase in mortality and a significant increase in the risk of HCC, with two cases or 0.5% being diagnosed over the period of follow-up[33]. NASH-related cirrhosis, however, the rate of HCC approached 10%[33]. In another study in Japan, among 82 NASH patients treated from 1990 through 2001, six patients with HCC were identified over 11 years of follow-up[34]. All six patients developed HCC in the setting of NASH-related cirrhosis[34]. These data highlight an association between NASH cirrhosis and an increase in the incidence of HCC over that of the general population. Therefore, regular HCC surveillance is imperative in patients with NASH cirrhosis.

In advanced fibrosis, an absence of steatosis may be appreciated, a finding which can obscure identification of the underlying etiology of liver injury in these patients, in this case, patients might be classified as having cryptogenic cirrhosis (cirrhosis due to unidentified causes). In a United States study that examined 105 consecutive patients with HCC, after HCV, cryptogenic cirrhosis was the most common etiology of liver injury[35]. Furthermore, only 23% of patients with cryptogenic cirrhosis were undergoing surveillance for HCC in comparison to 61% of subjects who had a history of HCV-related liver disease[35]. These observations emphasize the importance of HCC surveillance in this group of patients and the failure thus far to appropriately screen for HCC in this disease process[18].

### Obesity

The prevalence of obesity has increased to epidemic proportions over the last three decades. Excess body mass is classified as overweight if the body mass index (BMI) is $> 25$ kg/m$^2$ and $< 30$ kg/m$^2$, or obese if the BMI is $\geqslant 30$ kg/m$^2$. In addition to the increase in an array of disease processes observed with being overweight or obese, both classifications of excess body mass are associated with a higher risk of developing all cancers, including liver cancer[13].

In one population-based study from Sweden, 28 cases of HCC were diagnosed in 28129 patients from 1965 to 1993, thus conferring an almost threefold higher risk of HCC in obese patients[36]. A recent European case-control study observed a significantly increased risk of HCC among obese or diabetic patients without viral hepatitis. This risk of HCC was even greater if both obesity and diabetes were present in co morbid conditions[37].

A Danish study further confirmed these results, finding a twofold increase in liver cancer incidence in obese subjects compared to non-obese subjects[38]. Generally, it was concluded that patients who were overweight had a 17% increase in risk of developing HCC, whereas obese patients had an 89% increase in risk[39]. Based on the prevalence of HCC, it was estimated that 28% of HCC cases in men and 27% in women were due to being overweight or obese[39].

In addition to an increased risk of developing HCC, overweight or obese patients appear to be at increased risk for HCC-related mortality. In a population-based study of cancer mortality and BMI, men with a BMI of 30-34.9 were found to have a twofold increase in the risk of death from HCC, with a 4.5-fold increase noted in men with BMI $> 35$[13]. Lastly, *via* the pathway of the metabolic syndrome with resultant NASH cirrhosis, obese patients have been found to be at an increased risk for HCC occurrence.

Many lines of evidence point to the role of cirrhosis as a mediator in these patients. Patients presenting with cryptogenic cirrhosis were found to have a significantly higher prevalence of obesity than patients with cirrhosis from non-alcoholic hepatitis C or autoimmune liver disease, but a similar prevalence of obesity when compared to patients with documented NASH[40]. These data are

supported by a case-control study in which 49 patients with cryptogenic cirrhosis were compared to 98 matched controls with an established cause of cirrhosis. In that study, obesity was significantly more prevalent in the cryptogenic cirrhosis patients[41].

Therefore, being overweight and obesity, secondary to cryptogenic cirrhosis, or more likely undiagnosed NASH cirrhosis, can increase the risk of developing HCC. Clearly, these data suggest that screening is important for diagnosis of asymptomatic HCC and highlight the need for surveillance in this population.

### Diabetes

Diabetes has been found to increase the risk of developing chronic liver disease and HCC[15]. The mechanisms are yet to be elucidated but insulin resistance with secondary hyperinsulinemia is the most supported hypothesis since it may have a mitogenic effect by activating insulin-like growth factor-1 receptor[42]. Studies that have compared patients with cryptogenic cirrhosis to patients with a known etiology of their cirrhosis have shown a significantly higher prevalence of diabetes among the latter group[40,41]. As noted with the overweight and obese, a similar prevalence of diabetes has been observed among patients with cryptogenic and NASH cirrhosis[40].

In a recent systematic review of 13 case control studies, 11 supported an association between diabetes and the development of HCC[38]. Among the 13 case-control studies, subjects with diabetes were found to have a two-fold increase in the risk of HCC, an association that was further strengthened by excluding studies with significant heterogeneity[43].

The presence of diabetes remained an independent risk factor for HCC after adjustment for alcohol use or viral hepatitis[43]. However, as dictated by the limitations of the studies available in the literature, further well-defined studies are required to account for dietary factors and obesity[18].

### Diet

Several studies have examined whether alterations in diet have an effect on the risk of HCC. A trial from Italy has examined a broad range of dietary habits among 185 patients with HCC and 412 patients without cancer[44]. HCC were more likely to consume a large amount of calories, were five times more likely to be former drinkers, and were 30 times more likely to be infected with either HCV or HBV.

Among dietary compounds, consumption of iron and thiamine were associated with a significant threefold and twofold increase in risk of HCC, respectively. An association between intakes of iron was also evaluated according to the presence or absence of viral hepatitis[44]. When compared to appropriate controls, consumption of iron among patients without viral hepatitis was associated with a significantly increased risk of HCC[44]. This increase in risk was not conferred to those with HCV or HBV, Conversely, β-carotene and linoleic acid consumption was associated with a reduced risk of HCC[44].

In a similar study, those subjects with consumption in the highest quartile for yogurt and milk, white meat and eggs had a significantly lower likelihood of developing HCC[45]. This effect was observed in patients with and without viral hepatitis[45]. Other studies from Japan and Europe have found those who consume a large amount of green vegetables have a significantly lower likelihood of developing HCC[46,47]. Sauvaget *et al*[47] added that eating green vegetables daily had a protective effect against the development of HCC, as compared with consumption fewer times per week.

In summary, there is evidence to suggest that consumption of yogurt and milk as well as vitamin supplements offers a protective effect against HCC. The enthusiasm for these findings however should be tempered by the fact that the majority of these studies were retrospective in nature[18].

### Food containing N-nitroso compounds

Nitrites are found in smoked and cured fish, cheeses, bacon, hotdogs and other cured meats[48]. Nitrites are mainly manufactured as a food preservative. Both nitrates and nitrites are used extensively to enhance the color and extend the shelf life of processed meats. Nitrate is a normal component of the human diet, with the average daily intake from all sources estimated at 75 milligrams. Upon ingestion, about 5% of the nitrate taken in by healthy adults is converted (reduced) to nitrite by bacteria in saliva; further nitrate is converted by bacteria inside the alimentary tract[49].

Certain conditions in the stomach can increase the conversion of nitrate to nitrite, specifically when the pH of the gastric fluid is high enough (above 5) to favor the growth of nitrate-reducing bacteria. This process is of major concern for infants, whose gastrointestinal systems normally have a higher pH than those of adults. Nitrites in the stomach can react with food proteins to form N-nitroso compounds; these compounds can also be produced when meat containing nitrites or nitrates is cooked, particularly using high heat[49].

Animals with low or long-term exposure to N-nitroso compounds in food or drinking water recorded liver cancer[50]. However, all animals exposed to N-nitroso compounds suffered internal bleeding, usually followed by death[51]. It is not yet known if these compounds will cause similar effects in humans. However, there is a high probability that breathing or touching N-nitroso compounds causes liver disease and cancer[51].

### Alcohol

The mechanism by which alcohol consumption increases the risk of HCC is primarily through the development of cirrhosis. It has been suggested that heavy alcohol consumption of > 80 g/d ethanol for at least 5 years increases the risk of HCC by nearly 5-fold[52]. The risk appears to be proportional to the amount of alcohol consumed. In addition to a daily dose response, persistent alcohol

consumption appears to have a long-term effect on the risk of HCC occurrence. A prospective case-control study from Japan has observed that heavy alcohol drinkers, defined as > 600 L of alcohol during a lifetime, had a five-fold increase in the risk of HCC in comparison to non-drinkers or those who consumed < 600 L of alcohol[53]. However, the risk of HCC among those who consume low or moderate levels of alcohol remains unknown[4].

An association between genetic polymorphisms of the enzymes participating in the metabolic pathway of ethanol and the increased risk of HCC in heavy alcohol drinkers has been also proposed as a mechanism by which HCC develops. The frequency of aldehyde dehydrogenase 2 (*ALDH2*) genotype polymorphisms is significantly associated with increased risk of HCC in heavy alcohol drinkers[53].

Glutathione S-transferases (GST) are a super family of detoxifying enzymes involved in the neutralization of endogenous by-products of oxidative stress and exogenous chemicals of proven carcinogenicity. A study from Italy has observed that, among subjects who consumed > 100 g/d of ethanol and were bearers of the GST M1 (*GSTM1*) null genotype (*i.e.*, partial deletion of the coding sequence causes the total absence of enzymatic function) had twice the risk of HCC compared with bearers of the *GSTM1* non-null genotype[54].

### Smoking

Several studies have evaluated the association between smoking and development of primary liver cancer. An effect of tobacco in the development of HCC is biologically plausible, due to the carcinogenic potential of several of the ingredients in tobacco that are metabolized in the liver[55]. A prospective cohort study including 4050 men aged ⩾ 40 years who were followed-up for an average length of 9 years observed that those who smoked had a threefold increased risk of primary liver cancer when compared to never smokers[56]. Additionally, a study from Korea has found a 50% increase in the risk of primary liver cancer for current male smokers compared to never smokers[57]. In contrast however, a recent population-based case-control study from the United States did not observe a significantly increased risk of primary liver cancer among current male smokers[58]. Male ex-smokers, however, had a significant increase in risk of primary liver cancer, which suggests that there is perhaps a dose or duration response underlying this association[56-58]. Although the amount of smoking did not alter the risk of HCC, the duration of smoking significantly increased the risk of HCC for subjects who had smoked for > 20 years when compared to those who had smoked for < 10 years[59].

The association between tobacco and liver cancer and its reliance on host factors such as genetics, sex, and an underlying history of viral hepatitis has also been explored. With respect to the role of genetics, a small study from Japan has evaluated 78 patients with HCC and genetic polymorphisms of tobacco and alcohol-related metabolizing enzymes and 138 hospital controls without cancer. They have demonstrated that cigarette smokers did not have a significantly increased risk of HCC when compared with non-smokers[53]. To analyze the effect of sex, a prospective cohort study that included 83885 patients followed up for 8 years observed a positive association between smoking and HCC in women who smoked > 10 cigarettes per day[60]. However, no significant increase in the risk of HCC was demonstrated among male smokers[60].

In addition to an increase in the risk of developing HCC, it is also suggested in the literature that smoking increases the risk of death in HCC. In the Korean Cancer Prevention cohort study, men who were current smokers had an increased risk of death from HCC[59]. Women who were current smokers did not have the same elevation in risk of HCC-related death as that observed in men[59]. Marrero *et al*[55] showed a synergistic interaction between heavy alcohol consumption, heavy tobacco smoking and obesity on the risk of HCC. However, the biological mechanism for the synergy between tobacco, alcohol and obesity is unknown.

Lastly, to determine the effect of viral hepatitis on the association between HCC and tobacco, a prospective study of 12008 men observed that smoking significantly increased the risk of HCC only in anti-HCV-positive patients but not in those who were anti-HCV-negative when compared to anti-HCV-negative nonsmoking individuals[61].

### Oral contraceptives

Prior to the widespread use of oral contraceptives (OCs), benign liver tumors in young women were rarely observed[18]. In current literatures, therapy with oral contraceptives appears to be associated with the development of benign liver tumors such as hepatic hemangioma, hepatocellular adenoma or focal nodular hyperplasia[62]. Although not well researched, it has been proposed that OCs might also be associated with malignant liver tumors including HCC[63].

Rarely, malignant transformation can occur within the context of hepatic adenomas. It is unclear, however, whether the use of OCs influences the likelihood of developing adenoma and that these benign tumors transform into tumor[64]. Within the literature, there have been 14 cases of hepatic adenoma with focal malignant transformation to HCC in women taking OCs[64,65]. The mean age of these patients at the time of diagnosis of malignant transformation was 36 years (range: 23-57 years) and the mean duration of OCs use was 11 years (range: 1 mo-20 years)[66]. The frequency of HCC among hepatic adenomas appears to vary from 5% to 18%[67,68].

To evaluate further the risk of HCC in the setting of OCs use, several observational studies have been conducted. A recent meta-analysis of 12 case-control studies, including 739 cases and 5223 controls, which evaluated the risk of HCC among women using OCs indicated that there was no increase in risk of HCC with short-term use; defined as < 5 years of exposure[69].

An adjusted analysis, which accounted for variables

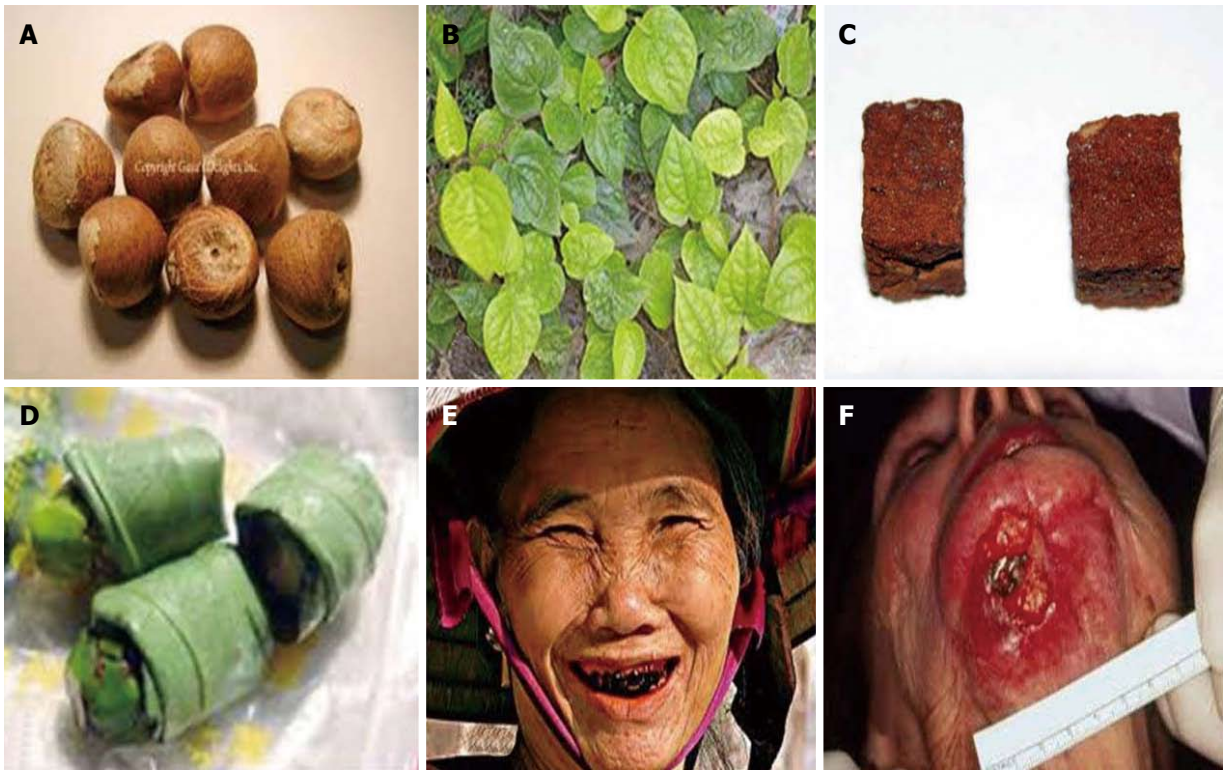


**Figure 1 These ingredients have been shown to have genotoxic, mutagenic and tumorigenic properties.** A, B: Nuts and leaves of Piper betle; C, D: Different forms of betel quid chew; E, F: Side effects of betel quid chewing. (A: medicalinspection.net; B: iamshaman.com; C: wholesaleshamanicherbs.com; D: gethealthyclarkcounty.org; E: vietnamgrouptour.com; F: medianlinspection.net.)

such as age, race and parity, did not yield significant findings[69]. On the contrary, another study has observed a significantly increased risk of HCC among women taking OCs for > 5 years; an increase in risk of 2-20 fold[69]. However, given the variable periods of duration used in the study, a pooled estimate of risk could not be generated[69]. Based on these results, further studies are required to evaluate the association between OCs and the risk of HCC and how such risk is modified by duration of OCs use. Additionally, it should be noted that an association between new-generation OCs with lower doses of hormones and the risk of HCC has not yet been explored[18].

### Betel quid

Betel quid is one of the most addictive substances used in Asia and among migrated communities in Africa, Europe and North America. The chewing of betel quid is woven into the cultural fabric of up to 20% of the world population. Betel quid consists of the nut of the *Areca catechu* palm (areca nut), betel leaf or fruit from *Piper betle* and red slaked paste[70]. These ingredients have been shown to have genotoxic, mutagenic and tumorigenic properties[71] (Figure 1).

A case-control study from Taiwan has shown that betel quid chewing was an independent risk factor for liver cirrhosis[72]. Contrary, a prospective case-control study from Asia has observed a significant association between betel quid chewing and the incidence of HCC. This study included 263 pairs of age- and sex-matched patients with HCC and healthy controls and observed that betel quid chewing was a dependent risk factor for HCC, with a threefold risk noted. The aggregate risk increased with increasing duration and/or quantity of consumption[70]. These data were further supported by a study from Taiwan, including 420 age- and sex-matched patients with HCC and liver cirrhosis, liver cirrhosis only and healthy controls. In this study, a nearly six fold and nearly twofold increased risk of HCC was observed in patients with HCC compared with healthy controls and patients with liver cirrhosis, respectively[73].

### Aflatoxin

Aflatoxin B1 (AFB1) is the major metabolite of the molds *Aspergillus fumigatus* and *Aspergillus parasiticus*. These molds grow on a variety of food products that are stored in warm and damp conditions or are cultivated in countries with hot and humid climates[6]. AFB1 induces a single nucleotide substitution in codon 249 in the *p53* tumor suppressor gene, which results in the change of the amino acid arginine to serine[74] which is indigenous to geographic regions with high exposure to AFB1[75]. On the other hand, this mutation is absent in patients with HCC from regions with low exposure to AFB1[75]. Moreover, it has been recently demonstrated that AFB1-albumin adducts in patients with HCC correlate significantly with the presence of plasma DNA hypermethylation and mutations in the *p16* and *p53* tumor suppressor genes[76].

Several studies have evaluated an association between

the risk of HCC and exposure to AFB1. A prospective case-control study from China which included 18244 middle-aged men showed that individuals with the presence of urinary aflatoxin biomarkers had a significantly increased risk of HCC after adjusting for HBV surface antigen seropositivity and cigarette smoking[77]. These data were further supported by a community-based cohort study from Taiwan which found that elevated AFB1 exposure measured by detectable AFB1-albumin adducts was an independent risk factor for HCC after adjustment for important confounders.

In Egypt, Dilber *et al*[78] detected a significant higher percent of aflatoxins in the serum of Egyptian patients with HCC compared to their controls; with a twofold increased risk. Hifnawy *et al*[79] revealed the prevalence of AFB1 contamination in corn, wheat, peanut, lupine, white rice, cowpea, fava bean and brown rice by 64.7%, 53%, 53%, 47%, 47%, 41%, 29.4% and 29.4%, respectively.

It should be stressed that areas with high exposure to AFB1 are also characterized by a high prevalence of HBV infection. AFB1 is independent of the risk conferred by HBV; however concomitant exposure to both HBV and AFB1 markedly increases the risk of HCC. The risk of HCC was 60 times higher in patients with HBV infection and a concomitant elevation of urinary AFB1 markers[80]. Patients with HBV infection and normal urinary AFB1 markers had sevenfold increase in risk of HCC when compared to those without HBV infection[81].

### Coffee

In addition to its reported association with reductions in bladder cancer and colorectal cancer, coffee consumption has also been extensively studied and appears to have a potentially favorable effect on the prevention of liver diseases, including HCC[82]. There are several hypotheses that could explain why consuming coffee attenuates the risk of developing HCC. One hypothesis argues that coffee intake lowers serum levels of γ-glutamyl transferase, which is associated with a lower incidence of HCC[83,84]. Coffee consumption has also been linked to a lower incidence of cirrhosis, which is a major risk factor for the development of HCC[84].

An analysis of two large prospective studies of 70000 participants in Japan has shown that those who drank one or more cups of coffee daily had a significantly lower risk of developing HCC[85]. A case-control study of 2746 people has found that those who drank three or more cups of coffee were 40% less likely to develop HCC[84].

In summary, those who drank any coffee compared to non-drinkers had a significantly lower risk of HCC. The greater the coffee consumption, the greater the attenuation in HCC risk. Low coffee consumption was associated with a 30% reduction in risk and high consumption with a 55% reduction in HCC risk[85].

Although these results are impressive and consistent, one must consider that the findings of an inverse relationship between coffee consumption and the risk of HCC might be influenced by bias. Coffee metabolism is impaired in cirrhotic livers as compared to the normal liver. This altered metabolism generates an increase in the untoward side effects of the beverage. Therefore, the presence of liver disease might lead affected patients to consume less coffee. This could result in a falsely negative association. Therefore, the potential bias of this association in the liver disease patient cannot be discounted[18].

### Schistosomiasis

Schistosomiasis, caused by infestation with trematode blood flukes, is endemic in tropical areas of Africa, South America, Asia and the Caribbean. Three species of schistosomes, *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi* preferentially infect the liver, however, only *S. japonicum* has been classified as possibly carcinogenic in humans[86]. A recent study has supported the role of *S. japonicum* infection in HCC as a cofactor with HBV and HCV infections rather than as a primary hepatocarcinogen[87].

### Pesticides

Occupational exposure to pesticides may have a contributory role in the etiology or progression of HCC[10]. According to McGlynn *et al*[88] no statistically significant associations between HCC and household application of pesticides were observed for urban males or for females. As expected, the strongest risk factors for HCC were HCV and current HBV infection. This study therefore suggested that exposures to organophophorus and carbamate pesticides are additive risk factors to current HCV and HBV infection among rural males. Future investigation should address the possible hepatocarcinogenicity of pesticides using biomarkers of exposure and other techniques to better estimate dose-response relationships[10].

### Thorotrast

Persons exposed to Thorotrast, an X-ray contrast medium (thorium dioxide) have found a 120-fold increased risk of primary liver cancer, largely due to risks of angiosarcoma and intrahepatic cholangiocarcinoma[89].

### Alpha-1 antitrypsin deficiency

It is an autosomal recessive disorder resulting in the expression of a defective alpha-1 antitrypsin protein as a consequence of the presence of an abnormal allele. Liver disease in alpha-1-antitrypsin deficiency is caused by a gain-of-toxic function mechanism engendered by the accumulation of a mutant glycoprotein in the endoplasmic reticulum[20]. HCC is common in children with alpha-1 antitrypsin deficiency and cirrhosis as well as in adults who are 50-60 years of age. In the adult cases of alpha-1 antitrypsin with cirrhosis, HCC is reported to occur in 31%-67% of cases[90]. The hepatic endoplasmic reticulum and mitochondrion in individuals with alpha-1 antitrypsin deficiency demonstrate morphologic and biochemical abnormalities. As a result, the sum of the many different cellular injuries associated with oxidative stress especially with mitochondrial injury is thought to be the driving force for HCC development in cases of alpha-1 antitryp-

sin deficiency[91].

### Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a disease of unknown etiology[21]. It is an inflammation of the liver that occurs when immune cells mistake the liver's normal cells for harmful invaders and attack them. It is an anomalous presentation of human leukocyte antigen class Ⅱ on the surface of hepatocytes, possibly due to genetic predisposition or acute liver infection that causes a cell-mediated immune response against the body's own liver. Researchers think a genetic factor may make some people more susceptible to autoimmune diseases. About 70 percent of those with autoimmune hepatitis are female. The disease is usually quite serious and, if not treated, gets worse over time. Autoimmune hepatitis is typically chronic, meaning it can last for years, and can lead to cirrhosis the liver. Eventually, liver failure can result[92].

The risk of HCC among patients with AIH is believed to be low compared with other chronic liver diseases. The risk of HCC among AIH patients with cirrhosis is 1.9% per year. This is comparable to HCC risk among patients with cirrhosis secondary to HBV, HCV, hemochromatosis, or alcohol-related liver disease[93]. Meza-Junco *et al*[21] added that HCC occur in 7% of patients with AIH and cirrhosis of at least 5 year durations, with an incident of 1 per 350 patients-years. When this study excluded HCV infection, they found that one case of HCC with 212 patients with HIA (0.5%) in absence of viral infection.

### Porphyries

Hepatic porphyries are a group of inherited diseases caused by partial enzyme defects in haem biosynthesis. They manifest with either neurological complications ("acute") or skin problems ("cutaneous"), or occasionally both. The term derives from the Greek, *porphyira,* meaning "purple pigment". The name is likely to have been a reference to the purple discolouration of feces and urine in patients during an attack[94]. The commonest types are acute intermittent porphyria (AIP) and variegate porphyria. Clinically these porphyrias are characterized by occasional acute attacks consisting of abdominal pain and various neuropsychiatric symptoms. The prognosis of patients with acute hepatic porphyria has improved greatly during recent decades[95].

An association between HCC and AIP was first suggested by Mogl *et al*[96] in Sweden. Kauppinen *et al*[19] recorded that in acute hepatic porphyria, the calculated risk of hepatocellular carcinoma is increased 61-fold. In addition, a significant iron overload, as found in hereditary hemochromatosis, is a risk factor for HCC and may also promote the symptoms of porphyria cutanea tarda.

### Wilson disease

Wilson disease (WD), an inborn copper metabolism defect, is traditionally diagnosed on the basis of clinical features, positive family history, biochemical parameters, the presence of Kayser-Fleischer rings on slit lamp eye examination, and neurologic abnormalities[97].

Carcinogenesis in WD is thought to be the result of accumulated copper in the liver and underlying cirrhosis[22]. Although copper deposition in the liver is actually a risk factor for the development of HCC, some researchers have observed that decreased copper in patients following D-penicillamine and other chelator treatments may enhance the risk of developing HCC[98]. Guan *et al*[99] reported the occurrence of HCC in a young woman with Wilson's disease who had never been took oral contraceptives or exposed to hepatitis B virus. Therefore, all newly researches indicated that WD is a risk factor for HCC[22].

### Primary biliary cirrhosis

Several studies have indicated that primary biliary cirrhosis (PBC) may be associated with increased risk of some cancers and HCC[100]. PBC primarily affects females and is rarely complicated by HCC. Although HCC incidence in PBC patients is low, several characteristics and risk factors associated with its development have been reported. Males are at risk of developing HCC at any histological stage of PBC. Therefore, male PBC patients in particular should be carefully screened for HCC from the early stages of PBC[101].

### Congestive liver disease

Muguti *et al*[102] found that among 17 patients with hepatic focal nodular hyperplasia (FNH), FNH was found in association with hepatocellular carcinoma in three, one of whom also had peliosis and an hepatic adenoma. FNH was also found in association with other conditions which may affect hepatic function, structure or circulation, including chronic obstructive airways disease, congestive cardiomyopathy, chronic active hepatitis, granulomatous hepatitis, coeliac artery stenosis and metastatic malignant melanoma. This observation draws attention to a possible link between FNH, hepatic malignancy and conditions which may disturb the hepatic circulation. Therefore, patients with FNH should be investigated thoroughly and an aggressive management policy should be adopted.

### Family history of liver cancer

In a study conducted in the United States, individuals with a first-degree family history of liver cancer (liver cancer in a parent, sibling, or child) were roughly four times more likely to develop liver cancer than individuals without such a family history. This increased risk was observed even in the subset of people without viral hepatitis[9,103]. This study suggests that either genetic factors or shared environmental factors influence the risk of liver cancer.

## CONCLUSION

Multiple non-viral factors have been implicated in the development of HCC. Hemochromatosis and iron overload

syndromes have consistently been shown to dramatically increase the rate of HCC. Additionally, factors such as obesity and diabetes, which operate *via* NASH cirrhosis or perhaps independently, have also been demonstrated to increase the risk of HCC. With respect to other exposures, although alcohol and tobacco clearly increase the risk of HCC development and mortality, other exposures such as coffee and high levels of vegetable consumption may be protective against this condition.

Further studies are urgently needed to determine the pathogenesis that underlies the occurrence of HCC in the setting of these exposures, as well as the way in which such risk is modified by environmental and host characteristics such as genetics.

Clarification of relevant non-viral causes of HCC will help to focus clinicians on those risk factors that are modifiable. With more information, future surveillance efforts will be more appropriately targeted toward populations at greatest risk.

This multilevel preventative approach will hopefully lead to a reduction in incidence of non-viral HCC, and a decrease in the patient morbidity and mortality as well as the societal economic burden associated with HCC.

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MINIREVIEWS

# Hepatocellular carcinoma in patients co-infected with hepatitis C virus and human immunodeficiency virus

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**Key words:** Hepatocellular carcinoma; Hepatitis C virus, Human immunodeficiency virus; Co-infection

**Core tip:** Hepatitis C virus and human immunodeficiency virus co-infected patients with Hepatocellular carcinoma, undergo the same therapeutic protocol as their mono-infected counterparts, but special issues such as interaction between regimens, withdrawal of therapy and choice of immunosuppressive agents, demand a careful approach by specialists.

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## Abstract

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) share a common route of transmission so that about one third of HIV infected individuals show HCV co-infection. Highly active antiretroviral therapy has offered a longer and better life to infected patients. While has removed AIDS-related diseases from the list of most common causes of death their place has been taken by complications of HCV infection, such as cirrhosis, end stage liver disease and hepatocellular carcinoma (HCC). HIV/HCV co-infection requires complex management, especially when HCC is present. Co-infected patients with HCC undergo the same therapeutic protocol as their mono-infected counterparts, but special issues such as interaction between regimens, withdrawal of therapy and choice of immunosuppressive agents, demand a careful approach by specialists. All these issues are analyzed in this minireview.



## INTRODUCTION

Co-infection with hepatitis C virus (HCV) and human immunodeficiency virus (HIV) is a common problem both in the United States as well as in Europe, for two main reasons. Firstly, both viruses share a common route of transmission (sexual or intravenous). Secondly, the introduction of highly active anti-retroviral therapy (HAART) has extended life expectancy for HIV infected individuals. These positive results, however, make these patients vulnerable to opportunistic infections or infections such as HCV. Furthermore, HCV/HIV co-infected patients cannot fully tolerate anti-HCV treatment due to adverse effects of the combination with HAART. While HIV subjects receiving HAART are at lower risk of dying from acquired immunodeficiency syndrome (AIDS)-related diseases, for those with HCV co-infection, end stage liver disease and hepatocellular carcinoma (HCC) have emerged as leading causes of morbidity and mortal-

ity. In the present report we try to evaluate epidemiological characteristics of co-infected patients, the risk of development of HCC, as well as the suggested treatment modalities presented in the pertinent literature.

## EPIDEMIOLOGY

In the United States, about 25% to 35% of patients with HIV are co-infected with HCV, totaling nearly 300000 people, while less than ten years ago this number was only about 50000, with a higher prevalence among United States military veterans[1-4]. The prevalence of HCV infection among HIV infected individuals varies, with the co-infection rate being higher when transmission occurs *via* the parenteral route compared to infection through sexual contact. HIV infected individuals who receive the virus through intravenous drug abuse or blood/blood products transfusion have a prevalence of HCV co-infection rate of between 75% to 90%[3,5]. Bollepalli *et al*[6] reported that intravenous drug abuse, sharing toothbrushes or razors, being in prison and tattooing are the most common non-sexual related risk factors while among the sexual related risk factors, sex for money or drugs, sex with intravenous drug abusers and men having sex with men, are significant risk factors. However, it is very difficult to determine the true contribution of the above mentioned risk factors, as many of them interfere with one another. It is, though, true that the absolute number of patients with HCV/HIV co-infection is increasing and as the AIDS-related causes of death are minimized, the complications of HCV infection (end stage liver disease and HCC) have become the main cause for the morbidity and mortality in this subgroup of patients.

## CLINICAL IMPACT

As described above, in the recent years there have been major efforts in the treatment of HIV infected individuals, maximizing therapy by introducing HAART. In the era of HAART, HIV infected subjects avoid the progression towards AIDS and its lethal complications, and achieve a prolonged viral suppression, significant immune system restoration, improvement of quality of life and a resultant prolongation of life expectancy[7-10]. As HIV and HCV share common routes of transmission, and HIV infected individuals under HAART face no longer the risk of death due to AIDS-related conditions, HCV infection and its complications have become the major issue.

A further issue is that the interaction between the two viruses and their impact on liver surgery is not completely understood. HCV is not directly cytotoxic and the pathogenesis of liver injury is believed to be result of host immune-mediated cytolytic response[11]. The presence of HIV infection alters the natural history of HCV infection. After acquiring HCV, the infection becomes chronic in almost 90% of HIV patients and once chronic infection is established liver fibrosis progresses much faster, resulting in higher frequency of cirrhosis and its complications, compared to mono-infected HCV patients[12,13]. A meta-analysis including 8 studies with 1871 HCV-positive patients showed, in the subgroup of those co-infected with HIV patients, a relative risk of 2.92 for more severe disease, 2.07 for histological cirrhosis and 6.14 for decompensated liver disease[12]. Similarly there is a higher incidence of HCC in co-infected patients[14,15]. Co-infected patients are younger and have a shorter duration of HCV infection than patients with HCC and HCV mono-infection. Another characteristic of this group of patients is that tumors commonly show an infiltrative pattern and an advanced stage at presentation as well as more frequent extranodal metastases[16]. Therefore an effective treatment of both viruses is the gold standard for achieving a favorable outcome in co-infected patients.

## TREATMENT STRATEGIES

The achievement of optimal treatment of HCV in HIV patients is a challenge. An initial assessment of viral load of HIV and HCV along with a CD4 count should be performed. The current recommendation is to suppress HIV before starting anti-HCV treatment[16]. The combination of pegylated interferon and ribavirin seems to be the treatment of choice in order to stop progression of fibrosis and prevent liver-related disease and death in mono-infected patients[16,17]. However, adverse effects lead to discontinuation of treatment or doses modification in the majority of patients. The most common side effects are flue-like symptoms while about one third of patients experience a drop in hematological parameters[18-20]. The treatment of HCV in HIV co-infected patients is more complicated due to the additive drug toxicities of ribavirin and the nucleoside reverse transcriptase inhibitors didanosine, zidovudine and stavudine[21-23]. Recent studies, however, reveal that a nucleoside-free HAART is feasible in the context of anti-HCV therapy and it is at least not disadvantageous for the patients, and could also provide great improvements in treatment response rates[24].

## HCC ISSUES

The result of HCV infection is, in the majority of cases, the development of liver cirrhosis. Once cirrhosis is established, the annual risk of HCC, liver disease progression and death in HCV infected patients reaches approximately 1% to 7%, 5% and 2% respectively[25]. As described above, co-infected patients have been shown to develop liver cirrhosis more quickly than HCV mono-infected individuals and demonstrate a more aggressive course of HCC. In a study by Benhamou *et al*[13], HIV-HCV co-infected patients had a mean rate of fibrosis progression of 0.181 fibrosis units per year, which translated into a mean duration from HCV infection to cirrhosis of 26 years. HCV mono-infected patients had a mean rate of fibrosis progression of 0.135 fibrosis units per year, or a mean duration of 38 years from HCV infection to cirrhosis. Thus the eradication of HCV in these pa-

tients remains the gold standard of treatment.

According to current guidelines, treatment of HCC is the same for patients with and without HIV infection although the outcome seems to be worse for HIV-positive patients than their HIV-negative counterparts[26]. Chemotherapy seemed not to be a favorable treatment strategy until recently as HCC was considered as a chemoresistant tumor. However, sorafenib is a new tyrosine kinase inhibitor targeted against several biological factors (including vascular endothelial growth factor, platelet derived growth factor and Raf kinase) which demonstraties the ability to inhibit tumor proliferation and angiogenesis *in vitro*. Monotherapy with oral sorafenib (400 mg twice daily) prolonged median overall survival and delayed the median time to progression in patients with advanced hepatocellular carcinoma, according to the results of a randomized, double-blind, placebo-controlled, multicenter, phase Ⅲ trial (the Asia-Pacific trial)[27]. Two hundred and seventy-one patients from 23 centers in China, South Korea and Taiwan were enrolled in the study. Of these, 226 patients were randomly assigned to the experimental group ($n$ = 150) or to the placebo group ($n$ = 76). Median overall survival was 6.5 mo in patients treated with sorafenib, compared with 4.2 mo in those who received placebo. Median time to progression was 2.8 mo (2.63-3.58 mo) in the sorafenib group compared with 1.4 mo (1.35-1.55 mo) in the placebo group[27]. Sorafenib has been approved both in Europe Union and United States and has changed the natural course of unresectable HCC.

The efficacy of sorafenib, however, has not been proved in the setting of HCC in HCV-HIV co-infected patients as there are only individual cases described in the pertinent literature and no larger trials. In these cases there has been a remarkable prolongation of patient survival after administration of sorafenib[27]. Furthermore, metabolism of sorafenib occurs primarily in the liver, mediated *via* cytochrome P450, and concomitant administration of cytochrome inducers or inhibitors could alter the active sorafenib concentration[28]. Some agents (fosemprenavir and ritonavir) used in the HAART are cytochrome inhibitors and this could mediate a potent increase in the active dose of Sorafenib, resulting in a favorable outcome for the patient. Further studies are needed in order to strengthen these results.

Another very serious issue regarding HCC is recurrent disease after initial treatment. Several treatment modalities have been introduced, with interferon the most popular among them. A meta-analysis examining the effect of interferon on patient survival, was favorable to interferon with a pooled risk ratio of 0.65, and without statistical heterogeneity. Interferon treatment also significantly reduced the risk of tumor recurrence with a pooled risk ratio of 0.86[17]. The significant positive effect of interferon is, however, diminshed by its moderate or severe side effects. Interferon possesses several properties including antiviral, immunomodulatory, antiproliferative and antiangiogenic actions. Such activities could explain why the beneficial effect of interferon is greater for survival than for tumor recurrence. In particular the antiviral effect might delay further progression of cirrhosis and deterioration of liver function.

The last but very interesting issue in the setting of HCV-HIV co-infection with the presence of HCC, is the possibility of liver transplantation (LTx). Previously the presence of HIV infection was a contraindication for LTx despite the fact that LTx is the treatment of choice for end-stage liver disease or HCC. However, during the last decade things have changed dramatically and in the HAART era, 1- and 3-year survival rates after LTx have reached 87% to 91% and 64% to 73%, respectively[29]. Further epidemiological studies reveal that the outcome after LTx in HIV-HCV co-infected patients is worse than mono-infected either with HIV or HCV[30,31]. Norris *et al*[30] reported that at 12 mo, 4 of 7 (57.1%) of those coinfected with HCV were still alive, but by 25 mo a further 2 had died. The survival rate of HCV/HIV co-infected individuals was clearly lower than in the HCV mono-infected candidates who received organs during the same period. The latter had actuarial 1- and 2-year survival rates of 87.5% and 83.9%, respectively.

Several factors regarding the outcome of LTx in HIV infected individuals should be highlighted. Firstly should be pointed out that HIV-positive individuals with hepatitis B or hepatitis C virus infections should be referred to transplant centers at an early stage, in order for the transplant experts to choose the optimal time for transplantation (not too late and not too early, depending on the cause of liver failure). The criteria for LTx are the same for both HIV-positive and for HIV-negative patients, requiring low virus load and absolute CD4 cells not less than 100 cells/mL. Similarly, opportunistic infections previously considered as a contraindication now should be evaluated before decisions on transplantation are made[32].

Another controversial issue is the choice of immunosuppressive regimen after LTx. Two issues require special attention, the first being the avoidance of rapid withdrawal of steroids in the HCV co-infected population, due to the evidence of accelerated fibrosis. The second issue is the interaction between immunosuppressive treatment and HAART, as many of the immunosuppressive medications are metabolized in the cytochrome P450 system. Some antiretroviral drugs (*e.g.*, ritonavir) can reduce metabolism of calcineurin inhibitors (cyclosporine, tacrolimus), so that dosage of these agents must be reduced by up to 75%. On the other hand immunosuppressive agents like mucophenolate mophetil interact with nucleotide analogues altering the activity of antiviral medication[33,34].

## CONCLUSION

HIV infection is a serious social problem, in developed countries as well as in the developing world, and as any vaccine is still far from everyday clinical practice, this is becoming ever more dangerous. HIV and HCV share common routes of transmission, resulting in about 30% of HIV infected individuals being co-infected with

HCV. Treatment of HIV/HCV co-infected subjects is more complicated for than mono-infected individuals. In the HAART era, HIV infected subjects live longer and enjoy a very good quality of life, so that the complications of HCV infection (cirrhosis, end stage liver disease and HCC) are the most common causes of mortality and morbidity in the co-infected subgroup of patients. Treatment of HCV and its complications in co-infected patients is a difficult dilemma due to interactions between medications and frequent withdrawal of therapy or dose modification due to adverse effects. Treatment of HCC in co-infected patients is the same as in other HCC patients, including surgical techniques, chemotherapy with sorafenib, palliative treatment modalities and liver transplantation.

Future directions can be divided into two main categories. In the first category are clinical and experimental studies, ranging from new therapeutic agents to vaccination. Until this becomes reality, we should follow the second category which includes a very close clinical and laboratory examination of co-infected patients and an early reference to centers of expertise.

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BRIEF ARTICLE

# Normal vitamin D levels are associated with spontaneous hepatitis B surface antigen seroclearance

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## Abstract

**AIM:** To investigate a possible association between serum vitamin D levels and spontaneous hepatitis B surface antigen (HBsAg) seroclearance.

**METHODS:** Fifty-three patients diagnosed with chronic inactive hepatitis B and spontaneous HBsAg seroclearance were followed up in two Israeli liver units between 2007 and 2012. This retrospective study reviewed medical charts of all the patients, extracting demographic, serological and vitamin D rates in the serum, as well as medical conditions and current medical therapy. Spontaneous HBsAg seroclearance was defined as the loss of serum HBsAg indefinitely. Vitamin D levels were compared to all patients who underwent spontaneous HBsAg seroclearance.

**RESULTS:** Out of the 53 patients who underwent hepatitis B antigen seroclearance, 44 patients (83%) had normal levels of 25-hydroxyvitamin vitamin D compared to 9 patients (17%) who had below normal levels. Multivariate analysis showed that age (> 35 years) OR = 1.7 (95%CI: 1.25-2.8, $P$ = 0.05), serum vitamin D levels (> 20 ng/mL) OR = 2.6 (95%CI: 2.4-3.2, $P$ = 0.02), hepatitis B e antigen negativity OR = 2.1 (95%CI: 2.2-3.1, $P$ = 0.02), low viral load (hepatitis B virus DNA < 100 IU/mL) OR = 3 (95%CI: 2.6-4.2, $P$ = 0.01) and duration of HBsAg seropositivity (> 8 years) OR = 1.6 (95%CI: 1.15-2.6, $P$ = 0.04) were also associated with spontaneous HBsAg seroclearance.

**CONCLUSION:** We found a strong correlation between normal vitamin D levels and spontaneous HBsAg seroclearance.



**Key words:** Hepatitis B; Vitamin D; Immune disease; Seroclearance; Viral load

**Core tip:** Vitamin D has recently been linked to many autoimmune diseases. Hepatitis B is a viral disease but shows many autoimmune characteristics. Spontaneous hepatitis B seroclearance is an unexplained phenomenon. The hypothesis of this paper was that normal vitamin D levels may be linked to a positive effect on hepatitis B. We showed that normal vitamin D levels correlate positively with spontaneous hepatitis B seroclearance. This finding may help to expand the therapeutic options for this disease.

Mahamid M, Nseir W, Abu Elhija O, Shteingart S, Mahamid A, Smamra M, Koslowsky B. Normal vitamin D levels are associated with spontaneous hepatitis B surface antigen seroclearance.

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## INTRODUCTION

The natural history of chronic hepatitis B virus (HBV) infection involves three sequential phases. The initial immune tolerant phase occurs when patients are positive for hepatitis B e antigen (HBeAg) and express normal levels of alanine aminotransferase (ALT). The immune clearance phase occurs when HBeAg-positive patients encounter an abnormal ALT elevation. The final phase takes place when HBeAg undergoes seroconversion to its antibody and ALT levels normalize, proceeding the transition to the inactive residual phase[1]. Although one third of these so-called inactive hepatitis B surface antigen (HBsAg) carriers might come across HBV reactivation and develop HBeAg-negative chronic hepatitis, most inactive carriers remain permanently inactive over a lifetime and some may ultimately clear HBsAg from the serum[2]. Spontaneous HBsAg seroclearance is defined as the loss of serum HBsAg remaining consistent on multiple examinations[3]. Spontaneous HBsAg seroclearance is a rare event in the natural history of chronic HBV infection and this phenomenon is more common in Caucasians than in Asians. The annual rate of spontaneous HBsAg seroclearance varied between 0.12%-2.38% in cohorts from Asian countries and 1.54%-1.98% in cohorts from Western countries[4,5]. Older age, male gender, normal ALT levels, steatosis, cirrhosis, HBeAg negative at baseline, HBV DNA negative at baseline, genotype and hepatitis C virus (HCV) superinfection have all been shown to have a significant correlation with spontaneous HBsAg seroclearance[3]. Infection by HBV is accompanied by a number of immunopathological manifestations[6]. A link between infection and autoimmunity is well documented for HCV infection but HBV infection has also been shown to provoke immunological reactions. These manifestations range from production of autoantibodies to overt autoimmune diseases, including thyroiditis, autoimmune hepatitis, cryoglobulinemia, glomerulonephritis and vasculitis[7-9]. Vitamin D deficiency has been reported in more than one billion people worldwide, including in sun-rich countries like Israel[10,11]. The key role played by vitamin D combined with calcium in bone health is well known but other non classical effects of vitamin D are recognized. Interaction with the immune system is one of the most well established non classical effects of vitamin D[12,13]. Vitamin D deficiency has also been associated with increased risk of respiratory disease, including infections (such as influenza and mycobacterium tuberculosis) and chronic respiratory diseases such as cystic fibrosis[14,15]. Considerable data about the connection between vitamin D deficiency and development of immune mediated diseases have been published. Studies suggest a link between vitamin D deficiency and autoimmune diseases, such as rheumatoid arthritis, systemic sclerosis and systemic lupus erythematosus (SLE)[16,17]. In this study, we aimed to look for a possible association between serum 25-hydroxyvitamin D [25 (OH) D] levels and the occurrence of spontaneous HBsAg seroclearance. Clinical, anthropometric and laboratory factors were also checked to find a correlation with HBsAg seroclearance.

## MATERIALS AND METHODS

A retrospective study carried out between 2007 to 2012 included adult patients with spontaneous HBsAg seroclearance who were followed up at the liver unit of the Shaare Zedek Medical Center (SZMC), Jerusalem, Israel and the liver unit of the Holy Family Hospital, Nazareth, Israel. The study was reviewed and approved by the local ethics committee of each hospital. All patients aged 18-60 years with spontaneous HBsAg seroclearance between 2007 and 2012 were included. Exclusion criteria included patients with liver disease due to acute or chronic hepatitis C, hepatitis A and human immunodeficiency virus (HIV). All patients with another metabolic, infectious, autoimmune or inflammatory liver disease other than steatosis were excluded. Additionally, patients with an alcohol intake > 10 mg/d, receiving chronic immunosuppressive therapy, history of antiviral treatment, prior liver transplantation or the absence of 25 (OH) vitamin D levels in serum were all excluded. The medical charts of the patients were reviewed and multiple data were collected, including age, gender, body mass index (BMI), serum 25 (OH) vitamin D, year of HBsAg appearance, the status of HBeAg, antibodies for HBeAg and viral load (HBV DNA polymerase chain reaction). Information concerning medical conditions, drug therapy and results of laboratory tests were extracted from the medical charts of each subject. Spontaneous HBsAg seroclearance was defined as the loss of serum HBsAg on two occasions at least 6 mo apart and still absent at the last visit.

The normal range of 25 (OH) vitamin D levels was considered to be > 30 ng/mL. Levels of 25 (OH) vitamin D of 20-30 ng/mL were considered an insufficiency and levels < 20 ng/mL were considered a deficiency.

### *Statistical analysis*

Data was analyzed using SPSS version 19 (IBM SPSS, Chicago, IL, United States). Continuous variables are expressed as the mean ± SD. The $\chi^2$ test was used to test differences in categorical variables between the cases and analysis of variance or the Student's *t* test was used for comparisons of continuous variables. Spearman rank correlation and univariate regression analysis was used to determine the strength of the relationship between the factors for spontaneous HBsAg seroclearance, namely age, gender, BMI, serum 25 (OH) vitamin D, duration of HBsAg positivity, the status of HBeAg, antibodies for HBeAg and hepatitis B viral load. A multiple logistic regression analysis was done to determine the association between the different factors and spontaneous HBsAg

**Table 1 Laboratory, demographic and clinical data of the two groups *n* (%) or (mean ± SD)**

| Characteristic | Normal levels of 25 (OH) vitamin D (*n* = 44) | Below normal levels of 25 (OH) vitamin D (*n* = 9) | *P* value |
|---|---|---|---|
| Sex (male) | 30 (68) | 5 (55) | NS |
| Age (yr) | 37 ± 12.3 | 33 ± 15.1 | NS |
| BMI | 25 ± 5.4 | 27 ± 3.2 | NS |
| C-reactive protein (mg/L) | 0.9 ± 2.57 | 0.7 ± 1.23 | NS |
| Duration of HBsAg positivity (yr) | 7.2 ± 3.4 | 8.4 ± 4.8 | NS |
| HBeAg-positive | 7 (16) | 2 (22) | NS |
| Mean levels of 25 (OH) vitamin D (ng/mL) | 31 ± 4 | 13.5 ± 7.2 | < 0.001 |

Comparison of demographic and laboratory characteristics between patients with normal and below normal levels of serum vitamin D. Normal levels of 25-hydroxyvitamin [25 (OH)] vitamin D > 30 ng/mL. Below normal levels of 25 (OH) vitamin D ⩽ 30 ng/mL. NS: Not significant; BMI: Body mass index; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

seroclearance. A significance level of $P < 0.05$ was used in this test.

## RESULTS

The medical charts of 68 adult patients with spontaneous HBsAg seroclearance were reviewed during the years 2007-2012. Fifteen patients were excluded due to evidence of HCV antibodies ($n = 2$), alcohol intake > 10 mg/d ($n = 2$), chronic steroid use ($n = 1$), suspected autoimmune hepatitis ($n = 1$) and an unknown vitamin D status ($n = 9$). Altogether, 53 patients with spontaneous HBsAg seroclearance were included in the study. The patients were separated into 2 groups, one group with normal 25 (OH) vitamin D levels and the other with 25 (OH) vitamin D levels below normal, including insufficiency and deficiency. Age, gender, BMI and C-reactive protein (CRP) levels were similar between the two groups (Table 1). When comparing the two groups according to vitamin D levels, the normal vitamin D group had 44 (83%) patients, compared to 9 patients (17%) with below normal vitamin D levels. The duration of HBsAg and positivity of HBeAg did not show a significant difference between the two groups.

When performing a multiple logistic regression analysis, adjusted by age, gender, BMI, serum 25 (OH) vitamin D, duration of HBsAg positivity, the status of HBeAg, antibodies for HBeAg and the viral load, statistically significant findings were associated with spontaneous seroclearance of HBsAg. Age over 35 years, absence of HBeAg, low viral load (< 100 IU/mL) and duration of HBsAg (> 8 years) were all associated with spontaneous HBsAg seroclearance (Table 2).

**Table 2 Results of multiple logistic regression analysis of spontaneous hepatitis B surface antigen seroclearance**

| Variables | OR (95%CI) | *P* value |
|---|---|---|
| Age > 35 (yr) | 1.7 (1.25-2.8) | 0.05 |
| HBV DNA < 100 IU/mL | 3 (2.6-4.2) | 0.01 |
| Serum 25 (OH) vitamin D > 20 ng/mL | 2.6 (2.4-3.2) | 0.02 |
| HBeAg-negative | 2.1 (1.2-3.1) | 0.02 |
| Duration of HBsAg-positivity > 8 years | 1.6 (1.15-2.6) | 0.04 |

Multiple logistic variables found to add a risk for spontaneous hepatitis B antigen clearance. HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; 25 (OH): 25-hydroxyvitamin.

## DISCUSSION

Vitamin D deficiency has been associated with several adverse health consequences that include autoimmune diseases, cardiovascular diseases and infections[16]. 1,25-dihydroxyvitamin D3 acts as an immunomodulator targeting various immune cells, including monocytes, macrophages and dendritic cells, as well as T-lymphocytes and B-lymphocytes, hence modulating both innate and adaptive immune responses[18]. Prospective studies in the involvement of vitamin D in autoimmune disorders are conceptually limited but most cross-sectional studies have shown an inverse relationship between vitamin D levels and disease activity[19]. A study performed on patients with rheumatoid arthritis concluded that the serum concentrations of vitamin D were inversely related to disease activity[19,20]. An *in vitro* study concluded that when vitamin D was added, many immunological abnormal characteristics of SLE were resolved, thus suggesting that vitamin D deficiency shifts the immunological response towards the loss of tolerance[20]. Our study supports this possible link between normal vitamin D levels and the likelihood of a positive clinical and serological response. To the best of our knowledge, this is the first study that has investigated the association between vitamin D levels and spontaneous HBsAg seroclearance. Our findings suggest a link between normal vitamin D levels and the occurrence of spontaneous HBsAg seroclearance. Normal levels of vitamin D had a statistically significant association with spontaneous HBsAg seroclearance. The mechanisms that link vitamin D normal levels with spontaneous HBsAg seroclearance are unknown. HBV infection has also been associated with a variety of immunological manifestations, including non-organ-specific autoantibodies, membranous and membranous proliferative glomerulonephritis, mixed cryoglobulinemia and polyarteritis nodosa[6]. Moreover, about one third of patients with polyarteritis nodosa are infected by HBV, the vasculitic lesions usually appear during primary HBV infection and are related to the presence of HBeAg. Anti-HBe seroconversion, either spontaneous or induced by antiviral treatment, may lead to a resolution of the vasculitic process[21]. Another finding of our study was the importance of host and virological factors in spontaneous HBsAg seroclearance, similar to previously published data that indicate that older age, male gender, low viral load and HBeAg-seronegativity are associated with spontaneous HBsAg seroclearance[3]. Our data supported these findings.

Our study contains some limitations. The link be-

tween vitamin D levels and HBsAg seroclearance was not shown to be causal but associative. The retrospective pattern of this study was unable to determine the cause effect of vitamin D levels to HBsAg seroclearance. More studies with a larger number of patients and with a prospective and controlled design are needed to confirm this hypothesis. Furthermore, this study did show that a very high percentage of spontaneous converters do have high levels of vitamin D but this percentage was not compared to a similar group of patients with hepatitis B without a spontaneous seroclearance. Other limitations are that the study had a small number of participants and did not exclude obese or overweight patients. These patients may have low levels of vitamin D. Patients with hepatic steatosis were also included in our study, although it is known that steatosis is an important predictor host factor for spontaneous HBsAg seroclearance.

In summary, we found a strong correlation between normal vitamin D levels and spontaneous HBsAg seroclearance. Vitamin D deficiency may be a significant risk factor for the lack of HBsAg seroconversion.

## COMMENTS

### Background

Vitamin D has recently been linked to many autoimmune diseases. Hepatitis B is a viral disease but shows many autoimmune characteristics. Spontaneous hepatitis B seroclearance is an unexplained phenomenon.

### Research frontiers

A possible association between serum vitamin D levels and spontaneous hepatitis B surface antigen seroclearance should be investigated.

### Innovations and breakthroughs

The authors showed that normal vitamin D levels correlate positively with spontaneous hepatitis B seroclearance.

### Applications

This finding may help to expand the therapeutic options for this disease.

### Peer review

The authors have performed a cross-sectional study examining the association between serum 25-hydroxyvitamin vitamin D levels and the severity of fatty liver disease in overweight and obese children. They report that vitamin D deficiency was significantly greater in obese *vs* overweight children, and that low vitamin D levels were independently associated with severity of fatty liver disease. This is an interesting finding, which is consistent with other reports of vitamin D deficiency in liver disease, and this paper provides a useful basis for further study.

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CASE REPORT

# Coadministration of telaprevir and transcatheter arterial chemoembolization in hepatitis C virus-associated hepatocellular carcinoma

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## Abstract

The use of direct-acting antiviral agents (*e.g.*, telaprevir, boceprevir) has improved response rates in patients with hepatitis C virus (HCV) genotype 1 infections. Substantial number of drug-drug interactions are anticipated with the use of telaprevir, a cytochrome P450 3A and P-glycoprotein substrate and inhibitor. Herein we describe a patient with HCV-associated hepatocellular carcinoma treated simultaneously with a telaprevir-containing regimen and localized chemotherapy (transcatheter arterial chemoembolization) with doxorubicin. No clinically relevant interactions or adverse events developed while on antiviral therapy.



**Key words:** Hepatitis C virus; Cancer; Hepatocellular carcinoma; Transcatheter arterial chemoembolization; Telaprevir; Interactions

**Core tip:** This case suggests that therapy for chronic hepatitis C virus (HCV) infection may be given simultaneously with localized chemotherapy in patients with hepatocellular carcinoma (HCC). The use of telaprevir has improved response rates in patients with HCV genotype 1 infections. Substantial number of drug-drug interactions are anticipated with the use of telaprevir, a cytochrome P450 3A and P-glycoprotein substrate and inhibitor. Herein, we describe a patient with HCV-associated HCC treated simultaneously with a telaprevir-containing regimen and localized chemotherapy (transcatheter arterial chemoembolization). No clinically relevant interactions or adverse events developed while on antiviral therapy.

Torres HA, Mahale P, Miller ED, Oo TH, Frenette C, Kaseb AO. Coadministration of telaprevir and transcatheter arterial chemoembolization in hepatitis C virus-associated hepatocellular carcinoma. *World J Hepatol* 2013; 5(6): 332-335 Available from: URL: http://www.wjgnet.com/1948-5182/full/v5/i6/332.htm DOI: http://dx.doi.org/10.4254/wjh.v5.i6.332

## INTRODUCTION

The use of direct-acting antiviral agents (*e.g.*, telaprevir, boceprevir) has improved response rates and in many cases shortened treatment durations in patients with hepatitis C virus (HCV) genotype 1 infections[1-3]. In the wake of this development, the American Association for the Study of Liver Diseases recently updated its practice guidelines for the treatment of chronic HCV infections[4]. However, owing to a lack of information about the safety and interactions of these direct-acting antiviral agents, these new guidelines failed to address the issue of HCV infection in special populations, including patients with cancer.

In HCV-infected cancer patients, antiviral therapy is not recommended during chemotherapy or immunosuppressive therapy for the fear of potentiating myelosuppression and causing life-threatening cytopenia. Authors have reported hepatic dysfunction because of acute exacerbation of chronic HCV infection in cancer patients necessitating discontinuation of chemotherapy or immunosuppressive therapy owing to persistently increased aminotransferase levels[5-7]. Even though this acute exacerbation of chronic HCV infection does not lead to fulminant hepatitis, it interrupts the administration of potentially life-saving chemotherapy[8,9].

Information about concomitant HCV treatment in cancer patients undergoing chemotherapy or immunosuppressive therapy is scarce. A small case series looked at management of severe hepatic dysfunction with pegylated interferon-alpha-2a and ribavirin in three children with hematologic malignancies and HCV infections[10]. The investigators started HCV therapy only after dose reduction and intermittent discontinuation of chemotherapy failed to control the hepatic dysfunction and made administration of chemotherapy impossible. Two of the three patients had sustained virological responses, both of whom had genotype 1b infections. More importantly, oncologists were able to initiate chemotherapy in all three cases.

HCV-related hepatocellular carcinoma (HCC) represents a particular challenge, since the majority of patients have poor liver reserve. Therefore, systemic chemotherapy trials in HCC indicated poor tolerance with no survival benefit. Recently, transcatheter arterial chemoembolization (TACE) modality was approved for unresectable HCC, and was extended to patients awaiting liver transplantation as a "bridging therapy"[11,12].

## CASE REPORT

Herein we describe the case of a 68-year-old male with chronic HCV infection with genotype 1b and HCC deemed to be a candidate for TACE and liver transplantation (Table 1). We initiated HCV therapy with pegylated interferon-alpha-2a and ribavirin to prevent allograft infection and normalize alanine aminotransferase levels, as the elevated transaminases were preventing the administration of TACE. Three months after initiation of HCV-targeted treatment with pegylated interferon-alpha-2a and ribavirin as salvage therapy, the patient's transaminases improved, and we were able to perform the first TACE procedure with doxorubicin drug-eluding beads (Figure 1). The patient had only a partial virological response (reduction in HCV RNA level < 2 $\log_{10}$ IU/mL below baseline) at 24 wk after treatment initiation; therefore, HCV therapy was discontinued. Three months later, we restarted treatment of HCV, now with telaprevir, pegylated interferon-alpha-2a, and ribavirin following the standard guidelines for patients without cancer[4]. Less than a month after treatment initiation, the patient underwent a second TACE procedure with doxorubicin (Figure 2). The transaminases continued to improve after TACE, and the patient's HCV RNA level was below 43 IU/mL at week 4 of therapy and became undetectable 8 wk after treatment initiation. The patient received dual therapy with pegylated interferon-alpha-2a and ribavirin following 12 wk of the triple combination therapy described above.

**Table 1 Patient characteristics**

| Characteristics | |
|---|---|
| Age, yr | 69 |
| Sex | Male |
| Race | African-American |
| HCV treatment history | Partial responder |
| *IL-28B* polymorphism | CT |
| Treatment duration before liver transplant, wk | 24 |
| Antiviral treatment toxicity | Hematologic (anemia, neutropenia, thrombocytopenia) |

HCV: Hepatitis C virus; CT: Computed tomography; IL-28B: Interleukin-28B.

Patient met the Milan criteria[13] and he underwent liver transplantation when a suitable donor organ became available at week 24 of total antiviral therapy. Liver transplantation was complicated with viremic recurrence first noted 4 wk after transplant, without abnormalities of liver enzymes or graft dysfunction.

During the 24 wk of antiviral therapy, adverse side effects of HCV therapy included anemia, thrombocytopenia, and neutropenia that necessitated administration of growth factors and reduction of the pegylated interferon-alpha-2a and ribavirin doses. HCV therapy with telaprevir-containing regimen did not lead to side effects that were different than those encountered during dual therapy with pegylated interferon-alpha-2a and ribavirin.

## DISCUSSION

The increased incidence of HCC in the United States has resulted in a dramatic rise of patients listed for orthotopic liver transplantation[14] with concomitant increased waiting-times for all patients. This prolonged wait time allows consideration of treatment of HCV while waiting for transplantation in those patients with adequate liver function who are listed for HCC-related reasons as

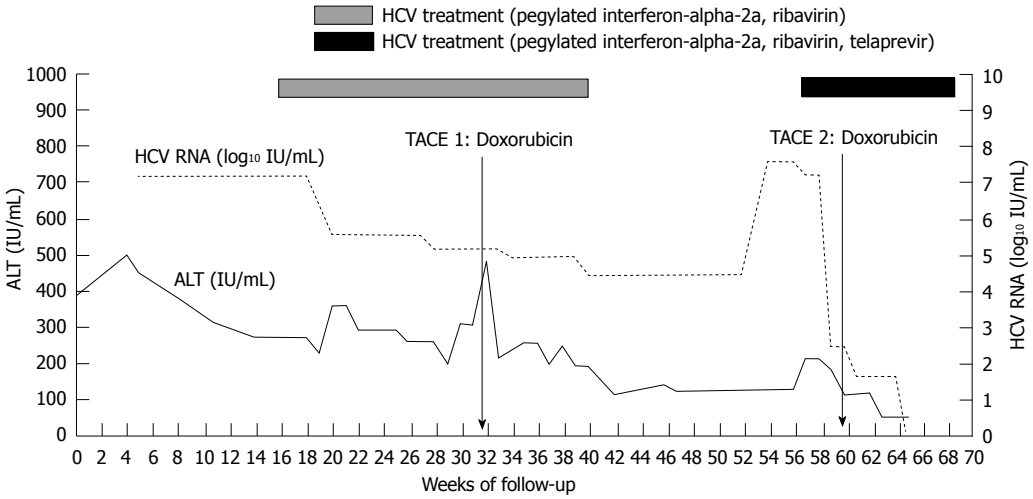


**Figure 1 Hepatitis C virus RNA and alanine aminotransferase levels according to duration of hepatitis C virus treatment and transcatheter arterial chemoembolization.** HCV: Hepatitis C virus; TACE: Transcatheter arterial chemoembolization; ALT: Alanine aminotransferase.

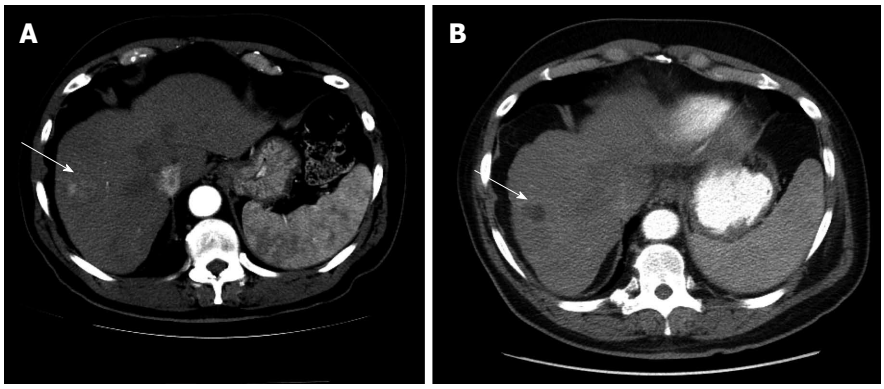


**Figure 2 Computed tomography scan image.** A: Illustrating a hypervascular hepatocellular carcinoma lesion (arrow) in arterial phase pre-treatment with transcatheter arterial chemoembolization; B: Indicating treatment response with loss of vascularity of the lesion (arrow) in arterial phase following transcatheter arterial chemoembolization procedure treatment.

achievement of sustained virological response prior to transplantation could eliminate the risk of HCV recurrence post-transplant[15,16].

A recent study by Garg *et al*[17] concluded that co-administration of telaprevir, a cytochrome P450 3A and P-glycoprotein substrate and inhibitor**,** and cyclosporine or tacrolimus was associated with major interactions with significantly increased blood concentrations of these immunosuppressive agents, which could lead to serious or life-threatening adverse events. We did not encounter any clinically relevant adverse effects of administration of the telaprevir-containing regimen during TACE with doxorubicin used and loco-regional therapy.

To our knowledge, pharmacokinetic studies have not been conducted looking for drug-drug interactions between doxorubicin (used as part of TACE) and telaprevir. Although such interactions remain theoretical, they are possible as systemic concentrations of doxorubicin can be identified following TACE. For example, in one study using a rabbit liver tumor model, plasma concentration of doxorubicin after TACE was as high as 360.5 ng/mL[18]. In a phase 2 study designed to establish the efficacy and safety of drug eluting beads loaded with doxorubicin for the TACE treatment of HCC patients, doxorubicin Cmax and AUC were 78.97 ± 38.3 ng/mL and 662.6 ± 417.6 ng/mL respectively[19]. However, TACE procedure with doxorubicin drug-eluding beads is associated with minimal systemic exposure of the chemotherapeutic agent with negligible systemic toxicity[20].

This case suggests that therapy for chronic HCV infection may be given simultaneously with a localized chemotherapeutic modality (TACE) in patients with HCC, given the tolerability of this procedure in compensated liver cirrhosis. However, this intervention should be used with caution and only in the salvage setting, as more studies are required to evaluate the interactions of direct-acting antiviral agents with chemotherapeutic agents.

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CASE REPORT

# Progressive multi-organ expression of immunoglobulin G4-related disease: A case report

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## Abstract

A 63-year-old Caucasian man presented with a cholestatic syndrome, renal failure and arthralgias. A laboratory examination revealed high immunoglobulin G (IgG) and IgG4 levels (5.95 g/L; normal range: 0.08-1.4 g/L), pointing to a diagnosis of systemic IgG4-related disease, with definite radiological evidence of biliary and pancreatic expression, and plausible renal, articular, salivary and lacrimal glands involvement. Due to the rarity of the condition, there are currently no random control trials to point to the optimal therapeutic approach. The patient has been on steroid therapy with the subsequent introduction of azathioprine, with a complete resolution of all symptoms, a rapid reduction to normalization of all blood tests, and a complete regression of the radiological picture. Our experience underlines the complexity of IgG4-related disease and its variable and sometimes progressive presentation, while pointing out the need for a careful and complete assessment for possible multi-organ involvement.



**Key words:** Immunoglobulin G4 related-disease; Autoimmune cholangitis; Autoimmune pancreatitis; Renal failure

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## INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) is a recently recognized disease[1] with a presumed autoimmune pathogenesis, characterized by high levels of IgG4 and a good response to immunosuppressive therapy[2]. Its clinical pattern is variable and may present with single organ expression (pancreatitis, cholangitis, sialadenitis, dacryoadenitis, nephritis, inflammatory pseudotumor and retroperitoneal fibrosis; other organs may occasionally be affected) or with multi-organ involvement[3,4]. All these localizations of IgG4-RD have a homogenous histological pattern, *i.e.*, lymphoplasmacytic infiltration with abundant IgG4-positive cell and storiform fibrosis. The etiology remains unknown, although a modified Th2 response with activation of regulatory T cells and overexpression of transforming growth factor beta and interleukin-4, 5, 10, 13 could be involved[5]. We report a patient with an insidious onset of IgG4-RD who proceeded to a full multi-organ expression.

## CASE REPORT

A 63-year-old Caucasian man was admitted to our unit in July 2011 for a cholestatic syndrome of 4 mo duration. His medical history included heavy smoking (about 50 cigarettes/d) and an active consumption of 6 alcohol units/d, a previous diagnosis of "rheumatoid arthritis"

**Table 1 Laboratory tests at onset and during follow-up**

| Parameter | Normal range | Values | | | | | |
|---|---|---|---|---|---|---|---|
| | | March 2011 | April 2011 | July 2011 (admission) | August 2011 (4th week of follow-up) | October 2011 (12th week of follow-up) | March 2012 (36th week of follow-up) |
| Alkaline phosphatase (U/L) | 40-129 | 401 | 190 | 490 | 97 | 83 | 74 |
| GGT (U/L) | 8-61 | 380 | 91 | 506 | 32 | 25 | 21 |
| Bilirubin total/direct (mg/dL) | < 1 | 6.3/5.98 | 1/0.8 | 4.5/4.3 | 0.7/0.2 | 0.5/0.1 | 0.4/0.1 |
| Amylase (U/L) | 28-100 | 210 | 66 | 230 | 85 | 99 | 76 |
| Lipase (U/L) | 13-60 | 121 | 60 | 130 | 50 | 58 | 36 |
| AST (U/L) | < 37 | 56 | 30 | 110 | 16 | 15 | 20 |
| ALT (U/L) | < 41 | 64 | 35 | 130 | 19 | 13 | 19 |
| Creatinine (mg/dL) | 0.67-1.17 | 1.7 | 1.65 | 2 | 1.1 | 1 | 1.1 |
| Gamma-globulins (g/dL) | 0.67-1.56 | - | - | 2.94 | 1.09 | 1.5 | 1.45 |
| IgG4 (g/L) | 0.08-1.4 | - | - | 5.95 | 1.2 | - | - |

GGT: Gamma-glutamyltransferase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; IgG4: Immunoglobulin G4.

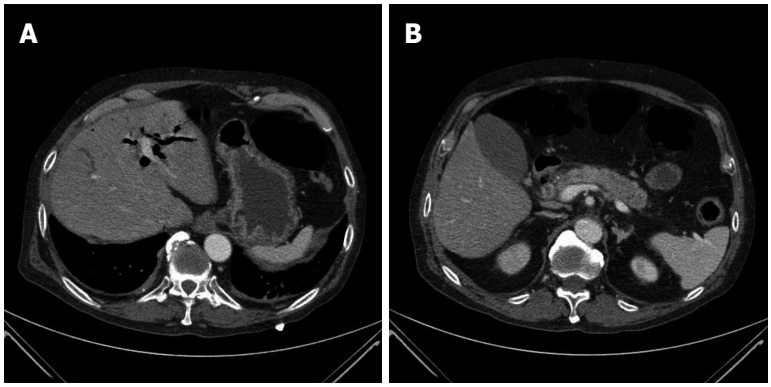


**Figure 1 Computed tomography scans of the abdomen performed on admission.** A: Dilatation of intrahepatic bile ducts; B: Dilatation of extrahepatic bile ducts with wall thickening and contrast enhancement in the arterial phase of distal common bile duct and increased volume of the pancreas with loss of physiological lobular appearance.

treated with intermittent steroid therapy for several years, a histological diagnosis of interstitial nephritis three years before, and no history of allergic disease. In March 2011, at the onset of jaundice, he had been admitted to another hospital. At that time, cholestatic tests [total/direct bilirubin 6.3/5.98 mg/dL, alkaline phosphatase 3 × upper limit of normal (ULN), gamma-glutamyltransferase (GGT) 6 × ULN] and pancreatic enzymes (amylase and lipase 2 × ULN) were raised (Table 1). Abdominal ultrasound (US) and computed tomography (CT) scans of the abdomen revealed a dilatation of the intrahepatic and extrahepatic biliary tract, without evidence of gallstones or biliary sludge, and an increased volume of the pancreas with loss of the physiological lobular appearance. A diagnosis of obstructive jaundice secondary to chronic pancreatitis was made and a plastic endoprosthesis was placed in the common bile duct by endoscopic retrograde cholangiopancreatography. During the following weeks, a progressive reduction of biochemical markers of cholestasis occurred (Table 1).

In July 2011, he was admitted to our unit for recurrence of jaundice and elevated markers of cholestasis.

Physical examination on admission was unremarkable, except for mild bilateral submandibular and lacrimal glands swelling. Laboratory tests showed hyperbilirubinemia (direct/total 4.5/4.3 mg/dL), alkaline phosphatase 3 × ULN, GGT 10 × ULN, aspartate aminotransferase and alanine aminotransferase 3 × ULN, pancreatic amylase and lipase 2 × ULN, gamma-globulins 3 × ULN, and creatinine 2 mg/dL (Table 1). Anti-hepatitis C virus and hepatitis B surface antigen and non organ specific autoantibodies (antinuclear antibodies, anti-mitochondral antibody, smooth-muscle antibodies, liver kidney microsomal antibody, liver cytosolic-1) were negative. Abdominal US revealed a hypoechoic lesion of 2.3 cm in the uncinate process of the pancreas, dilatation of intrahepatic and extrahepatic bile ducts (up to 9 mm for the common bile duct) and of Wirsung's duct (4 mm), with no gallstones or biliary sludge. CT scans of the abdomen showed an increased volume of the pancreas, especially in the head, loss of physiological lobular appearance, dilatation of intrahepatic and extrahepatic bile ducts, with wall thickening and contrast enhancement in the arterial phase of distal common bile duct (Figure 1), and a diffuse bilateral enlargement of the kidneys. The patient declined to have a liver and/or pancreatic biopsy performed.

IgG4 levels were 5.95 g/L (normal range: 0.08-1.4 g/L), pointing to a diagnosis of IgG4-related pancreatitis and possibly cholangitis. Suspecting the coexistence of IgG4-related kidney disease (IgG4-RKD), the etiology of renal failure was re-evaluated. Laboratory tests confirmed a creatinine value of 2 mg/dL, normal serum and urinary electrolytes, the absence of proteinuria and hematuria, and normal values of immunoglobulin free light chains in serum and urine. It was not possible to reassess the previous renal biopsy, performed elsewhere.

**Figure 2 Magnetic resonance imaging, performed at the 12th week of follow up, showed a resolution of the radiological picture, with persistence of minimal dilation of the left biliary branch.**

In view of the mild bilateral submandibular and lacrimal glands swelling and the worsening of previously present xerostomia and xerophthalmia, a salivary flow test and Schirmer's test were performed, showing a deficiency of both salivary and lacrimal secretion. Tests for anti-Sjögren syndrome A and B antibodies and anti-extractable nuclear antibodies were negative. A biopsy of the salivary glands showed the absence of lymphocyte and plasma cell infiltration.

Finally, the previous diagnosis of rheumatoid arthritis was ruled out because of no involvement of small joints, a normal X-ray of the hand, negative serology (rheumatoid factor and anticitrullinated peptide antibody) and normal acute-phase reactants (C-reactive protein and erythrocyte sedimentation rate).

The patient was given oral prednisone (0.6 mg/kg per day for 4 wk, then tapered over a period of 12 wk to a maintenance dose of 10 mg/d). After the first 4 wk, there was a marked general improvement, with regression of xerophthalmia and xerostomia and a rapid reduction to normalization of aminotransferases, alkaline phosphatase, GGT, bilirubin, creatinine, amylase, lipase, gammaglobulins and IgG4 levels (Table 1).

At the 12th week of follow up, abdominal US was negative and magnetic resonance imaging showed a resolution of the radiological picture, with persistence of minimal dilation of the left biliary branch (Figure 2).

Considering the coexistence of diabetes and osteoporosis, the dose of prednisone was reduced to 5 mg/d and azathioprine 1.5 mg/kg per d added as a glucocorticoid-sparing agent. At the 36th week of follow-up, abdominal US and biochemical tests were persistently normal (Table 1) and the patient is currently asymptomatic.

## DISCUSSION

IgG4-RD may involve several organs, including the pancreas, biliary duct, salivary glands, kidneys, lungs, retroperitoneum and lymph nodes. The peculiarity of our patient lies in the progression towards a systemic multi-organ expression of the disease.

Diagnostic criteria for systemic IgG4-RD are not fully established. To date, only the criteria for IgG4-related pancreatitis, cholangitis, nephritis and glandular disease are available. However, they are not suitable for the diagnosis of other organ involvement. In this case, the diagnosis of pancreatitis was confirmed by both Asian diagnostic criteria[6] and HISORt criteria for autoimmune pancreatitis[7]. Diagnosis of IgG4-related cholangitis was confirmed by HISORt criteria for IgG4-associated cholangitis[8]. Liver and/or pancreatic biopsies were not performed; they cannot be deemed essential for diagnosis, since two out of three for Asian diagnostic criteria and two out of five for HISORt criteria were satisfied. For evidence of renal damage and CT-documented enlargement of the kidneys in a context of an IgG4-RD, the etiology of renal failure was also re-evaluated. According to the criteria proposed by the Japanese Society of Nephrology[9], the diagnosis of IgG4-RKD was labeled as "possible". Because of the presence of xerostomia and xerophthalmia, a salivary glands biopsy was performed, showing a non-specific chronic inflammation. In the absence of specific histology, it was not possible to confirm the diagnosis of IgG4-related glandular disease because all diagnostic criteria were not satisfied[10]. Nevertheless, the probability of a false negative due to the previous long-term steroid therapy should be considered. The diagnosis of rheumatoid arthritis was finally ruled out and the persistent arthralgias may be related to IgG4-RD.

Despite the absence of histological confirmation, IgG4-related involvement of kidneys, salivary and lacrimal glands was strengthened by the full clinical and biochemical remission of respective manifestations after steroidal therapy.

Treatment with immunosuppressive agents is effective in IgG4-RD. Due to the rarity of the condition, there are currently no RCTs to point to the optimal therapeutic approach. Following a consensus statement from 17 referrals centers in Japan[11], we treated the patient with prednisone as first line therapy, with subsequent introduction of azathioprine, obtaining a complete clinical, biochemical and radiological response with good tolerability.

Our experience underlines the complexity of IgG4-RD and its variable and sometimes progressive presentation, while pointing out the need for a careful and complete assessment for possible multi-organ involvement.

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CASE REPORT

# Multiple focal nodular hyperplasias induced by oxaliplatin-based chemotherapy

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## Abstract

Focal nodular hyperplasia (FNH) is a benign condition that affects normal liver with low prevalence. Recently, the extensive use of oxaliplatin to treat patients with colorectal cancer has been reported to be associated with the development of different liver injuries, as well as focal liver lesions. The present work describes two patients with multiple bilateral focal liver lesions misdiagnosed as colorectal liver metastases, and treated with liver resection. The first patient had up to 15 small bilateral focal liver lesions, with magnetic resonance imaging consistent with colorectal liver metastases (CLM), and fluorodeoxyglucose (FDG)-positron emission tomography (PET) negative. The second patient had up to 5 small focal liver lesions, with computed tomography consistent with CLM, and FDG-PET negative. They had parenchyma sparing liver surgery, with uneventful postoperative course. At the histology the diagnosis was multiple FNHs. The risks of oxaliplatin-based chemotherapy regimens in development of liver injuries, such as FNH, should not be further denied. The value of the modern multidisciplinary management of patients with colorectal cancer relies also on the precise estimation of the risk/benefit for each patient.



**Key words:** Focal nodular hyperplasia; Colorectal cancer; Colorectal liver metastasis; Oxaliplatin; Systemic chemotherapy

**Core tip:** This report describes two interesting cases of patients who developed multiple focal nodular hyperplasias during oxaliplatin-based therapy for colorectal cancer. Such multiple bilateral focal liver lesions were misdiagnosed as colorectal liver metastases, and treated with liver resection. A review of the cases revealed that in both cases the fluorodeoxyglucose-positron emission tomography was negative. A brief review of the literature together with the authors' comments is included.

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## INTRODUCTION

Focal nodular hyperplasia (FNH) is a benign condition that affects normal liver with prevalence up to 2.6% in autopsy studies[1,2]. Most of the patients are asymptomatic, while few of them may develop portal hypertension[3,4]. The physiopathology of FNH remains unknown, but non-specific chronic distortion of the intrahepatic blood flow has been considered a potential cause[5]. Recently, the extensive use of oxaliplatin to treat patients with colorectal cancer has been reported to be associated

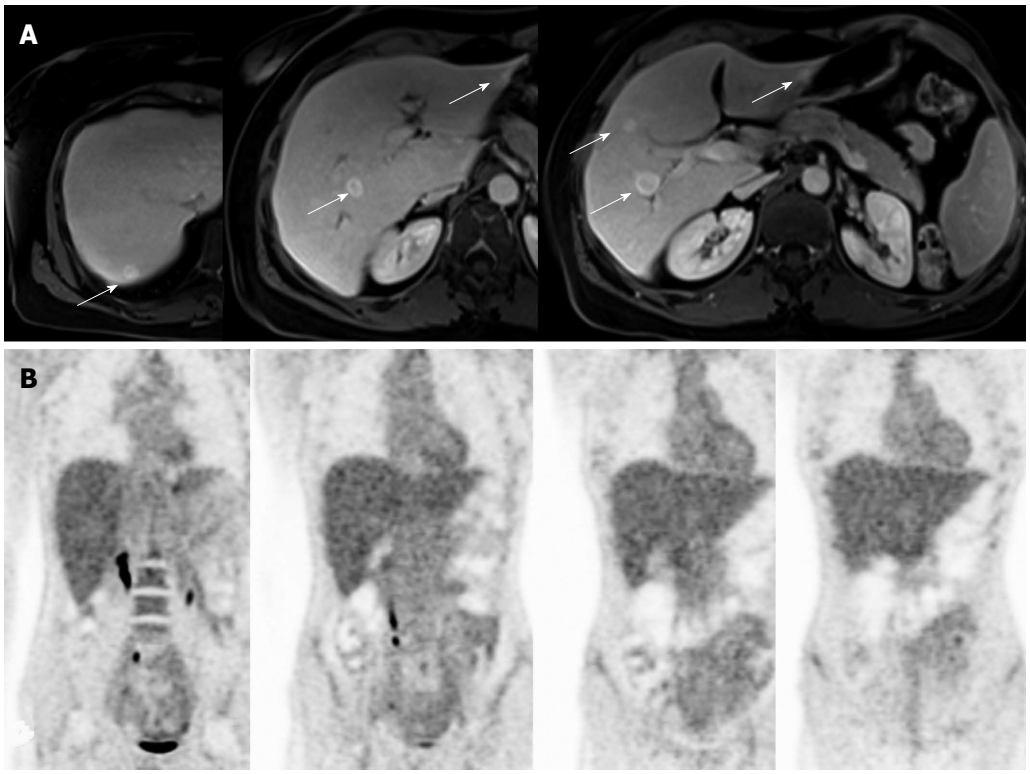


**Figure 1 Radiological imaging of case 1.** A: The abdominal contrast-enhanced magnetic resonance imaging showed multiple bilateral focal liver lesions (arrows); B: The fluorodeoxyglucose-positron emission tomography scan did not show any pathological uptake of the trace.

with the development of different liver injuries[5,6]. The present work describes two patients with multiple bilateral focal liver lesions misdiagnosed as colorectal liver metastases (CLM), and treated with liver resection.

## CASE REPORT

### *Case 1*

A 53-year-old woman presented at the liver surgery unit because of multiple focal liver lesions. In December 2007 in another institution after a preoperative staging comprehensive of an abdominal computed tomography (CT), which resulted negative for liver lesions, the patient had laparoscopic right colectomy because of colonic adenocarcinoma pathologically staged as pT3N2M0-G2. Then, she had 8 courses of systemic chemotherapy with FOLFOX regimen (oxaliplatin, leucovorin, and fluorouracil) followed by 4 courses of De Gramont regimen (fluorouracil and folinic acid). The modification of the chemotherapy regimen was due to oxaliplatin side effects, such as peripheral neuropathy, and thrombocytopenia. Then the follow-up, based on quarterly CT, was regular and negative till January 2010, when she developed up to 15 bilateral focal liver lesions. She was than referred to our institution where she underwent a diagnostic work-up comprehensive of abdominal magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan. MRI was consistent with the diagnosis of CLM, while FDG-PET was negative (Figure 1). Both the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) serum values were normal. The CEA was elevated before the colonic resection. Based on our weekly multidisciplinary meeting the patient was candidate to surgical resection. Therefore, after 14 mo from the end of the adjuvant chemotherapy, in March 2010 she had multiple ultrasound-guided liver resections for the removal of all 15 lesions. The postoperative course was uneventful. At gross inspection the lesions sized between 0.5 and 2 cm and were characterized by well-defined margins, lobulated appearance, and a central scar (Figure 2A). At histology the lesions were characterized by several fibrous septa highlighted by special stains (Figure 2B, Masson staining), and they showed a typical patter at glutamine synthetase immunostaining (Figure 2C). Yet, at higher magnification they contained several dystrophic vessels (Figure 2D). All these findings were in keeping with a diagnosis of multiple FNH without any evidence of malignant cells. She did not receive postoperative chemotherapy. After 32 mo the patient is alive, and free of tumoral recurrence. However, this patient developed 4 new small liver lesions consistent with multiple FNHs, which are stable after 13 mo of follow-up.

### *Case 2*

A 56-year-old man presented at the liver surgery unit because of multiple focal liver lesions. In July 2008 after a preoperative staging comprehensive of an abdominal CT, which resulted negative for liver lesions, the patient had laparoscopic left colectomy because of colonic adeno-

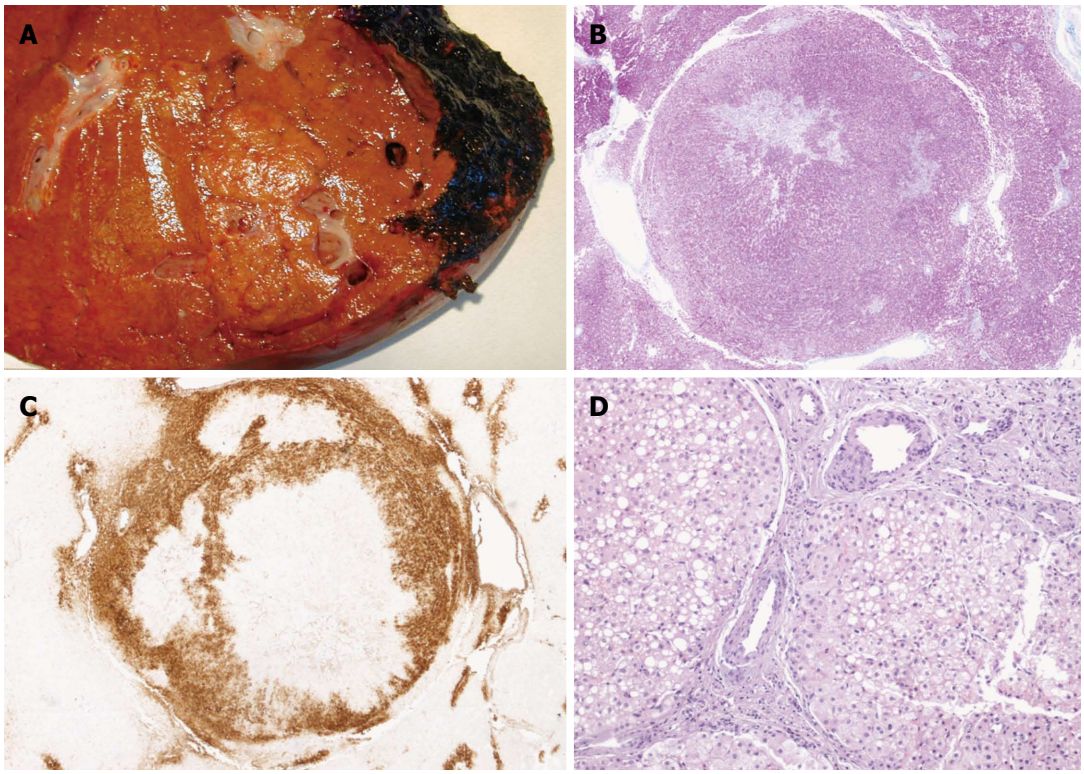


**Figure 2 Histology of case 1.** A: The gross inspection of the specimen showed lesions sized between 0.5 and 2 cm, with well-defined margins, and a central scar; B, C: At microscopy the lesions were characterized by several fibrous septa highlighted by special stains (Masson staining), and they showed a typical patter at glutamine synthetase immunostaining; D: At higher magnification they contained several dystrophic vessels.

carcinoma pathologically staged as pT3N1M0-G2. Then, the patient had 12 courses of systemic chemotherapy with FOLFOX regimen. The subsequent follow-up was regular and negative till March 2011, when he developed up to 5 bilateral focal liver lesions and was referred to out institution where he had abdominal CT and FDG-PET scan. CT was consistent with the diagnosis of CLM, while FDG-PET was negative (Figure 3). Both the CEA and CA19-9 serum values were normal, and they were within the normal range even before the colonic resection. Based on our weekly multidisciplinary meeting the patient was candidate to surgical resection, and in June 2011, 16 mo the end of adjuvant chemotherapy, he had multiple ultrasound-guided liver resections for the removal of all 5 lesions. The postoperative course was uneventful. Similarly to the previous patient, at gross inspection the larger lesion was 2 cm in diameter. They were characterized by well-defined margins, and the histology review showed some typical findings consistent with the diagnosis of multiple FNHs. He did not receive postoperative chemotherapy. After 20 mo the patient is alive and free of recurrence.

## DISCUSSION

The presented cases showed two patients affected by colorectal cancer with multiple FNHs potentially inducedby oxaliplatin-based chemotherapy. Both of them had no history of chronic liver disease, and the chronological correlation between the chemotherapy, its duration, and the appearance of the liver lesions suggests a cause-effect association.

There is a burgeoning use of preoperative chemotherapy in patients with CLM, and a corresponding burgeoning literature reporting non-tumoral liver lesions induced by different chemotherapy regimens[6]. Some direct correlations between chemotherapy agents, specific liver toxicity and postoperative morbidity have been also reported[7,8]. In particular, the development of FNH during oxaliplatin-based systemic chemotherapy has been reported up to 15% of the patients treated with preoperative chemotherapy[9]. Based on a recent review on such topic the damages associated with oxaliplatin-based chemotherapy are complex and heterogeneous. Both erythrocyte extravasation and hepatocytic plate disruption have been reported being signs of sinusoidal wall rupture[5,10]. However, the pathogenesis of FNH remains unclear. Changes in intrahepatic blood flow are supposed to be the primary cause. Such changes may be due to portal vein injuries at the level of the sinusoids, and the resulting portal hypertension plays an important role. The natural history of FNH remains unknown, too. Few spontaneous regressions after the suspension of the chemotherapy have been reported as well as some protective effects of bevacizumab on the development of this toxicity[5,11,12].

From the clinical standpoint their proper diagnosis is a delicate matter, since they occur in oncological patients with generally well-documented, and extensive negative

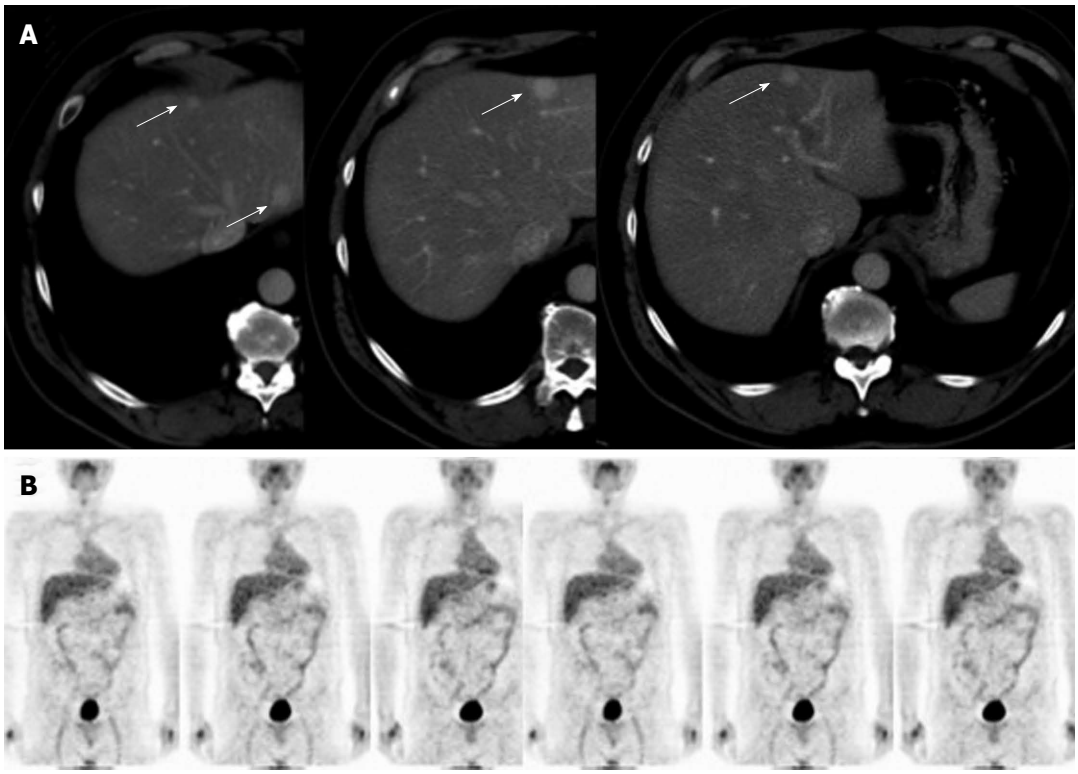


**Figure 3 Radiological imaging of case 2.** A: The abdominal contrast-enhanced computed tomography showed multiple focal liver lesions (arrows); B: The fluorodeoxyglucose-positron emission tomography scan did not show any pathological uptake of the trace.

imaging. In our two patients to these consideration the multinodular pattern has further biased the diagnostic conclusion. Indeed, only Hubert *et al*[11] previously reported two cases of multiple FNHs occurred in similar circumstances while other authors described patients with single lesions[5,6,9]. Our experience is conveying a further peculiarity, which could be useful for further discussion and experiences in this sense. Indeed, to our knowledge no previous studies on the use of FDG-PET in such specific clinical setting have been reported. Even if no conclusions can be drawn based on two cases, and considering also the tendency of lower accuracy of FDG-PET after chemotherapy[13], a potential value of such imaging modality should be further investigated, and taken into account during the workup in such circumstances.

In conclusion, an increasing proportion of patients with CLM nowadays receive oxaliplatin-based chemotherapy, including postoperative treatment after stage Ⅲ colon cancer, induction therapy in patients with extensive metastases, and perioperative treatment in patients with resectable metastases. The risks of such chemotherapy regimens in development of FNHs, as well as of other forms of liver injuries, should not be further denied. The value of the modern multidisciplinary management of patients with colorectal cancer relies also on the precise estimation of the risk/benefit for each patient.

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The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in square brackets in superscript at the end of citation content or after the cited author's name. For citation content which is part of the narration, the coding number and square brackets should be typeset normally. For example, "Crohn's disease (CD) is associated with increased intestinal permeability[1,2]". If references are cited directly in the text, they should be put together within the text, for example, "From references[19,22-24], we know that..."

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Pleased provide PubMed citation numbers to the reference list, e.g. PMID and DOI, which can be found at http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed and http://www.crossref.org/SimpleTextQuery/, respectively. The numbers will be used in E-version of this journal.

### *Style for journal references*

Authors: the name of the first author should be typed in bold-faced letters. The family name of all authors should be typed with the initial letter capitalized, followed by their abbreviated first and middle initials. (For example, Lian-Sheng Ma is abbreviated as Ma LS, Bo-Rong Pan as Pan BR). The title of the cited article and italicized journal title (journal title should be in its abbreviated form as shown in PubMed), publication date, volume number (in black), start page, and end page [PMID: 11819634 DOI: 10.3748/wjg.13.5396].

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### *Format*

**Journals**

*English journal article (list all authors and include the PMID where applicable)*

1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

*Chinese journal article (list all authors and include the PMID where applicable)*

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

*In press*

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

*Organization as author*

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

*Both personal authors and an organization as author*

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

*No author given*

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

*Volume with supplement*

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

*Issue with no volume*

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

*No volume or issue*

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

**Books**

*Personal author(s)*

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

*Chapter in a book (list all authors)*

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

*Author(s) and editor(s)*

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

*Conference proceedings*

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

*Conference paper*

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

**Electronic journal** (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

**Patent** (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

### *Statistical data*

Write as mean ± SD or mean ± SE.

***Statistical expression***

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as $\chi^2$ (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

***Units***

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; $CO_2$ volume fraction, 50 mL/L $CO_2$, not 5% $CO_2$; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23243641.

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***Italics***

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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