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REVIEW

Hepatocellular carcinoma and the risk of occupational exposure

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Abstract

Hepatocellular carcinoma (HCC) is the most common type of liver cancer. The main risk factors for HCC are alcoholism, hepatitis B virus, hepatitis C virus, nonalcoholic steatohepatitis, obesity, type 2 diabetes, cirrhosis, aflatoxin, hemochromatosis, Wilson's disease and hemophilia. Occupational exposure to chemicals is another risk factor for HCC. Often the relationship between occupational risk and HCC is unclear and the reports are fragmented and inconsistent. This review aims to summarize the current knowledge regarding the association of infective and non-infective occupational risk exposure and HCC in order to encourage further research and draw attention to this global occupational public health problem.

Key words: Hepatocellular carcinoma; Autophagy; Epigenetic events; Hepatitis B virus; Hepatitis C virus; Occupational exposure; Chemical agents; Mitophagy;

Arsenic; Cadmium

Core tip: Hepatocellular carcinoma (HCC) is the fifth most common human cancer. This review summarizes current knowledge regarding the occupational risk factors of HCC. In particular, we underline not only the infective but also non-infective occupational risk exposure, including chemical agents and toxic metabolites which are a major cause of liver damage.

Rapisarda V, Loreto C, Malaguarnera M, Ardiri A, Proiti M, Rigano G, Frazzetto E, Ruggeri MI, Malaguarnera G, Bertino N, Malaguarnera M, Catania VE, Di Carlo I, Toro A, Bertino E, Mangano D, Bertino G. Hepatocellular carcinoma and the risk of occupational exposure. *World J Hepatol* 2016; 8(13): 573-590 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i13/573.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i13.573

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is increasing worldwide. There are geographical areas with a high prevalence, as in Asia and Africa, and death from HCC has increased in the United States and Europe[1-5].

Aflatoxin[6], alcohol intake[7], hepatitis B virus (HBV)[4], hepatitis C virus (HCV) infection[5] and oral contraception[8,9] are known risk factors for HCC, whereas cigarette smoke, anabolic steroids and insulin resistance are suspected to be contributing factors[10-16].

The relationship between occupational risk and HCC is often unclear and the reports are fragmented and inconsistent[17-19]; however, it is very commonly reported that vinyl chloride monomer (VCM) induced angiosarcoma of the liver[20].

HCC mortality, assessed by standardized mortality ratio, has been reported in different categories of workers: Building and chemical workers, painters, subjects exposed to solvents and workers in the textile industry have often been reported to be at high risk for HCC[21-30]. However, such studies have often failed to identify a single agent responsible for the heightened HCC risk. There have been few investigations of occupational exposure and liver cancer. A number of factors and confounders have precluded drawing firm conclusions[31].

The possible associations between the risk of infection and non-infectious occupational hazards and HCC will be discussed, in the hope of drawing attention to this global public health problem.

REVIEW METHOD

The PubMed, Scopus and Web of Science databases were searched using the following keywords: "HCC", "occupational exposure", "chemical agents", "arsenic", "cadmium", "HBV", "HCV", "molecular hepatocarcinogenesis", "molecular immunological targets", "autophagy", "mitophagy" and "epigenetic events". Published data at the International Agency for Research on Cancer (IARC) were consulted.

INFECTIVE RISK FACTORS FOR HCC

Infection is one of the main contributors to cancer development[32]. There are 11 biological agents classified as IARC group 1 carcinogens[33,34]. HBV, HCV and AFB1 are responsible for HCC development[35]. The vast majority of the global cancer burden attributable to infection occurs in less developed regions (Table 1).

HEPATITIS INFECTIONS

Infection with HBV and HCV can be through parenteral or unapparent transmission[36-42].

Occupational exposure to hepatitis B

The risk of hepatitis from needlestick injury from an hepatitis B envelope antigen positive (HBeAg+) source is 22%-31%, whereas the risk of contracting clinical hepatitis from a needlestick injury involving an hepatitis B surface antigen positive (HBsAg+), eAg- source is 1%-6%. Post-exposure prophylaxis (PEP), including HBIG and the HBV vaccine, is believed to be 85%-95% effective. HBV vaccine or HBIG alone is thought to be 70%-75% effective[43-45].

Occupational exposure to hepatitis C

The risk of HCV transmission from percutaneous exposure is approximately 2%. HCV is rarely transmitted from mucous membrane exposure to blood (both documented cases have been when the source patient was human immunodeficiency virus/HCV co-infected) and it has never been documented following blood exposure to intact or non-intact skin. There is no known PEP for HCV exposure. According to a European case-control study, assessment of the risk of transmission after occupational HCV exposure should take into account the injury severity, device involved and the HCV RNA status of the source patient[46-50].

DEVELOPMENT OF HCC IN CHRONIC HBV INFECTION

Chronic HBV infection has a causal role in HCC development[36] since it promotes carcinogenesis through liver injury (necrosis and inflammation) and cirrhosis development (fibrosis and regeneration)[41,43-45]. Moreover, HBV and HCV co-infection causes a higher than 50-fold risk compared to HCC[51-54].

Risk factors for liver cancer in HBV patients include: (1) host-related risk factors: Older age, Asian ethnicity, male sex, alcohol intake and advanced liver disease[55-57]; (2) viral risk factors: HBV genotype C, mutations of pre-S, enhancer-H, core promoter, HCV or hepatitis

Table 1 Hepatocellular carcinoma and occupational exposure to infective agents

Risk agent	CAS No.	Occupational exposure	IARC class
Infective risk			
HBV	-	Health care workers[4,38,41,44], waste operators[38,44]	Group 1[34]
HCV	-	Health care workers[38,39,61]	Group 1[34]
Aflatoxin B1	1162-65-8	Paper mill and sugar factory; poultry production; rice mill; waste management; swine industry; agri-food industry; wheat handling; textile manufacturing[77,78,87-91,93,96]	Group 1[76]

IARC: International Agency for Research on Cancer; CAS No.: Chemical abstract service number; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

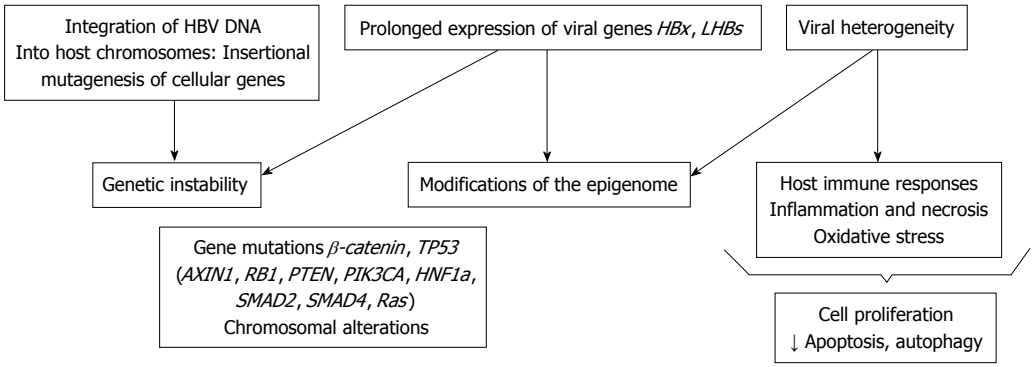

Figure 1 Pathogenesis of hepatitis B virus-related hepatocellular carcinoma. HBV: Hepatitis B virus.

Delta virus infection and PC/BCP HBV variants[45,58]; and (3) risk factors related to host-virus interaction: Cirrhosis, high HBV-DNA serum levels, prolonged HBeAg positivity, prolonged HBsAg positivity and high HBsAg serum levels[59-62].

Lastly, the HCC risk factors in chronic HBV infection are different and the pathogenesis is characterized by the combined action of different alterations involving genetic, epigenetic and immunological factors[63-71] (Figure 1).

DEVELOPMENT OF HCC IN CHRONIC HCV INFECTION

The mechanism by which HCV causes HCC is not wholly clear. It has been suggested that HCV proteins have direct oncogenic properties[5]. Chronic HCV infection leads to cirrhosis in 10%-20% of patients of whom 1%-5% develop liver cancer[5]. Central tumor suppressor genes and a number of proto-oncogenes, such as retinoblastoma tumor suppressor (*Rb*) and *P53*, have been suggested as targets of direct alteration by HCV proteins; the wnt/β-catenin and transforming growth factor-β pathways may also be directly affected[5].

Moreover, chronic infection, necrosis and cell regeneration, fibrosis and cirrhosis are, together with the direct mechanisms, the high risk factors for HCC. Finally, HBV or HCV chronic infection has immunomodulatory and immunosuppressive effects[71-73].

AFLATOXINS

The aflatoxins are metabolic products of certain fungi, Aspergillus flavus and parasiticus that develop in cereals (maize), oilseeds (groundnuts) and dried fruit and are chemicals of the furanocoumarins type. To date, we have isolated 17 aflatoxins and 5 are relevant to dissemination and toxicity. High exposure concentrations cause acute hepatitis. Chronic exposure causes the development of liver cancer. This could be caused by the aflatoxin ability to determine the mutation of the p53 tumor suppressor gene, which in normal conditions induces the apoptosis processes[74-77].

The risk of HCC increases when the exposure occurs in the presence of HBV infection, as occurs in the Chinese population[78-96].

NON-INFECTIVE RISK FACTORS FOR HEPATOCELLULAR CARCINOMA

A wide range of occupational activities may involve worker exposure to a variety of chemical agents. The liver is the main organ involved in metabolism and in toxicokinetics of a xenobiotic. However, it is frequently also a target organ because of its blood supply and the many metabolic and excretory processes in which it has a role. Adverse effects of chemical exposure involving the liver (hepatotoxicity) comprise hepatocellular damage, cholestatic injury, fatty liver, granulomatous disease, cirrhosis and malignancies, including HCC. A variety of chemicals comprising VCM, organic solvents, chlorinated pesticides and arsenic exert adverse effects on the liver[97] (Tables 2 and 3).

VCM AND POLYVINYL CHLORIDE

VCM, chemical abstract service number (CAS No.

Table 2 Hepatocellular carcinoma and occupational exposure to chemical agents

Risk agent	CAS No.	Occupational exposure	IARC class
Non-infective risk			
VCM	75-01-4	Plastics, plumbing, cabling, house framing, waterproof clothing, medical devices and food packaging industry[98,99,102,103,105-108,111,112,114-120]	Group 1[76]
TCE	79-01-6	Dry cleaning; paint stripping; metal degreasing; production of chlorinated chemical compounds; shoe manufacturing; aircraft/aerospace, electronics and printing industry[125,127]	Group 1[129]
PCE	127-18-4	Dry cleaning; textile processing; metal degreasing[138]	Group 2A[129]
DDT	50-29-3	Farming industry[141,145]	Group 2B[148]
N-nitrosamines	35576-91-1	Plastic, rubber and pharmacological manufacturing; farming industry; metalworking; electrical component production and use; gasoline and lubricant additives, production and use[159-165]	Group[160,161]
TCDD	1746-01-6	Waste management; paper mill; timber manufacturing; iron and steel manufacturing; electric power industry[175,179]	Group 1[76]
PeCDF	57117-31-4	Cement and metalworking industry; chemical manufacturing[171,172,175]	Group 1[76]
PCB	1336-36-3	Electrical industry, plastic and chemical industry; maintenance/repair technicians of PCB devices[175,186-190]	[1]Group[76,207]
PBB		Electronics recycling industry; maintenance/repair technicians of PBB devices[209-212]	Group 2A[207]
Chloral	75-87-6	Insecticides and herbicide production; polyurethane foam production and use[125,214,215]	Group 2A[216]
Chloral hydrate	302-17-0	Pharmaceutical producing; health care workers; laboratory research; water disinfection by chlorination[129,216]	Group 2A[216]
O-toluidine	95-53-4	Dye production and use; herbicide and pharmaceutical production; rubber industry; clinical laboratories[220-222,227,228]	Group 1[76]
MOCA	101-14-4	Rubber and polyurethane industry[220,230-232]	Group 1[76]
4-ABP	92-67-1	Rubber industry; dyes production[220,235-238]	Group 1[76]
BZD and dyes metabolized to BZD	92-87-5	Dye production and use; clinical laboratories[220,247]	Group 1[76]

[1]Not all of them are to be referred to group 1. VCM: Vinyl chloride monomer; TCE: Trichloroethylene; PCE: Perchlorethylene; DDT: 1,1,1-Trichloro-2,2-bis (p-chlorophenyl)-ethane; TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin; PeCDF: 2,3,4,7,8-Pentachlorodibenzofuran; PCB: Polychlorinated biphenyls; PBB: Polybrominated biphenyls; O-toluidine: Ortho-toluidine; MOCA: 4,4′-Methylene bis (2-chlorobenzenamine); 4-ABP: 4-aminobiphenyl; BZD: Benzidine; IARC: International Agency for Research on Cancer; CAS No.: Chemical abstract service number.

Table 3 Hepatocellular carcinoma and occupational exposure to metals

Risk agent	CAS No.	Occupational exposure	IARC class
Non-infective risk			
As	7440-38-2	Timber manufacturing; pesticide use; As extraction industry; lead processing; pharmaceutical industry; glass industry; leather preservatives; antifouling paints; agrochemical production; microelectronics and optical industries; non-ferrous metal smelters; coal-fired power plants[254-258]	Group 1[263]
Cd	7440-43-9	Cd mining; manufacturing of Cd-containing ores and products; Ni-Cd battery manufacturing, Cd alloy production[275,277,278]	Group 1[263]

As: Arsenic; Cd: Cadmium; IARC: International Agency for Research on Cancer; CAS No.: Chemical abstract service number.

75-01-4), is a chlorinated organic compound. VMC is found in cigarette smoke and is mainly used in the production of polymer polyvinyl chloride (PVC). VCM is rapidly absorbed after inhalation and is primarily metabolized by the liver.

Since PVC is harmless in its polymeric form, workers handling the finished goods are not at risk of exposure. The risk phases are those in which the workers are in contact with the material when still in the monomeric state. Many epidemiological studies have demonstrated the high prevalence of exposure to VCM in those working with the chemical. Thiodiglycolic acid is the main VCM metabolite detected in the urine of occupationally exposed subjects.

It has been shown in both human and animal models that VCM is able to induce liver angiosarcoma and HCC[98-104].

Maroni *et al*[105] reported the hepatotoxicity of VCM and other studies have shown the capacity of VCM to induce specific gene mutations in the liver[105-117].

Various European and Italian studies have reported the apparent association between the amount and timing of exposure to VCM and development of HCC in those exposed[118-120].

ORGANIC SOLVENTS

Organic solvents are substances that contain carbon and are capable of dissolving or dispersing one or more other substances. Millions of workers are exposed to organic solvents contained in products such as varnishes, adhesives, glues, plastics, textiles, printing inks, agricultural products and pharmaceuticals.

Many organic solvents are recognized by NIOSH as carcinogens (carbon tetrachloride, benzene and trichloroethylene), reproductive hazards and neurotoxins. Among the organic solvents, trichlorethylene (TCE) and perchlorethylene (PCE) have been reported to be

capable of promoting cancer in humans[121,122].

TCE (CAS 06/01/79) has been associated with a high prevalence of liver tumors in exposed workers. Although the hepatic metabolism of this solvent is known, the molecular alterations that cause liver cancer are not completely known[123-127].

It is hypothesized that TCE may be involved in various mechanisms, such as the reduction of programmed cell apoptosis and the uncontrolled proliferation induced by peroxisome activated receptor (PPAR). In fact, it has been proved that TCE is able to bind PPAR[128-132].

RAD51 is a eukaryote gene. The protein encoded by this gene is a member of the RAD51 protein family which assists in the repair of DNA. TCE binds the *RAD51*, consequently alters the DNA repair and can cause a certain degree of genomic instability.

Finally, it was reported that TCE can cause hypomethylation of DNA and hyperexpression of oncogenes (*e.g.*, *MYC* and *JUG*), responsible for uncontrolled cell proliferation[133-137].

A high prevalence of liver cancer was found in animal models exposed to PCE (CAS 127-18-4)[138,139].

Porru *et al*[140] showed that, in workers chronically exposed to organic solvents (toluene and xylene), there is an increased risk of HCC and that the risk is time-dependent.

PESTICIDES

Pesticides are widely used in agriculture to get the best quality products and appearance. Farmers and many workers in the agro-food chain are exposed to these substances as well as consumers who eat agricultural products that are not properly cleaned and decontaminated.

Among these substances, 1,1,1-trichloro-2,2-bis (p-chlorophenyl)-ethane (DDT) and its metabolite 1,1-dichloro-2,2-bis (p-chlorophenyl)-ethylene (DDE) have been extensively studied. DDT was used both in agriculture and for environmental disinfection until its use was later forbidden in both America and Europe because of its toxic effects on humans. However, in Africa and many parts of Asia it is currently used to control diseases delivered by an insect as a vector (*e.g.*, Leishmaniasis, malaria).

In humans, DDT contamination occurs through contact with the skin, mucous membranes and inhalation. After DDT absorption, it is distributed to all organs and a portion will be stored in fatty tissues, especially if the exposure was massive[141-146].

Many insecticides, including DDT, were reported to be responsible for leading the development of HCC[147-152]. This occurs through different mechanisms not yet completely understood. Moreover, DDT has an estrogenic effect, while DDE has anti-androgenic effects. DDT may also interfere with the *CYP3A1* gene involved in the inflammatory and immune responses in the liver. Probably none of these mechanisms is individually able to result in HCC but the simultaneous presence of these alterations may lead to the development of liver cancer. Furthermore, the presence of important cofactors, such as HBV, HCV and AFB1, amplifies the risk in exposed populations[152-158].

N-NITROSAMINES

Nitrosamines are carcinogenic chemical compounds produced when nitrite, a preservative added to certain foods (fish, fish byproducts, certain types of meat, cheese products, beer), combines with amino acids in the stomach. Nitrosamines can be also found in latex products and tobacco smoke. Moreover, nitrosamines are produced in research laboratories, in rubber and tyre manufacturing processes and may be found as contaminants in the final rubber product. Some nitrosamines have been found to be effective for a variety of purposes, including antimicrobial (No. 11) or chemotherapeutic agents (Nos. 5 and 9) in conjunction with others, herbicides (Nos. 5 and 6), additives to soluble and synthetic metalworking fluids (No. 3), solvents or gasoline and lubricant additives (No. 4), antioxidants, stabilizers in plastics, fiber industry solvents and copolymer softeners, and to increase dielectric constants in condensers. Contamination can occur with skin contact and by ingestion and/or inhalation.

Nitrosamines are carcinogenic and are implicated in nasopharyngeal, esophageal, stomach, liver and urinary bladder cancers[159].

From 1981 to 1991, the United States - National Toxicology Program conducted several investigations to characterize and assess the toxicological potential and carcinogenic activity of N-nitrosamines in laboratory animals (rats and mice). The results were reported in the second (1981) (N-nitrosamines: 2-7, 9-15) and sixth (1991) (N-nitrosamines: 1-8) annual report on carcinogens[159-163].

In environmental surveys of some European rubber factories, de Vocht *et al*[164] found the average N-nitrosamine levels well below the regulatory limits in force but high accidental exposures have still occurred. In fact, they detected high levels of urinary N-nitrosamines in exposed workers[162,164-166]. Recent studies have reported a correlation between exposure to N-nitrosamines and HCC which might be due to the shortening of telomeres among workers in the rubber industry. Telomeres are critical to maintaining the integrity of chromosomes and telomere length abnormalities are associated with carcinogenesis[163,165,167-169].

DIOXINS AND DIOXIN-LIKE COMPOUNDS

The dioxins and dioxin-like compounds are a class of heterocyclic organic compounds whose molecular structure fundamentally consists of a ring of six atoms, four carbon and two oxygen atoms; dioxin in the strict

sense is differently stable and comes in two different positional isomers. Commonly referred to dioxins are also compounds derived from furan, in particular dibenzofurans. Therefore, part of the dioxin-like compounds are polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans and among them, the most toxic is 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It has been shown that compounds of the family of dioxins are formed during the initial stage of the waste combustion when combustion generates gaseous HCl in the presence of catalysts, such as copper and iron. Organic chlorine, which is bound to organic compounds of polymers such as PVC, is mainly responsible for the formation of compounds belonging to the family of dioxins. Dioxins are generated even in the absence of combustion, for example in bleaching paper and tissues with chlorine.

About 90% of human dioxin, except for cases of exposure to specific sources such as industrial plants and incinerators, takes place through food (in particular the fat of animals exposed to dioxin) and not directly by air. The phenomenon of bioaccumulation is very important, *i.e.*, the possibility that dioxin enters into the human food chain from plants, through herbivores, carnivores and finally humans[170-176]. Dioxins are classified as definitely carcinogenic and are in the IARC group 1 carcinogenics for humans.

The National Institute for Occupational Safety and Health (NIOSH) has classified TCDD as an occupational carcinogen that can cause space-occupying liver lesions, both non-neoplastic and neoplastic, such as in HCC[177-181].

Many studies have indicated that the carcinogenic capacity of TCDD may be due to the interaction between TCDD and the aryl hydrocarbon receptor (AhR). This receptor is implicated in several xenobiotic metabolisms but there is evidence that AhR is able to control other genes, some of which have a pro-oncogenic capacity[182-184]. The TCDD is an important AhR agonist and is therefore able to induce and enhance HCC development and diffusion[184].

POLYCHLORINATED BIPHENYLS

Polychlorinated biphenyls (PCB) are synthetic chlorinated aromatic hydrocarbons, chemically stable and therefore persistent environmental contaminants. The contamination occurs by skin contact or inhalation, which also allows the possibility of developing vapors for equipment containing PCB overheating[185].

Studies in animal models have shown that these chemical compounds can cause chronic hepatitis as well as cancers, such as HCC and cholangiocarcinoma, especially if there is high exposure and a prolonged time. However, there is little data on liver injury in humans. In one case, exposure to olive oil accidentally contaminated with PCB resulted in death from hepatic cirrhosis. Other studies in workers exposed to the PCB have reported an increased incidence of liver tumors[185-188].

Some possible mechanisms by which PCB can cause cancer have been assumed: Reactive oxygen species (ROS) is produced through the enzymatic oxidation or autoxidation of PCB; PCB determines the increased expression of genes responsible for inflammation and apoptosis in the liver; and PCB has "toxic" effects on certain genes, such as the loss of part of a chromosome and chromosome breakage[189-199]. ROS are also able to reduce telomerase activity which can determine telomere shortening. The contribution of all or part of these alterations may facilitate the onset of tumors and more specifically HCC[200-205]. At present we have no conclusive data on the relationship between PCBs and HCC and further studies will be needed to establish the causal link. However, the evidence reported by animal model studies have made it possible to classify PCB in IARC group 1[206,207].

POLYBROMINATED BIPHENYLS

Polybrominated biphenyls are polyhalogenated derivatives of a biphenyl core[208] that are chemically stable and therefore persistent environmental contaminants. Whereas they were widely used just a few years ago, they are now subject to restrictive rules that limit their use in the European Union (Restriction of Hazardous Substances Directive).

Contamination can occur through skin contact, inhalation and ingestion[209-212]. Based on data obtained from animal research, PDDs are considered potential human carcinogens and can result in hematological, digestive system and liver malignancies. The pathogenic mechanisms by which they can result in PDD cancer are similar to those described for PCB which allows them to be defined as "probably carcinogenic for humans" (group 2A)[207].

CHLORAL AND CHLORAL HYDRATE

Chloral (or trichloroacetaldehyde) is a chemical compound with the formula C_2HCl_3O and CAS (chemical abstracts service) 75-87-6. Chloral is produced by the chlorination of ethanol and is also produced as an intermediate in the synthesis of various products, for example DDT. Chloral is used for production of chloral hydrate (formula $C_2H_3Cl_3O_2$ and CAS No. 302-17-0).

Chloral hydrate is an ingredient used in Hoyer's solution[213-216]. In mouse studies, oral administration of chloral in water induced liver nodules as well as hyperplastic nodules and HCC after 92 wk. Significant increases in HCC incidence were seen in treated mice surviving 104 wk[217,218]. Some studies indicate that chloral hydrate is able to produce genomic alterations, such as chromosomal aberrations, loss of cell apoptosis and rupture of the gap junction. There are limited studies on carcinogenicity in humans. However, thanks to evidence in animal studies, chloral and chloral hydrate are currently classified in group A2[216-219].

ORTHO-TOLUIDINE

Ortho-toluidine (O-toluidine) (CAS No. 95-53-4) is used in the chemical and rubber industry and is found in some colorants, herbicides and pesticides. O-toluidine can be an environmental contaminant if in the water used for irrigation of the cultivated fields. It has also been found in tobacco cigarettes. In animal models, O-toluidine caused bladder cancer and its exposure increased the incidence of HCC. Its carcinogenic power is probably due to the ability to determine the formation of DNA adducts, causing damage to the DNA structure. Therefore, O-toluidine is classified in group A[220-229].

4,4'-METHYLENE BIS (2-CHLOROBENZENAMINE)

4,4'-Methylene bis (2-chlorobenzylamine) (MOCA) (CAS No. 101-14-4), used in the rubber industry, can be absorbed through the skin in workers, while population exposure occurs by ingestion of vegetables grown in contaminated soil. The ingestion or subcutaneous injection of MOCA in rats results in an increased incidence of HCC and lung cancer[230-232]. MOCA has a documented detrimental effect on the genome; in fact, it is able to determine chromatin alterations and deletions[76,233]. MOCA is classified in IARC group 1.

4-AMINOBIPHENYL

4-aminobiphenyl (4-ABP) is used in the rubber industry as an antioxidant and a dye and is also found in cigarettes. It is classified in IARC group 1[76]. In rats, 4-ABP ingestion causes bladder cancer, angiosarcoma and HCC; subcutaneous or intraperitoneal exposure determines a high incidence of HCC[234]. The metabolism of 4-ABP determines the formation of N-hydroxyl ABP which is a mutagen. 4-ABP can form a DNA adduct. In human liver tissue, higher 4-ABP-DNA levels were observed in HCC cases compared with controls[235-241]. Although there was a dose-related increase in 4-ABP DNA (cigarettes smoked/day) and an association with mutant p53 protein expression in bladder cancers, there are currently no reports of p53 or other specific gene mutations caused by exposure to PAH or 4-ABP in HCC[242-244].

BENZIDINE AND DYES METABOLIZED TO BENZIDINE

In the past, benzidine (BZD) (CAS No. 92-87-5) and dyes metabolized to benzidine have been widely used in the production of dyes. Their use is currently banned in the United States and Europe. However, the use of products containing these substances may expose people to health risks[245-248]. Epidemiological data on the risk of tumors in humans are limited, but the ingestion of BZD in rats increases the incidence of HCC[249-252]. BZD and dyes metabolized to BZD are classified in group 1 carcinogens[76].

ARSENIC

Arsenic (As) (CAS 7440-38-2) is widespread in nature and, combined with other elements, forms very toxic inorganic compounds that can pollute the water and contaminate the population. The workers in mechanical industries are exposed to the risk of illness from dyes, chemicals and glass[253-258].

After oral intake and gastrointestinal absorption, it is metabolized in the liver where it is conjugated with glutathione and methylated[259,260]. The chronic exposure to small amounts produces chronic liver disease, cirrhosis and HCC.

In the 2004 IARC monograph, the result of inorganic As in HCC formation was called "limited". In contrast, more recent data from animal models have shown the possibility of a strong bond with liver tumor formation[261-268].

Various carcinogenic mechanisms, genetic and epigenetic, have been proposed: DNA methylation, oxidative damage, genomic instability and reduction of programmed cell death[269-274].

CADMIUM

Cadmium (Cd) (CAS No. 7440-43-9) is a chemical element used as an anti-corrosion coating and a pigment. It is combined with lithium in rechargeable batteries and is also in cigarette tobacco. In fact, a cigarette contains about 2.0 μg Cd, of which 10.2% is transferred to the smoke[275]. Cd in the blood and body of smokers are typically double those found in non-smokers[276]. Burning municipal waste leads to inhalation of Cd. Workers in the metal and plastic product industry and workers involved in the construction of solar panels are exposed to Cd[277,278].

In 2011, Cd production was estimated to be 600 metric tons in United States. Most of the Cd produced today is obtained from zinc and products recovered from spent Ni-Cd batteries. China, South Korea and Japan are the leading producers, followed by North America[278]. According to OSHA estimates, 300000 workers are exposed to Cd in the United States. Cd found in food and cigarette smoke accumulates in the liver, kidney and pancreas. Liver concentrations increase with age, peaking at 40-60 years.

Based on epidemiological data, the IARC states that there is no evidence of unequivocal carcinogenic effects of Cd[278-282].

However, many animal studies have demonstrated the ability of Cd to determine various tumors, including HCC. This risk is dose and time-dependent and it is conditioned on the exposure mode. Oxidative stress, DNA methylation, the failure of DNA repair, activation of oncogenes, uncontrolled cell growth and the loss of apoptosis are among the mechanisms hypothesized by

researchers[283-286]. Interestingly, Sabolić *et al*[287] have shown that the Cd can be internalized in the Kupffer cells which begin to produce cytokines, some of these are indicated as cofactors in the development of HCC.

Some studies have reported that chronic exposure to Cd increases the risk of tumors in humans[288-290]. However, large epidemiological studies are necessary to demonstrate whether long term Cd contamination is responsible for HCC development in humans, as in animal models.

DISCUSSION

Workplace risk prevention and safety rely chiefly on eliminating the risk itself (primary prevention) and, when it is not technically feasible, measures have to be enacted to reduce risk to a minimum[291].

When chemical agents are involved, primary prevention entails replacing a toxic agent with a non-toxic one. However, some mutagenic/carcinogenic agents can be produced in synthetic processes as intermediates or waste products[292]. As regards biological agents, it is critical to distinguish deliberate introduction of an agent into the working cycle, as in research centers, from the potential exposure resulting from its unwanted presence, as in the case of health care workers. Whereas the biological agent can be replaced in the former case, other measures have to be enacted in the latter[293].

When risk assessment determines the existence of a healthy risk, adequate risk control systems have to be implemented. Such systems are divided into general and personal protection devices (PPD). The former include adoption of technical and procedural measures, for instance the reduction of environmental pollutants, whereas PPD largely consist of devices worn by workers (*e.g.,* masks, gloves), preventing direct contact with vapors, fumes and/or potentially contaminated material, *e.g.,* biological fluids[294]. Biological risk prevention may involve mandatory vaccine prophylaxis, as in the case of HBV infection. Moreover, the fast pace of advances in vaccine development and protection equipment and devices requires continuous re-assessment of workplace protection systems[295,296].

In workplaces where risks are documented, safety procedures must be instituted in accordance with national guidelines. In case of flaws or deficiencies in such guidelines, those in charge of workplace safety are required to refer to the guidelines of internationally recognized organizations such as the Centers for Disease Control and Prevention, American Conference of Industrial Hygienists, NIOSH, *etc*.

The employer and occupational physician have key roles in preventing occupational risk and diseases. The occupational physician, besides carrying out biological monitoring and health surveillance (secondary prevention), is responsible for promoting workplace health[291].

As regards HCC prevention, all exposed workers should have HBV vaccination. In addition, campaigns against smoking and alcohol drinking should be organized, providing an explicit warning that these factors may contribute to the development of liver cancer[10-12,101].

Development and progression of HCC is still not a completely known multistage process. Genetic, epigenetic and immunological factors probably contribute to the development of HCC[7,11,13,37,38,50,51,101,297,298].

CONCLUSION

In conclusion, the precancerous milieu of chronic liver disease is characterized by neo-angiogenesis, inflammation with ROS production and fibrosis. Synchronous events occurring in this setting also include hypoxia, oxidative stress, apoptosis, mitophagy and autophagy[299-302].

Autophagy shows a double face in HCC. While autophagy helps to prevents tumorigenesis, it is also used by the cancer cells for survival against apoptosis by traditional chemotherapeutic drugs[303,304]. Initially, autophagy functions are as a tumor suppressor and later, when HCC has developed, the autophagy may contribute to its growth[303,305].

Microbes have evolved mechanisms to evade and exploit autophagy and both HBV and HCV use autophagy for their own survival[306]. Studies have shown that autophagy enhances viral replication at most steps of HBV replication and that autophagy proteins are likely to be factors for the initial steps of HCV replication[307,308]. In tumor cells with defects in apoptosis, autophagy allows prolonged survival.

Future directions

All these mechanisms are still being studied in order to provide new therapeutic approaches to HCC[309]. Despite the progress achieved in understanding the cancer process and the impact of this knowledge on treatment, primary prevention remains the most effective approach to reduce cancer mortality in both developed and developing countries for the near future[9,37,38,50,51,56,309].

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MINIREVIEWS

Innovative surgical approaches for hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with an increasing diffusion in Europe and the United States. The management of such a cancer is continuously progressing and the objective of this paper is to evaluate innovation in the surgical treatment of HCC. In this review, we will analyze the modern concept of preoperative management, the role of laparoscopic and robotic surgery, the intraoperative use of three dimensional models and augmented reality, as well as the potential application of fluorescence.

Key words: Hepatocellular carcinoma; Liver resection; Hepatectomy; New prespectives; Innovative surgical approaches

Core tip: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with an increasing diffusion in Europe and the United States. The management of such a cancer is continuously progressing and the objective of this paper is to evaluate innovation in the surgical treatment of HCC.

Memeo R, de'Angelis N, de Blasi V, Cherkaoui Z, Brunetti O, Longo V, Piardi T, Sommacale D, Marescaux J, Mutter D, Pessaux P. Innovative surgical approaches for hepatocellular carcinoma. *World J Hepatol* 2016; 8(13): 591-596 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i13/591.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i13.591

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with at least 1 million new cases each year[1]. Even if liver transplantation remains the ideal treatment, hepatic resection remains the only curative treatment for HCC. Considering the early experience of liver resection for HCC in the 1980s, results were discouraging, with a mortality rate in the range of 10% and a considerable morbidity. Improvements in patient selection, early diagnosis, preoperative and postoperative management, surgical technique and development of new technologies have allowed to obtain a lower mortality and morbidity, achieving 0% in certain high-volume centers. The development of laparoscopic and robotic surgery, associated with the application of new technologies in patient care and progress in the medical treatment of HCC, represent a modern era challenge to optimize the management of HCC with the objective of improving overall and disease-free survival. The aim of this article is to describe all innovations in the surgical treatment of HCC.

ADVANCES IN THE ASSESSMENT AND PLANNING OF SURGICAL TREATMENT

The onset of HCC in a normal liver is an extremely rare situation. It is associated with the presence of pathological liver, and cirrhosis in most cases (80%). The presence of a pathological liver requires a comprehensive study of liver function and patient condition, in order to prevent any postoperative liver failure which occurs in approximatively 8% of patients after major hepatic resections[2]. The preoperative planning of a surgical procedure has improved the safety of liver resection in cirrhotic patients. The introduction of the concept of future remnant liver (FRL)[3] as a predictor of liver failure has contributed to the development of the concept of liver volumetry. In case of pathological liver, FRL was usually set at 50% of functional liver to prevent any postoperative liver failure[3]. The necessity to calculate liver volumetry has increased the diffusion of three-dimensional (3D) surgical planning software[4], with the double function of simulating surgery and calculating liver volumes. Even if conventional 2D images [magnetic resonance imaging (MRI) or computed tomography (CT)-scanning] reveal all the required information concerning tumors, major vessels and the biliary tract, surgeons could come across difficulties in perceiving the relationships of these structures before surgery, and during surgical planning. This platform allows to explore hepatic veins and portal triads from the hepatic pedicle up to segmental branches, allowing to evaluate spatial relationships with the tumor. This software allows to identify the vascular territory supplied by isolated vessels, allowing to simulate anatomical segmentectomy and easy planning of major and minor hepatectomies[5]. Many software tools are now available to create a 3D model, offering a visualized model of patient organs and pathologies.

PORTAL VEIN EMBOLIZATION AND STEM CELLS APPLICATION

As previously mentioned, any hepatic resection must guarantee volume of FRL to prevent postoperative liver failure. In case of cirrhotic liver, the most common scenario in the presence of HCC, namely a portion of 40% to 50% of FRL, should be guaranteed so that liver function should not be affected. In case of insufficient FRL, portal vein embolization was suggested by Makuuchi *et al*[6] in 1990, in order to stimulate liver hypertrophy before surgery. This hypertrophy usually requires 4 to 6 wk, but in some cases, more time could be necessary, especially in case of pathological parenchyma. However, during this period, the tumor could continue its progression, and the patient could well become inoperable. One possibility to reduce this risk is to obtain a quicker hypertrophy, reducing the time between portal vein embolization and hepatectomy. Several studies have suggested that stem cells could have an important role in the process of tissue regeneration[7]. In case of acute or chronic liver suffering, stem cells can be stimulated from bone marrow. Among them, a subpopulation of cells ($CD133^+$) have been recognized as potentially involved in liver regeneration after portal embolization, with encouraging results in some case series, demonstrating an augmented capacity of liver parenchyma regeneration[7-11].

3D PRINT OF LIVER MODELS

Based on the data acquired by CT-scan which provide 2D information on geometrical measurements of tumors,

portal vein, hepatic vein and liver parenchyma, a 3D software edited model has been elaborated. 3D printing is a procedure which creates a solid 3D object based on a previous digital model. It is obtained *via* a 3D printer, which lays down thin layers of material in order to form a perfect 3D replica of the computer model. Initially developed to plan living donor liver transplantation[12], an application is currently being found for it in liver surgery[13]. The main objective for the development of this physical liver model is to overcome the limitation of conventional 3D models and 2D images such as the absence of reliable liver surface markers, the difficult appreciation of depth, and difficulties in identifying liver segmentation as well as the relationships between vascular and biliary structures. Another advantage is the possibility to use the 3D-printed model during liver surgery, packing the prototype into a sterilized nylon bag[14], which allows to adjust the model to the surgical situation and the surgical field in order to obtain a better understanding.

REAL-TIME IMAGE FUSION FOR RADIOFREQUENCY ABLATION

Radiofrequency is currently considered an important support for the surgical treatment of HCC or in some cases it is considered an alternative to surgical resection[15]. This treatment is highly operator-dependent, especially for targeting, monitoring and controlling, as well as in cases of very small lesions in a pathological parenchyma. The development of a real-time image fusion system is based on the fusion of real-time sonograms with images previously obtained on CT-scan or MR[15-23]. To obtain this image fusion, a probe is equipped with a magnetic sensor, which generates a magnetic field interfaced with previously stored images. This fusion could lead to the detection of small HCCs, with an extremely high tumor-targeting success rate of 90% to 100%[21-23]. Such encouraging results could improve the performance of RFA treatment for nodules, which could not be revealed by means of sonography. The development of this tool associated with a needle tracking system could be used to assess the efficiency of RFA, hence allowing for a 3D evaluation of the treated zone.

LAPAROSCOPIC SURGERY FOR HCC

Hepatic surgery still represents one of the most challenging and technical procedures requiring considerable experience. Despite such difficulties, some pioneers in laparoscopic surgery described the first laparoscopic liver resection in 1993[24]. Initially considered a standard procedure for patients with a single and subcapsular lesion of less than 5 cm, located in the left liver or in the anterior sectors of the right liver, it currently represents a valid alternative to open surgery for major hepatectomies, as it is considered a safe and feasible procedure for the treatment of malignant lesions[25]. Even if the diffusion of this minimally invasive approach has rapidly gained consensus, laparoscopic resection of pathological livers was considered contraindicated due to the quality of parenchyma and condition of patients. A continuous progression of surgical devices over the last decades has improved the diffusion and safety of these complex procedures. The development of an ultrasonic scalpel (Ultracision™, Ethicon Endosurgery, Cincinnati, OH, United States) allows for a bloodless dissection of liver parenchyma. The ultrasonic dissector (Dissectron, Satelec, Mérignac, France) allows to divide and identify pedicles before being divided and clipped. Large vascular elements were divided after being secured with Hem-o-lok™ clips. Hemostasis and biliostasis of small elements were performed using saline-assisted bipolar electrocautery. Automatic vascular staplers allow for a safer and quick division and suture of large vascular structures, thereby reducing technical difficulties of manual suturing of large vessels. A crucial role during laparoscopic hepatic resection is the one played by ultrasonography, as it is used to localize hepatic veins and portal pedicles, allowing for a continuous control during parenchymal transection to check for safety margins. All these improvements, associated with the enhanced postoperative management of patients and augmented surgical skills have allowed the development of laparoscopic liver resection on cirrhosis, becoming a gold standard for treatment of HCC[26]. Despite a strong association with augmented mortality and morbidity as compared to hepatic resection on non-pathological livers, liver resection guarantees several advantages, especially in the postoperative period[27-30], reducing blood loss, postoperative pain, abdominal wall infection, length of stay, and facilitating the surgical operation in case of future liver transplantation[31,32] due to a reduction of adhesions. As for non-pathological livers, and this is also true for HCC on cirrhosis, major hepatectomies, even associated with vascular resection[33], are feasible with similar morbidity and mortality rates[34].

ROBOTIC SURGERY FOR HCC

The development and diffusion of the da Vinci™ robotic surgical system (Intuitive Surgical, Inc., Sunnyvale, CA, United States) have introduced a novel approach in general surgery with an enormous potentiality of integration. The system is made up of a patient-site with four robotic operating arms and a surgeon-site equipped with a stereoscopic 3D camera. Using the robot, this system allows to replicate human hand movements with precise downscaling. As laparoscopy had reached a standardization in hepatobiliary surgery, difficult procedures could benefit from the integrated function of robotic surgery. The aim of robotic surgery is to improve clinical outcome. The two main limitations of laparoscopic surgery (visual and ergonomic limitations) have been totally overcome by the robotic system, allowing to perform advanced procedures with safety.

Precise dissections could be achieved, due to the possibility of using articulated systems with seven degrees of freedom and advanced 3D views. Major limitations of robotic surgery include operating costs and lack of haptic feedback. Once this limitation is overcome, the diffusion will be faster, and more cases will be described in the literature. Currently, regarding HCC, few case series[35-39] are available and about 500 cases are described in the literature for liver malignant conditions. No benefits have been described as compared to laparoscopic surgery in terms of morbidity, mortality, and oncological results[35,38]. This is probably due to the shortage of series and of patients and will require further studies.

ROBOTIC AND DEVELOPMENT OF AUGMENTED REALITY

The advent of robotic surgery has allowed the integration of the da Vinci™ robotic surgical system using virtual reality. During the surgical procedure, the 3D model reconstruction could be superimposed with real-time model mobilization, with the possibility to selectively view biliary structures, portal veins, the arterial system, hepatic veins, and lesions. This fusion is defined as augmented reality. This technique, initially described by Pessaux *et al*[40], use different skin landmarks associated with intra-abdominal landmarks to obtain a computer-assisted fusion of the 3D model with a real-time stereoscopic image of the operative field obtained *via* the 3D robotic camera. The superimposed image was used as a guide for the surgeon who, with the possibility to increase and decrease the transparency of the virtual model, could easily identify vascular structures as well as the correct localization of the lesion in order to obtain oncological resection margins. This modern era principle has found an application in other fields of surgery[40-44], with an extremely interesting application of the lesion initially detected on CT-scan or MRI but impossible to detect preoperatively with ultrasound, called missing lesions[45]. This superimposition of 3D model reconstruction of the first bi-dimensional imaging in which the lesion was available allows the robotic image to guide resection of the liver segment in which the lesion is supposed to be located, hence allowing to achieve satisfying oncological margins.

MINIMALLY INVASIVE APPLICATION OF FLUORESCENCE

Indocyanine green (ICG) is a non-toxic, non-radioactive and highly safe fluorophore with the capacity to appear green when excited by light in the near infrared spectrum. Historically used to predict liver failure[46], its elimination from blood depends on hepatic blood flow. Cellular uptake and biliary excretion are measured using the ICG-plasma disappearance rate (ICG-PDR). In case of augmented values of ICG-PDR[46,47], major hepatectomies could be contraindicated to prevent postoperative liver failure. Considering the integrtion of a fluorescence camera in the robotic da Vinci™ system and laparoscopic camera, fluorescence could be inte–grated in operative strategies during hepatectomies. Arteries and veins are the first structures to be visualized after venous injection of ICG (5-60 s), and this could allow for an easier recognition of anatomical variations and identification of structures in the hepatic hilum. After vascular capitation, approximately 45 to 60 min after injection, ICG accumulates in the liver and is secreted in the bile. This application could be valuable to prevent complications during difficult cholecystectomies[48], as it could allow to identify bile duct and cystic duct. In the future, it could well reduce the interest in using a perioperative cholangiogram, thereby reducing the exposure of patients to radiation.

Concerning the identification of liver neoplastic tissue, hemodynamic, metabolic and biliary excretion of ICG allow for the identification of tumoral parenchyma[49]. Poorly differentiated HCCs are characterized by a low capitation of the lesion with a fluorescent rim, due to a perilesional alteration of biliary excretion[50]. Well-differentiated HCCs have an intense fluorescent pattern[50]. This finding, as demonstrated for colorectal cancer liver metastasis, could allow to detect undetected lesions with previous conventional preoperative imaging[51], with a potentially significant impact on disease-free survival[52].

CONCLUSION

HCC still represent a challenge for the surgeon of the next era. Considering the rapid evolution and quick technological progress applied to surgery, additional solutions will be put forward to achieve lower morbidity and mortality rates, guaranteeing a more precise resection, which will offer better oncological results. This progress, associated with progress in diagnosis[53], advances in medical treatment, and an improvement of radiology and oncology will ensure a better future for our patients.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors for deterioration of long-term liver function after radiofrequency ablation therapy

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Abstract

AIM: To identify factors that influence long-term liver function following radiofrequency ablation (RFA) in patients with viral hepatitis-related hepatocellular carcinoma.

METHODS: A total of 123 patients with hepatitis B virus- or hepatitis C virus-related hepatocellular carcinoma (HCC) (n = 12 and n = 111, respectively) were enrolled. Cumulative rates of worsening Child-Pugh (CP) scores (defined as a 2-point increase) were examined.

RESULTS: CP score worsening was confirmed in 22 patients over a mean follow-up period of 43.8 ± 26.3 mo. Multivariate analysis identified CP class, platelet count, and aspartate aminotransferase levels as significant predictors of a worsening CP score (P = 0.000, P = 0.011 and P = 0.024, respectively). In contrast, repeated RFA was not identified as a risk factor for liver function deterioration.

CONCLUSION: Long-term liver function following RFA was dependent on liver functional reserve, the degree

of fibrosis present, and the activity of the hepatitis condition for this cohort. Therefore, in order to maintain liver function for an extended period following RFA, suppression of viral hepatitis activity is important even after the treatment of HCC.

Key words: Radiofrequency ablation; Hepatocellular carcinoma; Liver function; Hepatitis B; Hepatitis C

Core tip: This study was conducted to identify risk factors for liver function deterioration following radiofrequency ablation (RFA) in patients with hepatocellular carcinoma (HCC) and viral hepatitis. A total of 123 patients with hepatitis B virus- or hepatitis C virus-related HCC were enrolled. Cumulative rates of worsening Child-Pugh (CP) scores (defined as a 2-point increase) following RFA were examined. CP class, platelet count, and aspartate aminotransferase levels were identified as significant predictors of a worsening CP score. Suppression of viral hepatitis activity with anti-viral therapy is important even after the treatment of HCC in order to maintain liver function following RFA.

Honda K, Seike M, Oribe J, Endo M, Arakawa M, Syo H, Iwao M, Tokoro M, Nishimura J, Mori T, Yamashita T, Fukuchi S, Muro T, Murakami K. Risk factors for deterioration of long-term liver function after radiofrequency ablation therapy. *World J Hepatol* 2016; 8(13): 597-604 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i13/597.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i13.597

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant neoplasms worldwide[1] and most cases of HCC involve patients infected with hepatitis B virus (HBV) or hepatitis C virus (HCV)[2-4]. Radiofrequency ablation (RFA) is currently recognized as an effective local treatment for HCC[5,6] and has been shown to be a relatively low risk procedure[7-9]. However, deterioration of liver function has been observed during the long-term follow-up of these patients[10-12]. Therefore, the risk factors that contribute to deterioration of liver function need to be identified. Although a few reports have investigated changes in long-term liver function following RFA[10-12], long-term liver function in patients with viral hepatitis-related HCC is still uncertain. The goal of this study was to identify risk factors for liver function deterioration in patients with HCC and viral hepatitis.

MATERIALS AND METHODS

Patients

This retrospective cohort study was based on data obtained from a prospective database maintained by the Oita University and Oita Medical Center. Between January 2002 and December 2010, 479 patients underwent percutaneous RFA for HCC at these two institutions. This study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Ethics Committee of Oita University and Oita Medical Center.

A diagnosis of HCC was based on vascular findings obtained by dynamic computed tomography (CT) using early arterial uptake followed by washout in the portovenous and equilibrium phase. For patients with an uncertain diagnosis, a fine-needle biopsy was performed. Prior to RFA, patients with hyper vascular tumors underwent transarterial chemoembolization. All ablations were performed with a single needle electrode (COVIDIEN, Cool-tip RF Ablation System, Ireland). Furthermore, all RFA procedures were performed percutaneously with ultrasound guidance, and diazepam and pentazocine were routinely administered prior to insertion of the electrode. If necessary, physiological saline was infused into the chest or abdominal cavity to induce artificial pleural effusion or ascites to avoid injury to adjacent organs, or to facilitate visualization of the tumor. Effects of RFA were confirmed by dynamic CT three days after treatment. If the ablated margin was insufficient, additional ablation was performed until a sufficient ablated margin was obtained.

Inclusion criteria for patient selection in the present study included: (1) HCC occurring due to HBV- or HCV-related chronic liver disease; (2) first occurrence of HCC; (3) the presence of up to four nodules per patient, with each nodule having a diameter less than 5 cm; and (4) the presence of tumors only in the liver, with complete necrosis achieved by treatment with RFA. Of the 479 patients treated for HCC, 356 patients were excluded from this study due to: Non-B or non-C HCC (n = 77), recurrent HCC (n = 80), complete necrosis was not obtained (n = 4), advanced HCC (n = 33), simultaneous other malignancies (n = 8), nephrotic syndrome or advanced chronic kidney disease (n = 7), portal thrombus (n = 3), chronic debilitating disease (n = 1), poor food intake (n = 2), breakthrough hepatitis by resistant HBV (n = 2), treatment with warfarin (n = 3), received albumin around the same time as RFA treatment (n = 1), started interferon (IFN) therapy up to 1 year after RFA treatment (n = 17), uncontrollable progression of HCC up to 1 year after RFA treatment (n = 4), death due to other disease within 1 year (n = 2), documents not stored by the electronic system (n = 75), a follow-up period less than one year (n = 27), and treatment with a nucleoside analog within six months of RFA treatment (n = 10). The latter was included based on reports that significant improvement in liver function had been observed within six months of lamivudine treatment for decompensated cirrhotic HBV patients[13,14]. Although it was also reported that albumin levels increased during the first two years of IFN treatment for chronic hepatitis C patients with sustained virological response (SVR)[15], none of the patients in the current cohort met this

Table 1 Patient characteristics (n = 123) at the start of the follow-up period

Gender (male/female)	71/52
Age (yr)	69.7 ± 8.0
Hepatitis (HBV/HCV)	12/111
CP score (5/6/7/8)	79/22/15/7
CP class (A/B/C)	102/21/0
Size of tumor (mm)	20.6 ± 7.7
No. of tumor(s) (1/2/3/4)	78/30/13/2
Total bilirubin (mg/dL)	0.97 ± 0.4
Albumin (g/dL)	3.7 ± 0.6
Prothrombin time (%)	90.5 ± 15
Platelet count (10^4/μL)	11.1 ± 5.0
AST (IU/L)	58.2 ± 32.1
ALT (IU/L)	53.0 ± 39.7
Hepatitis condition RVH group/CAH group	13/110
Prior TACE with TACE/without TACE	110/13

HBV: Hepatitis B virus; CP: Child-Pugh; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; RVH: Remission status of viral hepatitis; CAH: Chronic active hepatitis; HCV: Hepatitis C virus; TACE: Transarterial chemoembolization.

criterion.

For the resulting 123 patients enrolled in this study, two groups were established in order to examine the influence of viral hepatitis activity. The first group included nine HBV patients who achieved complete remission of hepatitis (defined as a normal range of transaminase levels) by treatment with an oral nucleoside such as lamivudine, adefovir, or entecavir, two patients with non-active HBV, and four HCV patients who received IFN therapy and achieved a SVR. This group was referred to as the remission of viral hepatitis (RVH) group. The second group consisted of one HBV patient and 107 HCV patients with active hepatitis, and this group was referred to as the chronic active hepatitis (CAH) group.

Follow-up periods

The starting point for observation was the first day that patients underwent RFA. Follow-up periods concluded when recurrent HCC(s) were no longer able to be controlled with RFA. In addition, follow-up periods were ended when liver function was found to be deteriorating due to another disease, when treatment with IFN was initiated, when treatment with a nucleoside analog was initiated, when recurrent tumors were treated by surgery, or when a thrombus formed in the portal vein. During the follow-up period, abdominal CT or ultrasonography was performed every four months and blood assays were performed monthly.

Statistical analysis

All quantitative variables are presented as the mean ± SD. The endpoint used was a 2-point increase in Child-Pugh (CP) scoring. The cumulative rate of worsening CP scores (defined as a 2-point increase) was also calculated, and cumulative proportion curves were generated using the Kaplan-Meier method. Independent factors that influenced a worsening CP score were identified by univariate and multivariate analysis using Cox's proportional hazards model. A P-value less than 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics version 20.0 for Windows.

RESULTS

Patient profiles

A total of 123 patients (71 males, 52 females) with HBV infection (n = 12) or HCV infection (n = 111) were enrolled in this study. Additional characteristics of this cohort are provided in Table 1. Of the HBV patients, 9/12 were treated with nucleoside analogs [lamivudine (n = 1), lamivudine plus adefovir dipivoxil (n = 4), and entecavir (n = 4)] at least six months prior to RFA therapy. There were also two patients with non-active HBV carriers, and one HBV patient had an active case of hepatitis at the time of RFA. Of the HCV patients, 4/111 achieved a post-SVR state with IFN therapy. The CP class A group consisted of 102 patients which included: An active HBV carrier (n = 1), inactive HBV carriers that did not receive nucleoside analog treatment (n = 2), inactive HBV carriers that received nucleoside analog treatment (n = 8), patients with active hepatitis C (n = 87), and SVR patients with hepatitis C (n = 4). The CP class B group included an inactive HBV carrier who received nucleoside analog treatment (n = 1), and active hepatitis C patients (n = 20). During the follow-up period, the frequency of RFA treatment for recurrent tumors included a single treatment (n = 32), two treatments (n = 23), three treatments (n = 9), four treatments (n = 5), five treatments (n = 3), and six treatments (n = 2). There were 49 patients that did not receive any RFA treatment.

Liver function after RFA treatment

The follow-up period was ended for patients of this cohort due to: Loss of local control of tumor progression with RFA (n = 21), death or worsening of liver function due to another disease or accident (n = 7), induction of IFN therapy for HCV infection (n = 5), surgical treatment for recurrent tumors (n = 1), emergence of a portal thrombus (n = 1), and administration of a nucleoside analog for HBV infection (n = 1). In the latter case, a patient with HBV was enrolled in the CAH group since he initially refused treatment with entecavir. However, 12 mo later he consented to receive entecavir as a treatment, and consequently, the follow-up period for this case ended after 12 mo.

A worsening CP score was confirmed for 22 patients during a mean follow-up period of 43.8 ± 26.3 mo. Moreover, the 1-, 2-, 3-, 5- and 7-year cumulative rates for worsening CP scores calculated according to the Kaplan-Meier method were 2.4%, 6.9%, 10.0%, 19.3% and 33.2%, respectively (Figure 1). The variables listed in Table 1, as well as the frequency of RFA for

Table 2 Univariate analysis to identify risk factors that contributed to a worsening Child-Pugh scores following radiofrequency ablation (*n* = 123)

Variable	HR	95%CI	*P*-value
Gender (female *vs* male)	1.93	0.83-4.47	0.128
Age (yr) (< 70 *vs* ≥ 70)	1.05	0.45-2.44	0.906
CP class (B *vs* A)	5.03	2.17-11.7	0.000
Size of tumor (mm) (≥ 20 *vs* < 20)	2.01	0.84-4.81	0.116
Number of tumors (≥ 2 *vs* 1)	1.47	0.62-3.47	0.379
Total bilirubin (mg/dL) (≥ 1.0 *vs* < 1.0)	3.48	1.35-8.99	0.010
Albumin (g/dL) (< 3.5 *vs* ≥ 3.5)	8.52	3.12-23.2	0.000
Prothrombin time (< 80% *vs* ≥ 80%)	2.66	1.14-6.23	0.024
Platelet count (10^4/μL) (< 10 *vs* ≥ 10)	5.04	1.86-13.7	0.001
AST (IU/L) (≥ 40 *vs* < 40)	7.06	1.57-31.8	0.011
ALT (IU/L) (≥ 35 *vs* < 35)	4.01	1.32-12.2	0.015
Prior TACE *vs* no TACE	1.05	0.24-4.48	0.952
Frequency of RFA treatments for recurrent HCC (≥ 2 *vs* < 2)	1.51	0.64-3.53	0.344

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; TACE: Transarterial chemoembolization; CP: Child-Pugh; RFA: Radiofrequency ablation; HCC: Hepatocellular carcinoma.

Table 3 Multivariate analysis to identify risk factors that contributed to a worsening Child-Pugh scores following radiofrequency ablation (*n* = 123)

Variable	HR	95%CI	*P*-value
CP class (B *vs* A)	5.07	2.13-12.1	0.000
Platelet count (10^4/μL) (< 10 *vs* ≥ 10)	3.83	1.36-10.8	0.011
AST (IU/L) (≥ 40 *vs* < 40)	7.01	1.30-37.9	0.024
ALT (IU/L) (≥ 35 *vs* < 35)	1.21	0.35-4.19	0.761

A worsening Child-Pugh (CP) scores was defined as a 2 point increase. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

recurrent HCC, were selected as factors for analysis using Cox's proportional hazards model. In contrast, the type of infection (HBV or HCV), and the presence of an active hepatitis condition (RVH or CAH), were excluded from this analysis, since none of the patients in HBV or RVH group exhibited at least a two point increase in CP scores during the follow-up period. Risk factors that were found to contribute to worsening CP scores following RFA are listed in Tables 2 and 3. In a univariate analysis performed, CP class, total bilirubin, albumin, prothrombin time, platelet count, levels of aspartate aminotransferase (AST), and levels of alanine aminotransferase were found to be associated with a worsening CP score (Table 2). Accordingly, these factors were selected for multivariate analysis. Frequency of RFA treatments for recurrent HCC was not found to be associated with deterioration of long-term liver function. Since total CP class, bilirubin, albumin, and prothrombin time are factors that indicate liver function, CP class was selected as a factor representative of these variables. In the multivariate analysis performed, CP class, platelet count, and AST were identified as significant predictors of a worsening CP score (Table 3) (P = 0.000, P = 0.011 and P = 0.024, respectively). Cumulative rates of

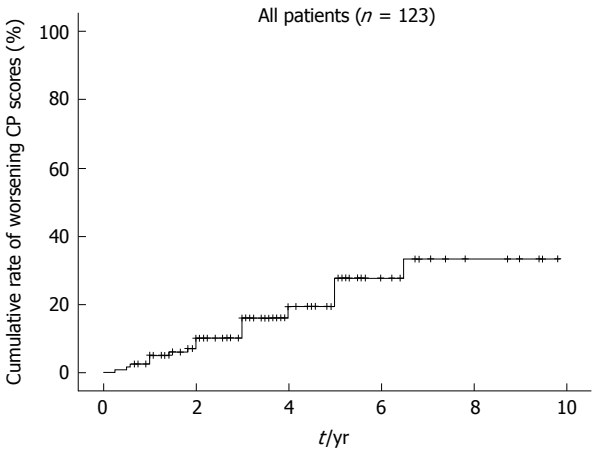

Figure 1 Cumulative rate of worsening Child-Pugh scores (defined as a 2-point increase) for all patients. The 1-, 2-, 3-, 5- and 7-year cumulative rates for worsening CP scores calculated according to the Kaplan-Meier method were 2.4%, 6.9%, 10.0%, 19.3% and 33.2%, respectively. CP: Child-Pugh.

worsening CP scores were generated using the Kaplan-Meier method and are shown in Figure 2.

Subpopulational analyses were also performed with respect to HBV, HCV, RVH and CAH. For the HBV group (n = 12, mean follow-up period: 64.0 ± 28.7 mo, CP class A (n = 11), CP class B (n = 1), CAH (n = 1), RVH (n = 11), platelet count: (10.4 ± 4.3) × 10^4/μL, AST: 26.3 ± 5.4 IU/L, frequency of RFA treatment after initial treatment (0/1/2/3 times): 4/6/1/1 patients, respectively), none of the patients exhibited deterioration of long-term liver function.

For the HCV group [n = 111, mean follow-up period: 41.6 ± 25.2 mo, CP class A (n = 91), CP class B (n = 20), CAH (n = 107), RVH (n = 4), platelet count: (11.1 ± 5.1) × 10^4/μL, AST: 61.6 ± 31.9 IU/L, frequency of RFA treatment after initial treatment (0/1/2/3/4/5/6 times): 45/26/22/8/5/3/2 patients, respectively], CP class and platelet count were both identified as significant predictors of worsening CP scores in the multivariate analysis performed (P = 0.000 and P = 0.009, respectively) (Table 4). None of the patients in the SVR group (n = 4) exhibited worsening of CP scores.

For the RVH group [n = 15, mean follow-up period: 65.4 ± 28.0 mo, HBV (n = 11), HCV (n = 4), CP class A (n = 14), CP class B (n = 1), platelet count: (11.7 ± 5.1) × 10^4/μL, AST: 25.7 ± 5.1 IU/L, frequency of RFA treatment after initial treatment (0/1/2/3 times): 8/6/0/1 patients, respectively], none of the patients exhibited worsening CP scores.

For the CAH group [n = 108, mean follow-up period: 40.8 ± 24.7 mo, HBV (n = 1), HCV (n = 107), CP class A (n = 88), CP class B (n = 20), platelet count: (11.0 ± 5.0) × 10^4/μL, AST: 62.7 ± 31.6, frequency of RFA treatment after initial treatment (0/1/2/3/4/5/6 times): 41/26/23/8/5/3/2 patients, respectively], CP class B and patients with a platelet count < 10 × 10^4/μL were associated with CP worsening (P = 0.000 and P = 0.010, respectively).

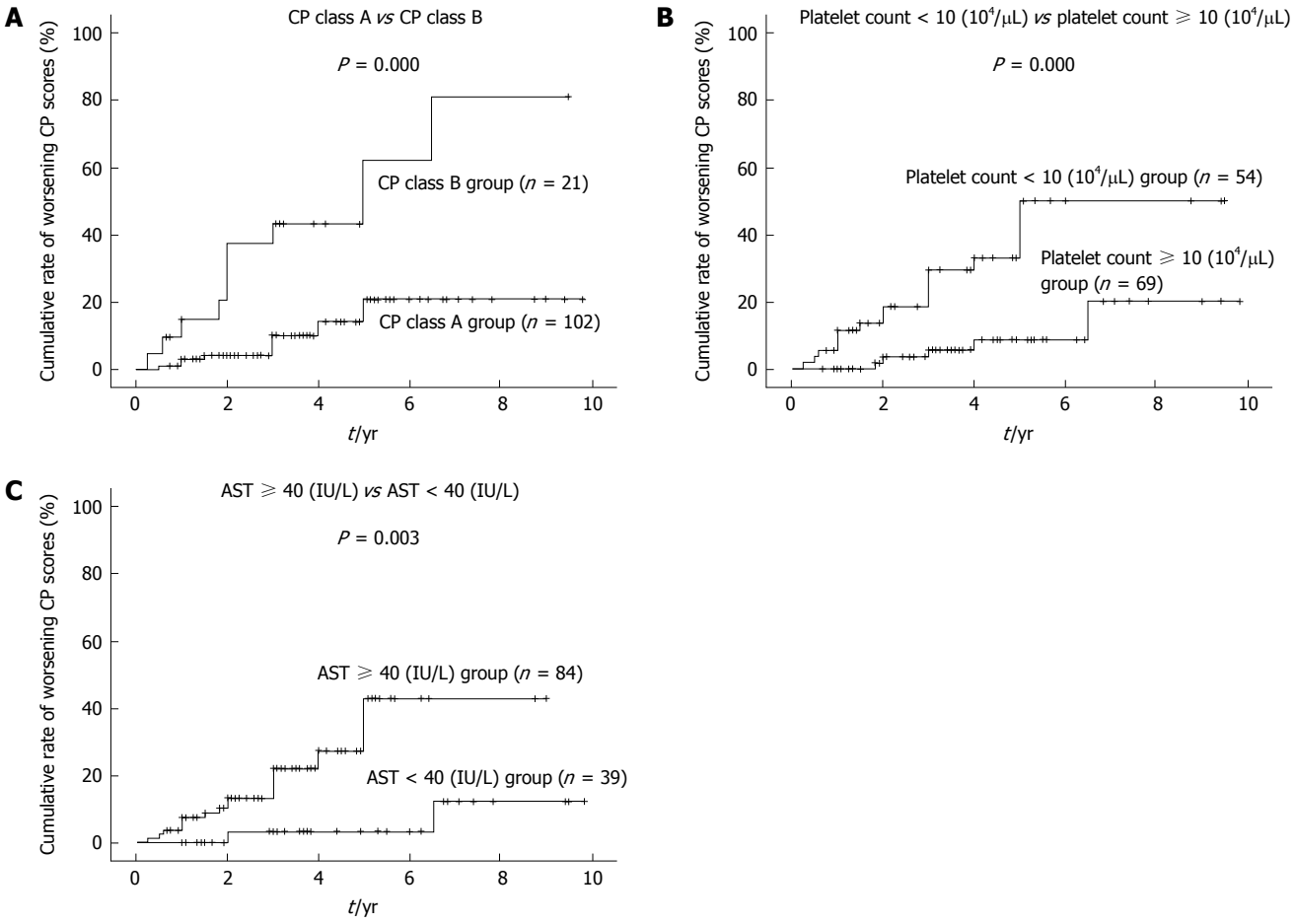

Figure 2 Comparison of cumulative rate of worsening Child-Pugh scores (defined as a 2-point increase) according to the Kaplan-Meier method. *P*-values were calculated using a log-rank test. Analysis according to: A: CP class: A (*n* = 102) and B (*n* = 21); B: Platelet count: < 10 × 10^4/μL (*n* = 54) and ⩾ 10 × 10^4/μL (*n* = 69); C: AST levels: < 40 IU/L (*n* = 39) and ⩾ 40 IU/L (*n* = 84). CP: Child-Pugh; AST: Aspartate aminotransferase.

Table 4 Multivariate analysis of risk factors that contributed to a worsening Child-Pugh scores following radiofrequency ablation for hepatitis C virus patients (*n* = 111)

Variable	HR	95%CI	*P*-value
CP class (B *vs* A)	4.90	2.05-11.7	0.000
Platelet count (10^4/μL) (< 10 *vs* ⩾ 10)	3.96	1.40-11.2	0.009
AST (IU/L) (⩾ 40 *vs* < 40)	5.25	0.98-28.0	0.052
ALT (IU/L) (⩾ 35 *vs* < 35)	1.11	0.33-3.73	0.865

A worsening Child-Pugh (CP) score was defined as a 2 point increase. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

DISCUSSION

Treatment of HCC generally involves a surgical approach and/or a non-surgical approach. In the latter case, transarterial embolization, radiation therapy, chemotherapy, and local puncture therapy are the main options available. While percutaneous ethanol injection therapy[16] is a type of local puncture therapy that has been performed since the 1980s, local ablative therapy such as microwave coagulation therapy[17] and RFA therapy were subsequently developed. Currently, RFA is the main form of local puncture therapy administered due to its ability to provide local control of HCC. The less invasive approach of RFA also represents a key advantage of RFA over surgical resection. However, since the recurrence rate of HCC following radical treatment is generally high, repeated RFA treatments are often needed. There have been reports that the application of repeated RFA for the treatment of recurrent tumors can increase the chances of long-term survival[8,9,18].

A few reports have referred to the influence of RFA on liver function. For example, Koda *et al*[10] reported that liver function in patients with low pre-treatment CP scores transiently deteriorated within the first month of observation, while patients with high pre-treatment CP scores exhibited a greater extent of deterioration over a longer term of observation, approximately 6 mo. In a study by Kuroda *et al*[11], changes in liver function were monitored one year after RFA, and it was observed that a CP score of 9 or higher represented a major risk factor for aggravation of liver function following RFA. Furthermore, in another report by Yokoyama *et al*[12], the influence of RFA treatments on long-term liver function was investigated. Approximately 15% of CP class A or CP class B patients were observed to progress to CP class C five years after RFA treatment. However, the factors that influence on long-term liver function in

patients with viral hepatitis-related HCC following RFA is still uncertain. There are various factors that may contribute to changes in liver function. Since tumor progression is an obvious factor that aggravates the liver function of HCC patients, the current analyses were performed with patients where tumor progression could be excluded. Based on the analyses performed, CP class B patients, patients with a platelet count < $10 \times 10^4/\mu L$, and patients with AST levels ⩾ 40 IU/L, were found to be significantly associated with a worsening of liver function after RFA. These results suggest that worsening of long-term liver function after RFA is dependent on liver function, the degree of fibrosis present, and the activity of a patient's hepatitis condition. However, repeated RFA was not found to be a factor that aggravates long-term liver function.

None of the RVH patients exhibited CP worsening, thereby suggesting that liver function can be maintained in RVH patients if HCC is controlled. This result also suggests that short-term functional damage of the liver that is caused by RFA does not influence long-term liver function. However, since almost all of the RVH patients in the present study belonged to the CP class A group, additional studies are needed to clarify whether long-term liver function is affected following RFA for RVH patients with poor liver function.

Nucleoside analogs such as lamivudine or entecavir are used to treat active cases of hepatitis B by inhibiting DNA synthesis with termination of the nascent proviral DNA chain. As a result, levels of both serum HBV-DNA and transaminase concentrations are rapidly reduced. When viral suppression is prolonged, this can result in histological improvement, including regression of fibrosis[19-22], and in patients with HBV-related HCC, liver function has improved[23-26]. For hepatitis C patients, IFN therapy has previously been the only treatment found to reduce levels of virus. For example, peginterferon plus ribavirin treatment has been a standard therapy for HCV infection until recently when telaprevir or simeprevir combined therapy was shown to improve the efficacy of IFN therapy[27,28]. However, since many cases of HCV-related HCC involved elderly patients, or a cirrhotic liver, there were many patients who could not receive radical treatment for HCV when HCC was detected. Other direct-acting antiviral agents have recently been investigated, and these have been found to increase SVR ratios[29,30]. Correspondingly, it is possible for HCC patients who are difficult to treat with IFN to be treated with IFN-free therapies.

While liver resection and RFA are still the standard treatments for many HCC patients, the long-term effects of surgical resection *vs* RFA remain controversial[31-33]. Thus, when many patients of HCV-related HCC become able to be treated with IFN-free therapies, this issue may be re-evaluated. In addition, further studies are needed to evaluate treatment modalities with respect to coexisting hepatitis conditions.

In conclusion, the results of the present study indicate that long-term liver function following RFA is dependent on functional reserve of the liver, the degree of fibrosis present, and hepatitis activity. Since viral eradication or suppression is currently the most effective method to improve these factors, anti-viral therapy is important even after the treatment of HCC.

COMMENTS

Background

There are only a few reports that have examined liver function following radiofrequency ablation (RFA). In particular, long-term liver function following RFA in patients with viral hepatitis-related hepatocellular carcinoma (HCC) has not been well studied.

Research frontiers

In the present study, long-term liver function in patients with viral hepatitis-related HCC that underwent RFA was found to be dependent on the functional reserve of the liver, the degree of fibrosis, and hepatitis activity.

Innovations and breakthroughs

In previous studies, liver functional reserve at the time of RFA treatment was identified as a risk factor for liver function deterioration following RFA. Here, the authors demonstrate that the degree of liver fibrosis and hepatitis activity are also associated with deterioration of liver function following RFA.

Applications

The strong and safe treatment regimen for patients with hepatitis B or hepatitis C that the authors have developed has the potential to maintain liver function following RFA treatment of patients with viral hepatitis-related HCC.

Peer-review

This is a very well done study, it demonstrates that RFA seems to be a well tolerated therapy without relationship with deterioration of liver function.

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LETTERS TO THE EDITOR

Antiviral therapy for hepatitis B virus-related hepatocellular carcinoma after surgery: A comment for moving forward

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Abstract

Recurrence rate of hepatocellular carcinoma remains quite high even after surgery, and no postoperative therapies have been definitively shown to prevent hepatocellular carcinoma recurrence. A previous study showed that therapy with nucleos(t)ide analogues given to such patients after surgery significantly improved survival. However, many questions still exist about the usage of nucleos(t)ide analogues for patients with hepatocellular carcinoma after surgery.

Key words: Antiviral therapy; Hepatocellular carcinoma; Hepatitis B virus; Unanswered question

Core tip: Some important points about the usage of nucleos(t)ide analogues for patients with hepatocellular carcinoma after surgery in clinic were pointed out.

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TO THE EDITOR

Recurrence rate of hepatocellular carcinoma (HCC) remains quite high even after curative resection or radiofrequency ablation (RFA), and no adjuvant thera-

pies have been definitively shown to prevent HCC recurrence[1,2]. A previous study showed that therapy with nucleos(t)ide analogues (NAs) given to HCC patients after resection significantly improved survival[3]. Whether the same holds for HCC patients after RFA was unclear until Lee *et al*[4] reported their important findings that postoperative NA therapy significantly reduced 2-year recurrence rate. The authors supported their conclusions using multivariate analysis and propensity score matching. These results provide by far the strongest evidence that postoperative NA therapy can benefit patients with hepatitis B virus (HBV)-associated HCC. At the same time, methodological limitations in that study raise several important questions that must be addressed in future work.

Several of these limitations are acknowledged by Lee *et al*[4] in their report. They did not take into account possible confounding effects due to differences in baseline viral load, HBeAg, liver function, or type of treatment after recurrence. In addition, their focus on recurrence rate as the most important outcome and the relatively short (2-year) follow-up prevented them from clarifying how NA therapy provided clinical benefit. NA therapy is not thought to directly affect tumor growth. Rather, it is thought to act in the short term by reducing the risk of HBV reactivation and improving liver function. Lee *et al*[4] did not measure these outcomes in their study, making it impossible to examine how NA therapy reduced the recurrence rate. NA therapy is also thought to act in the long term by: (1) suppressing viral replication, which might reduce the risk of *de novo* HBV-related HCC development; and (2) reducing chronic inflammation in the remnant liver, thereby improving hepatic functional reserve after surgery and improving the patient's treatment options. Lee *et al*[4] could not observe these mechanisms because they stopped follow-up at 2 years. As a result, Lee *et al*[4] were able to measure only early recurrence, not late recurrence, which occurs at least 2 years after surgery or RFA. The 2-year cut-off also prevented the authors from measuring overall survival, a key outcome for establishing the efficacy of any treatment.

The results of Lee *et al*[4] argue strongly for the therapeutic potential of postoperative NA therapy for patients with HBV-related HCC, but they fall short of definitively establishing the therapy as effective. To close this evidence gap, we recommend that future studies address the following questions[5]: (1) Do all patients with HBV-related HCC benefit from postoperative NA therapy? What are the indications for NA therapy? Should these indications include preoperative liver function and viral load? We note that most patients in the study by Lee *et al*[4] had early-stage tumors (< 3 cm) and cirrhosis. Also, all the patients in the former randomized controlled trial were all with relatively early-stage tumors[3]. In addition, almost all patients enrolled in previous studies had Child-Pugh A liver function[3,4,6,7]. So, further studies should investigate the benefit of NA therapy for patients with Child-Pugh B or C liver function. Last but not least, is NA therapy valuable for those with serum HBV DNA less than 500 copies/mL? (2) Which NA drug(s) are the most effective and safest? Lamivudine is the first antiviral drug. Although it suppresses the virus quickly, the frequency of drug resistance is too high. Other NA drugs include adefovir dipivoxil, entecavir, and tenofovir; (3) When is the optimal time to initiate NA therapy, and how long should it last? Nowadays, doctors and patients increasingly attach importance to the phenomenon of HBV reactivation. Therefore, NA therapy should be started before surgery. One of the purposes of NA therapy is to prevent tumor recurrence. Less than two years of therapy may be not enough; and (4) Are there benefits and risks to adding a second NA drug or continuing monotherapy? Many studies reported that combined therapy with two or more NA drugs were suitable for chronic hepatitis B. However, it is unknown for patients with HCC after surgery.

Addressing these questions will be essential for defining the NA treatment regimens most likely to provide clinical benefit, as well as for identifying the most suitable patient populations.

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