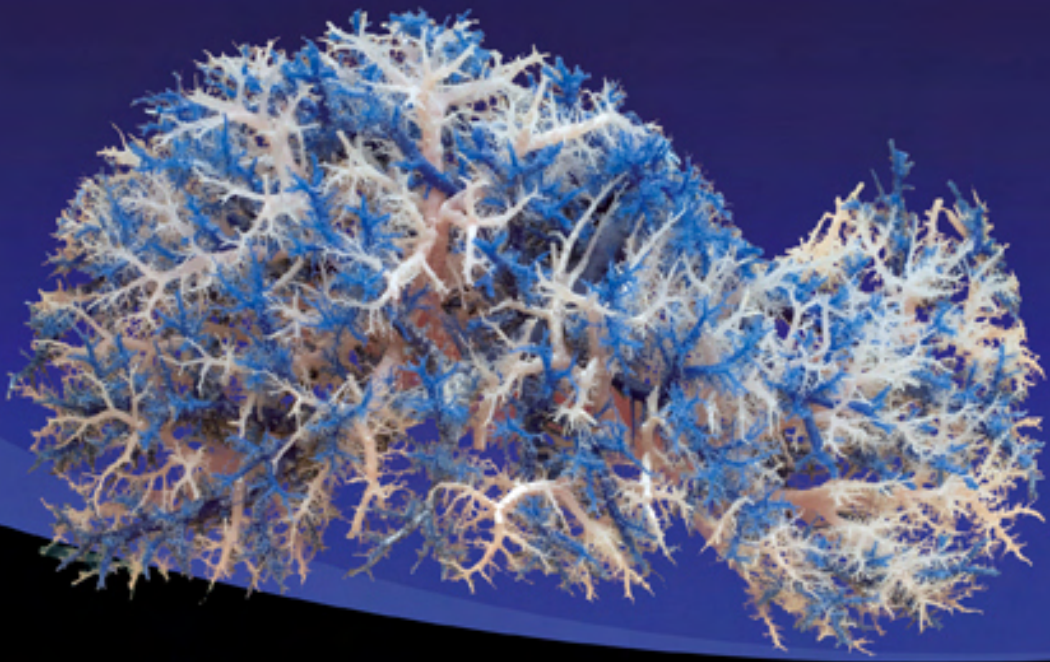
HEPATOCELLULAR CARCINOMA

Editor W. Y. Lau



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Editor

W. Y. Lau

The Chinese University of Hong Kong, Hong Kong

World Scientific

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Published by

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

Library of Congress Cataloging-in-Publication Data

Hepatocellular carcinoma / edited by W.Y. Lau.

p. ; cm.

Includes bibliographical references and index.

ISBN-13: 978-981-270-799-4 (hardcover)

ISBN-10: 981-270-799-9 (hardcover)

1. Liver--Cancer. I. Lau, W. Y.

[DNLM: 1. Carcinoma, Hepatocellular. WI 735 H5291 2007]

RC280.L5H452 2007

616.99'436--dc22

2007036670

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Typeset by Stallion Press

Email: enquiries@stallionpress.com

Printed in Singapore.

This book is dedicated to my wife Corinna, my daughter Stephanie, and my son Declan for their patience, support, encouragement, and love, and for the time stolen from them so that I can pursue an academic career.

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Preface

Hepatocellular carcinoma represents a leading cause of cancer death and a major health problem in developing countries. It has also become increasingly important with the increase in hepatitis C infection in developed countries.

Knowledge on hepatocellular carcinoma has progressed rapidly, and the paradigms for its treatment have changed in a major way during the past decade. Not too long ago, hepatocellular carcinoma was considered as a surgical disease, with liver resection being the only form of treatment with the potential for a cure; unfortunately, the operative mortality rate was very high. Now, not only has liver surgery become safe, but the best clinical practice encompasses a multidisciplinary approach including the disciplines of surgery, interventional radiology, medical oncology, hepatology, diagnostic radiology, pathology, molecular biology, and even epidemiology.

This is a multiauthor book on hepatocellular carcinoma, written by an international team of world-renowned experts covering topics in their respective areas of expertise. There are altogether 50 authors from 15 countries/regions, namely Australia, Canada, China (including mainland China, Hong Kong, and Taiwan), France, India, Italy, Japan, Singapore, Switzerland, South Africa, Thailand, the United Kingdom, and the United States of America.

This book aims to provide a fully current, fully referenced text that is as succinct as possible, but as comprehensive as necessary. It covers all topics in hepatocellular carcinoma: from epidemiology to prevention, from molecular biology to gross pathology, from anatomy to surgery, from screening to atypical presentations, from diagnosis to treatment, and from assessment to a multidisciplinary approach. It provides the

most updated knowledge in the rapidly advancing field of hepatocellular carcinoma. Controversial areas are discussed by highly regarded authorities who look at the problem from different perspectives. There is a good list of references at the end of each chapter; and there is an extensive use of diagrams, figures, and tables to make the text easy to read.

The intended readers of this book are clinicians and researchers who are interested in hepatocellular carcinoma, including liver surgeons, hepatologists, interventional and diagnostic radiologists, and basic researchers. General physicians, general surgeons, trainees, epidemiologists, hospital administrators, pathologists, and instrument manufacturers will also find this book useful as a reference.

W. Y. Lau

Acknowledgments

Acknowledgments are always difficult to write as it is never possible to acknowledge all of those who have helped contribute to a book.

I am deeply indebted to the contributions of the authors from different parts of the world who have helped to bring together this volume of information on this important subject. I am honored and thankful that so many of my friends who are renowned experts in their respective fields agreed to take time out of their busy schedules and personal lives to organize their thoughts and to share their experiences with us. In fact, the list of contributors reads like a "who's who" in the field of hepatocellular carcinoma.

From the production side at the World Scientific Publishing Company, I am grateful to Ms Sook Cheng Lim who believed that a comprehensive book on hepatocellular carcinoma was needed. The production team, especially Ms Wanda Tan, has been a joy to work with. I appreciate their dedication and professionalism to this project.

I am grateful to my secretary Ms Helena Lee for her support in compiling this book, and to Dr Eric Lai for doing the second proofreading for me.

W. Y. Lau

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1

Epidemiology

Trishe Y.-M. Leong and Anthony S.-Y. Leong

Introduction

Hepatocellular carcinoma (HCC) is one of the most common internal malignancies worldwide. In some countries of high incidence, HCC is the leading form of cancer; and overall, it rates as the seventh most common malignancy in males and the ninth most in females.[1–4]

Cancer statistics from many of the countries with a high incidence of HCC are incomplete; as such, much of the available data may represent underestimates.[5] At least one million new cases of HCC occur annually and mortality from the disease remains high despite treatment,[2–4] with recent results showing 1-year, 3-year, and 5-year overall survival rates of 66.1%, 39.7%, and 32.5%, respectively; and 93.5%, 70.1%, and 59.1% for early-stage patients, respectively.[6] Even in countries where the incidence is low, the median survival time after resection is 24.8 months compared to 5.8 months in symptomatically treated patients.[7]

Geographic Distribution

The geographic distribution of HCC worldwide is strikingly uneven (Fig. 1). Southeast Asian countries (Taiwan, Korea, Thailand, Hong Kong, Singapore, Malaysia, southern China) and tropical Africa show the highest incidence in the region of 10–20 per 100 000 population. The prevalence rates also vary among these countries, with an incidence of 150 per 100 000 population in Taiwan[2] and 28 per 100 000 population in Singapore.[8] Similarly high incidence rates are suspected in Cambodia, Vietnam, and Burma, but accurate documentation is lacking. The lowest rates of 1–3 per 100 000 population for HCC are found in Western countries, Australia, South America, and India[9]; with intermediate rates in Japan, the Middle East, and Mediterranean countries.[2–4,10,11]

In general, the incidence of HCC in migrant populations slowly equates to that of the local population with successive generations. Indians who have settled in Hong Kong and Singapore have acquired incidence rates close to those of the rest of the population and about double that of their home country, whereas the incidence among Japanese and Korean migrants in California and Hawaii has slowly decreased. The exceptions appear to be Chinese populations — who seem to be at high

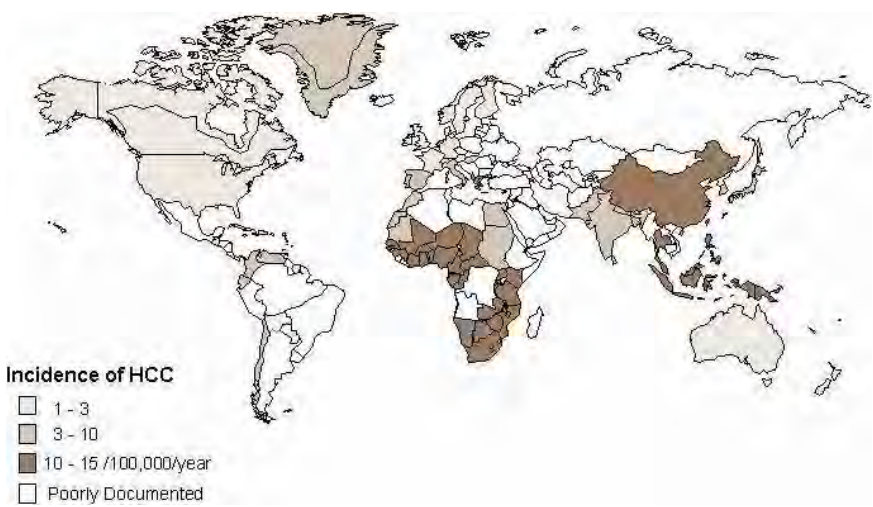

Fig. 1. Incidence of hepatocellular carcinoma worldwide.

risk regardless of location, whether it be Singapore, Shanghai, Hong Kong, or elsewhere — and Caucasians, who retain a low incidence even when living in areas of high prevalence such as Southeast Asia or Africa. This maintenance of risk has been attributed to the continuance of the lifestyle and environment of their home countries, and parallels the hepatitis B virus (HBV) carrier rates in these populations.[2,4,11,12]

This remarkable geographical distribution has prompted investigation into location-specific etiological factors. It is unlikely that HCC results from a single causative agent. As with other carcinomas, a multistep mechanism involving complex interactions between multiple etiological factors is more probable. Race and genetic factors have been found to be of no etiological significance; rather, environmental agents are closely related, in particular the prevalence of chronic HBV infection. Hepatitis C virus (HCV) infection is also emerging as a major etiological factor, with increasing rates of HCV infection thought to partly underlie the increasing incidence of HCC in the Western world.[13] The majority of HCCs arise in the setting of chronic hepatitis and cirrhosis. Carcinogenesis of hepatocytes represents a linear and progressive process in which successively more aberrant monoclonal populations of liver cells evolve. Regenerative hepatocytes in focal lesions in the inflamed liver give rise to hyperplastic nodules that progress to dysplastic nodules, which are thought to be the direct precursor of HCC. The neoplastic transformation often results from the accumulation of genetic changes during the repetitive cellular proliferation that occurs in the damaged liver.

Risk Factors

Lesser variations in the incidence of HCC have been observed in racially homogeneous countries such as Greece, Spain, and Italy. Such differences have been explained by differences in HBV carriage, alcohol consumption and smoking, or variations in exposure to hepatotoxins. Switzerland, for example, a highly developed and industrialized country, has a higher-than-average rate of HCC compared to other European nations, raising the possibility of additional risks such as exposure to hepatotoxic chemicals. In an astounding survey of 840 million people

in China during 1972–1977, it was found that the main endemic areas for HCC were along the southeast coast, particularly the deltas, valleys, and islands. In these areas, the standardized mortality rate from HCC was >60 per 100 000 people per year compared to <6 per 100 000 people per year in low-incidence areas of the country.[14] In Mozambique, a ninefold difference between the coastal and inland regions has been reported. Movement from a rural to an urban environment has also been associated with increased risk in countries like Norway and Poland, whereas the reverse seems to be true in South Africa.[2–4] Discrepancies in levels of exposure to environmental hepatotoxins and improvements in living standards are thought to be responsible for these differences.

In China, high mortality rates from HCC have been reported in coastal and riverside areas with stagnant and polluted water supplies. However, improved living standards can produce paradoxical effects: while it may reduce the incidence of HCC in some communities, studies on time trends show a steady but indisputable rise in liver cancer rates. In Japan, the rate of HCC has risen from 1.91% among 19 357 autopsies in 1958–1959 to 7.66% in 1986–1987.[5] A similar rise was observed in Los Angeles, where the rate rose from 0.15% in 1918–1953 to 1.48% in 1964–1983.[15] There seems to be a general increase in the incidence of liver cancer throughout the world, with reported increases among males and females in 24 and 26 out of 37 countries whose cancer registries were examined, respectively.[16] Florence (Italy) reported an eightfold increase; Shanghai, a twofold increase during 1959–1976; and Mexico, a twofold increase over a 25-year period.[17]

It is unlikely that HCC is due to a single causative agent. More likely, as with other carcinomas, this tumor is the result of a complex interaction between multiple etiological factors and through a multistep mechanism. The risk factors for HCC may be divided into genetic, environmental, and biological factors, the more common of these being discussed below.

Age and gender

HCC may occur from as early as 2 years of age in areas of high incidence.[18] In general, the incidence increases with age in all

populations and shows a slight decrease in the elderly. The age peak in a given region tends to be inversely related to the frequency of the tumor, i.e. the age peak is in younger patients in areas of high incidence and in elderly patients in areas of low incidence. In Mozambique, where 50% of patients with HCC are <30 years old, the incidence of the tumor among males aged 25–34 years is >500-fold that of the same age group in low-prevalence Western countries; this is in comparison to only a 15-fold difference between the elderly of both populations. Recent increases in incidence in countries such as the USA have been accompanied by a shift to a younger average patient age.[13]

HCC shows a strong male predilection, being four and eight times more common in males than females in low- and high-prevalence regions, respectively. While this finding may be partly attributed to the cumulative result of other associated factors, such as the higher incidence of cirrhosis in males as well as higher levels of smoking and alcohol intake, findings in experimental animals suggest that sex hormones and/or hormone receptors may play a role. Orchidectomy reduces the carcinogenic effects of chemicals in male rats to the level found in females. Implantation of stilbesterol or estradiol pellets produces a similar, but less marked, effect.[19,20] Most liver cancers show elevation of androgen receptors,[21,22] although the results of treatments targeting hormone action and receptors have produced variable or disappointing results.[23,24] The rate of DNA synthesis in cirrhotic livers, a factor related to the risk of carcinoma in such livers, is higher in men than in women.[25] Liver adenomas associated with androgenic or anabolic steroids may regress with withdrawal of the drug,[26] a phenomenon also seen in tumors induced by oral contraceptive steroids. Sex steroids most likely act in combination with other factors as promoters of abnormal growth.

HCC occurs in adolescence and childhood, and has been reported in children as young as 2 years of age in Hong Kong.[18] This is not unexpected in high-incidence populations, where the tumor is associated with HBV infection contracted early in life.[27] Congenital abnormalities and inborn errors of metabolism may account for some cases, especially in Western countries.[28] Other tumors, including hepatoblastoma and fibrolamellar carcinoma, have a predilection for the young.[29]

Genetic and congenital abnormalities

While a genetic susceptibility to cirrhosis and liver cancer has been demonstrated in inbred strains of mice, the same has not been established in man. Familial clustering of HCC has been described in Chinese and Alaskan natives[30,31] and cases of liver cancer have been recorded in children of several families for up to three generations,[32,33] but these have invariably been associated with chronic HBV infection as shown in the majority of cases. Analysis of major histocompatibility complex antigens among patients and controls in both South Africa and China has not revealed a link with HBV infection or liver cancer.

Rarely, liver cancer occurs in association with conditions that have a genetic, congenital, or metabolic origin. HCC has been rarely documented in familial polyposis coli,[34] ataxia telangiectasia,[35] familial cholestatic cirrhosis, congenital hepatic fibrosis, neurofibromatosis, *situs inversus*, and the fetal alcohol syndrome.[29,36]

Among the inborn errors of metabolism, the chronic form of hereditary tyrosinemia carries the highest risk of liver malignancy, with one report describing liver cancer in 16 of 43 patients.[37] Such patients showed a rapid progression from micronodular to macronodular cirrhosis within a period of a few months, and then to dysplasia and eventually HCC. To avert the latter complication, hepatectomy and liver transplantation before 2 years of age is now the recommended treatment for this condition.[38] Type I glycogen storage disease may be associated with adenomas, but carcinoma has rarely been reported. Hepatic porphyria of both intermittent and cutanea tarda types have a 61-fold increased risk for HCC.[39]

In one study of genetic hemochromatosis, 22% of patients died of HCC, representing a 219-fold increase over the general population.[40] Males are commonly affected with cirrhosis and the attendant risk of liver cancer. Iron has been suggested to have carcinogenic properties through the production of free radicals, but this has not been substantiated. Wilson's disease, another autosomal recessive disorder, also affects males more frequently and produces cirrhosis through the accumulation of copper in hepatocytes. A few cases of HCC have been reported in this

disorder, but have always been accompanied by cirrhosis. Rarely, HCC has complicated biliary cirrhosis, another condition in which excess of copper accumulates in the liver.

Alpha-1 antitrypsin (α1AT) deficiency is associated with jaundice and cirrhosis in early childhood, and with pulmonary emphysema and cirrhosis in adult life. The enzyme is synthesized in the liver and released into the blood. It is an inhibitor of serine proteinases, which include trypsin, chymotrypsin, and leukocyte elastase. In α1AT deficiency, the enzyme continues to be produced in the liver but is not secreted, accumulating as visible globules in the hepatocytes. Up to 75 allelic variants of the protease inhibitor (PI) genes control this enzyme. *PiZ* is the variant associated with low levels of serum α1AT and occurs as a homozygous, but more commonly as a heterozygous, form. The mechanisms behind the occurrence of α1AT deficiency and HCC are still not known. α1AT globules can also be seen in the tumor cells of both adenomas and carcinomas of patients who do not have the *PiZ* gene and who show no evidence of α1AT deficiency, suggesting that the failure to release the enzyme may have a promoting effect in carcinogenesis by allowing local proteases to destroy contact inhibition which otherwise occurs between transformed liver cells.[41] However, it is likely that other factors may also be operative, as the association with HCC appears to be statistically significant only for males.

Membranous obstruction of the hepatic portion of the inferior vena cava, a type of Budd–Chiari syndrome, has been associated with HCC. This condition is uncommon in the West, but is seen in Japan and India as well as among the blacks of South Africa. The lesion may be either congenital, such as due to malformation of the Eustachian valve; or acquired due to mechanical injury, infection, or thrombosis. In Japan, 29 (41%) of 71 cases developed HCC; and in South Africa, 20% of all cases with HCC showed the lesion at autopsy and 47.5% of patients with radiologically demonstrated caval obstructions developed HCC.[42] In this condition, passive congestion may act as a stimulus to hepatocyte regeneration, although the true mechanism leading to carcinoma is not known.

Cirrhosis

Cirrhosis is the most common association of HCC, being the underlying disease in 80%–90% of patients with primary liver cancer in most countries. Nonalcoholic posthepatitic cirrhosis is the most common association, but any condition that causes cirrhosis may potentially lead to HCC, including conditions such as inborn errors of metabolism, hereditary hemochromatosis, α1AT deficiency, and Wilson's disease.[37,40,43–45]

In a rare strain of rat in which severe hepatic necrosis occurs spontaneously, survivors invariably develop liver cancer after a period of chronic liver disease. Almost any form of chronic liver disease that leads to cirrhosis may be complicated by HCC; and cirrhosis, whatever the cause, is a precancerous condition.

It has been shown that cirrhotic livers with large nodules and thin intervening stroma are more commonly associated with HCC than livers with small nodules and thick stroma.[46] Larger nodules are thought to have greater regenerative activities, with increased DNA synthesis in hepatocytes, more rearrangements of DNA sequences, and hence greater vulnerability to mutagenesis following exposure to another cofactor. In patients with alcoholic cirrhosis, a higher incidence of carcinoma was noted among those who had abstained and whose micronodular cirrhosis had turned macronodular, perhaps similarly linked to the surge of regenerative activity that transforms small nodules to large ones. Clinically, patients with alcoholic cirrhosis seldom develop carcinoma while they are still imbibing.

Cirrhosis is clearly not a prerequisite for HCC, and the latter is not an inevitable consequence. The two conditions share a common cause, with some causes of cirrhosis (e.g. chronic HBV infection) being associated with a higher risk of HCC than others (e.g. alcohol).

Hepatitis B virus (HBV)

An etiological association between HBV and HCC has been clearly established, although the relationship is complex and involves other etiologic factors. About 80% of HCC cases worldwide are estimated to be etiologically associated with HBV infection,[47] and the incidence of

HCC parallels carrier rates of HBV infection. Improved control of HBV infection from universal vaccination has resulted in a recent decline in HCC in regions such as Taiwan and mainland China.[48,49]

Chronic infection with HBV imparts a 200-fold increased risk of developing HCC. Acquisition of HBV infection at birth or in early childhood is associated with the greatest risk of becoming a carrier and subsequently developing HCC. This is attributed to the immaturity of the immune system in this age group. The risk falls with increasing age to about 40% if infected in childhood and 10% risk of carrier state if infected as an adult.[50,51] Familial clustering of HCC is commonly due to HBV-related disease as a result of vertical transmission of the virus.

Carcinogenesis is thought to result from both the chronic hepatitis and cirrhosis caused by HBV, as well as from viral integration. While HBV antigens can readily be demonstrated by immunostaining in the nontumorous hepatocytes of carriers and patients with cirrhosis and HCC, they are less commonly found in the tumor cells. HBV cannot be visualized in tumor cells in a replicative form, but it can be demonstrated (once integrated) by molecular techniques. Integration of HBV DNA into the host genome always precedes the development of HCC, although the site of integration is random.[52,53] The precise effects of integration are yet to be determined. It may result in transactivation of proto-oncogenes, activation of growth factors, and inactivation of tumor suppressor genes, leading to abnormal cell growth. The *HBx* gene encoded by HBV may also contribute to the development of HCC through a variety of effects on multiple systems including cyclin A, protein kinases, and DNA repair. When HBV DNA was used as a genetic marker, identical patterns of integration were found in multifocal HCC as well as in primary tumors and their metastases, indicating an origin from a single clone of cells in which HBV integration had occurred before malignant transformation.[52,53]

Hepatitis C virus (HCV)

Hepatitis C virus is now emerging as the leading cause of HCC in Western countries. HCC rates in the United States have increased by 70% over the last two decades, with similar trends reported in

Canada and Western Europe.[47] While some of the documented increase may be artefactual as well as a result of greater availability of specialist medical services and thus increased reporting of cases,[54] at least half of this increase in the USA has resulted from HCV-related cases. Chronic infection by HCV is a leading risk factor in non-Asians.[55,56] The HCV carrier rate among Japanese blood donors is 1.2% and may be lower in Western countries. Antibodies to HCV have been found in as high as 76% of patients with HCC in Japan, Italy, and Spain.[4]

HCV causes chronic liver disease, with eventual development of cirrhosis and HCC. Unlike HBV, HCV is a single-stranded RNA virus that does not integrate into the host genome. There is currently no evidence that HCV is of itself oncogenic; however, HCC may rarely develop in noncirrhotic HCV-infected individuals, so a direct oncogenic effect cannot be excluded.

Interestingly, there are suggestions that the presence of the HBV gene in patients with chronic HCV-associated liver injury appears to promote hepatocarcinogenesis,[57,58] but this requires further confirmation. Human immunodeficiency virus (HIV) coinfection results in greater likelihood of chronicity and enhanced viral replication in both HBV and HCV infections. HIV coinfection hastens HCV-related liver disease with faster progression to cirrhosis, end-stage liver disease, and the occurrence of HCC. In contrast, current evidence suggests that HIV infection may have a negative impact on HBV-related liver disease progression, although the mechanisms for this are unclear.[59]

Other hepatitis viruses

Other hepatitis viruses have an uncertain role in hepatocarcinogenesis. There is an obligatory symbiosis between hepatitis D virus (HDV) and HBV, making the evaluation of the latter's role in hepatocarcinogenesis difficult. However, there is evidence indicating that HDV infection places additional burden on the already damaged liver, thus contributing to the risk of carcinoma. Hepatitis A and hepatitis E infections do not lead to chronic liver disease and have no carcinogenic role.

Plant carcinogens

Large doses of aflatoxins produced by the fungi *Aspergillus flavis* and *A. parasitans* are well recognized to cause severe hepatic injury. These fungi grow readily on grains, peanuts, and food products in the humid subtropical and tropical regions; and *A. flavis* is the most common cause of food spoilage in the tropics.

Regions where aflatoxin intake is common also tend to have high levels of HBV infection, making epidemiological analysis difficult, but it appears that chronic exposure to aflatoxin is carcinogenic. Chronic feeding of aflatoxin B1, the most hepatotoxic of the aflatoxins, induced liver cancer in many animal species. The intake of aflatoxin B1 by inhabitants of 10 villages in China was shown to correlate with HCC mortality rates.[60]

Higher HCC mortality rates have also been found in people who drink pond-ditch water contaminated with the blue-green algal toxin microcystin, which also causes hepatic hemorrhage and necrosis.[60] Other mycotoxins such as sterigmatocystin (produced by *Aspergillus*) as well as luteoskyrin and cyclochlorotine (metabolites of *Penicillium islandicum* found in spoilt rice and grain) have been demonstrated to have carcinogenic effects in experimental animals, but similar effects have not been established in humans.

Chemical carcinogens

Variations in HCC incidence rates within a region may also be explained by differences in levels of exposure to chemical carcinogens. Improved living conditions can result in the increased use of a wide variety of chemicals in industry and in items such as processed foods, cleaning reagents, cosmetics, and pharmaceuticals. Other chemicals like nitrites, hydrocarbons, solvents, organochlorine pesticides, primary metals, and polychlorinated biphenyls have also been implicated as potential carcinogens. Many of these are hepatotoxic and have been experimentally shown to have carcinogenic potential. Sweden, a highly developed and industrialized country, has a higher HCC rate compared to other European nations. Chinese farmers from the Qidong province who drank

ditch water contaminated with pesticides such as DDT, which was once widely used, were found to have a crude death rate from HCC of 62–110 per 100 000 population, compared to 0–11.9 deaths per 100 000 population among well-water drinkers. The sinking of more wells in the country resulted in a 20%–30% reduction in the frequency of liver cancer.[61]

Radiation and Thorotrast

The victims of the Hiroshima and Nagasaki atomic bombings did not show evidence of increased liver cancer, although there is good evidence that internal α and β radiation is carcinogenic. Thorotrast, colloidal thorium dioxide, used as an angiographic agent in the 1930s, emits high levels of α, β, and γ radiation with a long physical and biological half-life. Thorotrast accumulates in the macrophages of the reticuloendothelial system, particularly the liver; and produces hepatic fibrosis, angiosarcoma, cholangiocarcinoma, and HCC. Angiosarcoma was more commonly associated with Thorotrast in Western countries; while in Japan, both cholangiocarcinoma and HCC were more common. HCC developed at least 10 years after the deposition of Thorotrast in the liver compared to shorter intervals required for the other two tumors.

Miscellaneous factors

Malnutrition is common in many of the geographic areas with high prevalence of HCC, but the association is more likely due to HBV infection and hepatotoxins that are also prevalent in these areas. Existing information suggests that overnourishment is more likely to promote neoplastic growth, as shown by the association of a high intake of animal fat and cholesterol as well as obesity with cancer of the breast, endometrium, colon, and pancreas.[62] Prolonged parenteral nutrition in infancy may be complicated by cholestasis, liver fibrosis, and cirrhosis, with rare cases of liver cancer.[63]

There is no evidence to link parasitic infections with HCC, although the relationship between liver flukes and cholangiocarcinoma is well recognized. It is possible that certain types of medication may expedite

hepatocarcinogenesis. Anecdotal case reports have incriminated azathioprine, methotrexate, denazol, tamoxifen, and cytoproterone acetate in this role. There are also very rare reports of HCC developing in various forms of chronic liver disease, including autoimmune chronic hepatitis and primary biliary cirrhosis.

Chronic alcohol abuse often complicates HCC, especially in low-incidence areas where HBV infection is uncommon. While alcohol has been incriminated in the causation of carcinomas in the larynx, mouth, and esophagus, it has not been shown to have a carcinogenic effect in the liver. Alcohol may have a role as a cocarcinogen with other agents such as HBV, HCV, hepatotoxins, and tobacco. A population-based, case-control study of 295 HCC cases and 435 controls matched for age, gender, and race in the USA found synergistic interactions on HCC risk between heavy alcohol consumption and viral hepatitis as well as between heavy alcohol consumption and diabetes.[64] The same study also found an independent twofold-to-threefold increase in the risk of HCC with heavy alcohol consumption after adjustment for HBV and HCV serology.[64] Alcohol may also have a role through its induction of the microsomal cytochrome P450 system, which is responsible for the metabolic activation and inactivation of diverse chemical carcinogens including aflatoxins. The cytochrome P450 system is also highly inducible by smoking, which is a significant risk factor for HCC and thus has a synergistic effect with alcohol and chronic HBV infection.[65]

While a vast array of naturally occurring substances found in drinking water, foodstuffs, and native and herbal remedies have been suspected carcinogens, most of them have not been proven to be so. Among these substances are the pyrrolizidine alkaloids found in species of *Senecio, Crotalaria*, and *Heliotropium* plants; comfrey, which is used as a green vegetable; tea; and animal fodder. Cycads that contain the glycoside cycasins have been shown to be hepatotoxic and can produce liver tumors in many animals. Other substances like tannic acid in tea and coffee, as well as safrole in oils used for medicines and flavoring, are carcinogenic in rodents. Habitual betel quid chewing has also been found to be an independent risk factor for the development of HCC in humans, in addition to having a synergistic effect with HBV and

HCV infection.[66] The exact pathogenic mechanism for this is unknown, but may be related to the high proportion of safrole in betel leaf and the frequent infestation of betel nut by aflatoxin-producing species of *Aspergillus*.

Precancerous Changes and Hepatocarcinogenesis

The concept of premalignant lesions of the liver and cellular alterations preceding fully developed HCC has been controversial. Recent refinements in imaging allow the identification and resection of nodular lesions of <1 cm in diameter, and liver transplantation occasionally provides explanted liver tissues with early or premalignant lesions for more exacting morphological and molecular examination.

The diagnostic criteria for early HCC include nuclear crowding, increased cytoplasmic basophilia, and microacinar formation.[67] These criteria have been successfully employed for evaluating ultrasound-guided needle biopsies of nodular hepatic lesions.[68] Tumor size is another important criterion, as one study involving 58 resected small nodular lesions revealed every lesion exceeding 1.5 cm in diameter to be an early carcinoma.[69] However, the sizes of benign and early malignant lesions may overlap, and adenomas can exceed 2 cm in diameter. The liver cell populations that precede the development of overt metastasizing HCC are characterized by hyperplastic expansive collections of hepatocytes, which may have clear, basophilic, or acidophilic cytoplasm or may show pleomorphism and megalocytosis. The gradual loss of adult liver enzymes and the appearance of fetal enzymes accompany these features. Such changes are recognized as dysplastic nodules (adenomatous hyperplasia) and liver cell dysplasia.

Dysplastic nodules are composed of normal-appearing hepatocytes arranged in plates of one or two cells thick with areas of fatty change, and are devoid of portal tracts. It has been suggested that an increased number of arteries without corresponding bile ducts (i.e. unpaired arteries) is evidence of a dysplastic nodule.[70,71] Low-grade dysplastic nodules are defined by the absence of cellular or architectural atypia, although areas of large cell dysplasia may be present, making distinction from

ordinary regenerative nodules difficult. High-grade dysplastic nodules show focal or diffuse cytologic or architectural atypia in the form of diffuse small cell dysplasia or microacinar formation. The areas of atypia appear as subnodules or nodule-in-nodule, pushing against the surrounding hepatocytes within the dysplastic nodule. These subnodules have been shown to proliferate more rapidly than the surrounding nodule, and may be difficult to distinguish from well-differentiated HCC. They may also display iron resistance in an otherwise siderotic nodule, increased copper, fatty change, Mallory's hyaline, clear cell change, or thickened trabeculae. Details of such precancerous changes are described in Chapter 9.

In one study, about 50% of patients with biopsy-proven dysplastic nodules developed carcinoma over a 6–50-month period.[72] Cases in which carcinomas were clearly embedded within adenomatous lesion have been described, and in one report, a HBV-related carcinoma within an adenomatous lesion was shown to have an identical clonal HBV integration pattern as the surrounding hepatocytes, indicating a common origin.[73] There is also evidence that these nodules are monoclonal in nature.

Relationship of Etiological Agents and Molecular Events

It is accepted that neoplastic development is a stepwise process involving at least two or more genetic events cumulating in unrestrained cell growth, tissue invasion, and metastasis. These genetic changes may be inherited as germline mutations, which predispose to an increased risk for the development of cancer. More often, they are acquired and are the result of any one or a combination of chemical, physical, or biological insults to the cell.[74] An alternative view is that neoplastic development results from adaptive responses to environmental perturbations.[75]

Colonic carcinogenesis is the best-characterized human cancer model. The so-called adenoma–carcinoma sequence in the colon formed the basis for studying the underlying molecular events and the responsible genes. While some animal models of hepatic carcinogenesis satisfy such a sequence of events, the situation in human HCC is not as well defined.

HCCs display numerous genetic abnormalities including chromosomal deletions, rearrangements, aneuploidy, gene amplifications, and mutations, as well as epigenetic alterations such as modulation of DNA methylation. Such genetic and epigenetic alterations combine to activate positive mediators of cell proliferation and inactivate negative mediators of cell proliferation including tumor suppressor genes, resulting in autonomous growth properties. Because HCCs exhibit a high degree of genetic heterogeneity, it is likely that multiple molecular pathways may be involved in the production of subsets of hepatocellular tumors.

A detailed discussion of the molecular events in hepatocarcinogenesis is found in Chapter 10, and so only aspects associated with the epidemiology are briefly related here. HCC has revealed allele losses from chromosomes 4, 5q, 11p, 13q, 16q, and 17p (especially the latter). Mutations of *p53* have been documented in HCC-derived cell lines and in as many as 80% of liver cancers in China and southern Africa.[76,77] These mutations have commonly consisted of a transversion of G to T to C at the third base of codon 249. While *p53* mutations may have an important role in hepatocarcinogenesis, such mutations represent one of the most commonly recognized changes in human carcinomas and are generally a late event in carcinogenesis. Aflatoxin B1 causes transversion of G to T almost exclusively and preferentially binds to G residues in the GC-rich regions in codon 249 of the *p53* gene, suggesting that this mycotoxin may have a carcinogenic role in a subset of patients with HCC.

Changes in DNA methylation have been proposed to be an essential step in carcinogenesis, as they relate to the regulation of gene expression and cellular differentiation. DNA hypomethylation has been reported in chemical hepatocarcinogenesis,[78] but increases in deoxycytosine methylation have been reported following ingestion of the carcinogen methapyriline.[79] Prolonged feeding of diets deficient in sources of transferable methyl groups such as choline and methionine induced a high incidence of HCC in rats.[80]

The relationship between cirrhosis and HCC is well accepted, but the reason is largely unknown. It has been suggested that a deficiency in the ability to repair O^6-methylguanine DNA underlies this

increased risk, although this may be only one of several contributory factors.[81] A proposed sequence of hepatocarcinogenesis has been described.[82]

Alcohol cannot be considered as a *bona fide* promoting agent for HCC, and appears to act through its induction of cirrhosis and through the modulation (in an as yet ill-defined manner) of the process of carcinogenesis with other recognized carcinogenic agents such as HBV and HCV.[83] The association of HBV and HCC is strong; and in addition to the supporting arguments made earlier, hepatoma cell lines have successfully produced hepatitis B surface antigen (HBsAg) and have been demonstrated to have integrated HBV DNA. HBV DNA integration is almost invariably present in HBsAg-positive HCCs. The presence of such integration in the nontumorous hepatocytes of these livers further indicates that integration precedes carcinogenesis; however, no oncogenes have been identified yet within the HBV genome. While the virus is frequently fragmented after it integrates into the hepatocyte genome, the *HBx* gene appears to be consistently retained in a functional form, leading to speculation of its role in carcinogenesis. In tissue cultures, the X protein acts as a transcriptional transactivator of viral genes, and it is possible that this protein may alter host gene expression in a manner that leads to HCC formation. Transgenic mice harboring the *HBx* gene develop multifocal areas of altered hepatocytes, benign adenomas, and eventually HCC.[84] Studies in *HBx* transgenic mice indicate that the *HBx* gene has mitogenic activity both *in vitro* and *in vivo*, and suggest that the *HBx* gene contributes to hepatocarcinogenesis by driving cells into deregulated cell cycle control.[85]

Finally, a causal association between HBV and HCC is supported by numerous studies of three hepadnaviruses, which are phylogenetically related to the human HBV. These occur in the Eastern woodchuck (*Marmota manax*), Beechey ground squirrel (*Spermophilus beecheyi*), and Peking duck (*Anas domesticus*), in which persistent antigenemia is associated with the development of HCC.[86]

Much important information has been accumulated on the molecular and genetic events leading up to HCC, especially in the experimental model. However, the genes involved and the mutations necessary for hepatocarcinogenesis still remain largely unknown.[87,88]

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2

Liver Terminology and Anatomy

Steven M. Strasberg

This chapter presents modern terminology of liver anatomy and resection. It is also an introduction to surgical anatomy of the liver. No single chapter can describe the anatomy of the liver in detail. The intention is to provide an anatomical foundation for performing liver resection and a terminological foundation for describing those procedures so that surgeons around the world can understand each other when they communicate orally or in writing. Surgically unimportant anatomic features are omitted. The chapter has two parts. The first part deals with terminology; the anatomical concepts introduced are those necessary to explain the basis of the terminology selected. The second part deals more formally with surgical anatomy.

Terminology

The importance of hepatic terminology

Terminology (or nomenclature) is the vocabulary of technical terms used in a particular field, subject, science, or art. The *terminology of hepatic*

anatomy and liver resections is the basis for communication among hepatic surgeons. Before the introduction of the Brisbane 2000 terminology of liver anatomy and resections under the auspices of the International Hepato-Pancreato-Biliary Association (IHPBA),[1] there was no terminological system sanctioned by a major international organization. Surgical texts and articles usually contained a jumble of confusing terms, and oral presentations were likewise often difficult to comprehend. This problem still persists today because, although the IHPBA terminology is being widely used, it has yet to achieve universal penetration.

The Brisbane 2000 terminology of liver anatomy and resections

The anatomical divisions of the liver are based on vascular and biliary anatomy rather than on surface markings. The anatomical ramifications of the hepatic artery and bile ducts are regular and virtually identical. The Brisbane 2000 terminology is based on the arterial and biliary watersheds in the liver.[1] Liver anatomy and the basis for hepatic terminology are best understood by first following these structures through a series of three orderly divisions.

First-order division

The first-order division is based on the terminal branching of the proper hepatic artery into the right and left hepatic arteries (Fig. 1). This results in the division of the liver into two parts or volumes, referred to as *right and left hemilivers or livers* (Fig. 2). The right hepatic artery supplies the right hemiliver, and the left hepatic artery supplies the left hemiliver. The plane between these two zones of vascular supply is called a watershed. The watershed of the first-order division is a plane that intersects the gallbladder fossa and the fossa for the inferior vena cava (Fig. 2). This plane is called the *midplane of the liver*. It has previously had at least eight other names,[2] most of which are either linguistically or anatomically incorrect (e.g. Cantlie's line). The right liver usually has a larger volume than the left liver (60:40), although this is variable.

The bile ducts, which are supplied with blood along their course exclusively by the hepatic artery, have a branching pattern identical to

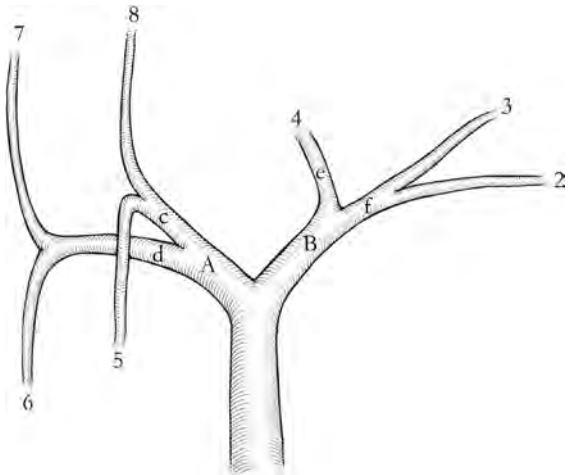

Fig. 1. Ramification of the hepatic artery in the liver. The prevailing pattern is shown. The proper hepatic artery divides into the right (A) and left (B) hepatic arteries, which supply the right and left hemilivers (Fig. 2), respectively. The right hepatic artery divides into anterior (c) and posterior (d) sectional arteries, which supply the right anterior and right posterior sections (Fig. 3). The right anterior sectional artery divides into two segmental arteries that supply Sg 5 and Sg 8 (Fig. 4), while the right posterior sectional artery divides into arteries that supply Sg 6 and Sg 7. The left hepatic artery (B) also divides into two sectional arteries, the left medial (e) and left lateral (f) sectional arteries. The former supplies the left medial section (Fig. 3), also called Sg 4; while the latter supplies the left lateral section. The left lateral sectional artery divides into segmental arteries to Sg 2 and Sg 3 (Fig. 4). The caudate lobe (Sg 1 and Sg 9) is supplied by branches from A and B. Bile duct anatomy and nomenclature are similar to those of the hepatic artery.

the arteries and divide into right hepatic and left hepatic ducts. They drain the same liver volumes as the arteries supply. Because flow in bile ducts is into ever-larger ducts as opposed to hepatic arteries, the union of two bile ducts is more properly referred to as a *confluence* rather than a branch.

Second-order division

The second-order division (Figs. 1 and 3) is based on the terminal branching of the right and left hepatic arteries into two sectional

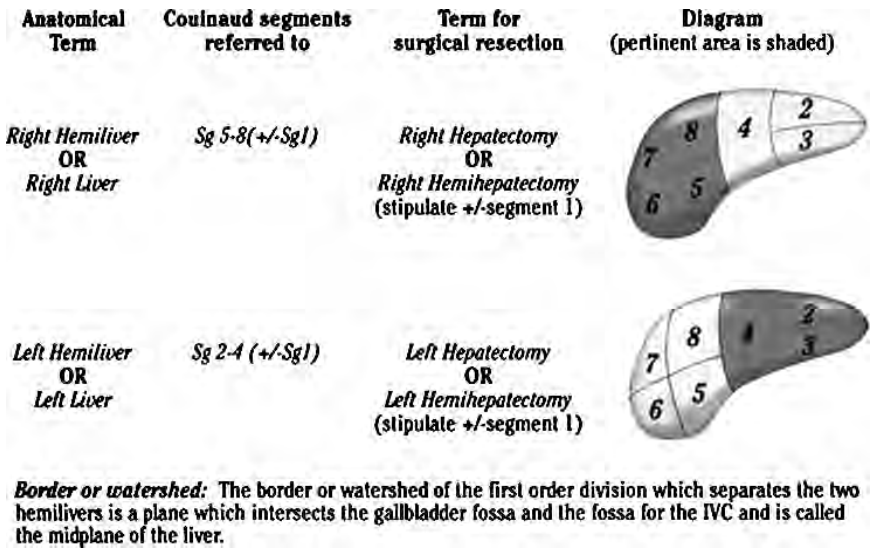

Fig. 2. Nomenclature for first-order division anatomy (hemilivers) and resections.

branches. Each of these sectional vessels supplies a defined volume referred to as a *section*; therefore, there are four hepatic sections in total. On the right side, there is a *right anterior section* and a *right posterior section*. These sections are supplied by the right anterior sectional hepatic artery and the right posterior sectional hepatic artery (Fig. 1), respectively. The sections are also drained by a right anterior sectional hepatic duct and a right posterior sectional hepatic duct, respectively. The plane between these sections is the *right intersectional plane*. Unlike the midplane and the left intersectional plane, the right intersectional plane has no markings on the hepatic surface.

The left liver is divided into a *left medial section* and a *left lateral section* (Fig. 3). These sections are supplied by a left medial sectional hepatic artery and a left lateral sectional hepatic artery (Fig. 1), respectively, and are drained by a left medial sectional hepatic duct and a left lateral sectional hepatic duct, respectively. The plane between these sections is referred to as the left intersectional plane, and corresponds to the umbilical fissure and the line of attachment of the falciform ligament to the anterior surface of the liver.

Anatomical Term	Couinaud segments referred to	Term for surgical resection	Diagram (pertinent area is shaded)
Right Anterior Section	*Sg 5,8*	Add (-ectomy)to any of the anatomical terms as in *Right anterior sectionectomy*	
Right Posterior Section	*Sg 6,7*	*Right posterior sectionectomy*	
Left Medial Section	*Sg 4*	*Left medial sectionectomy* **OR** *Resection segment 4* (also see Third order) **OR** *Segmentectomy 4* (also see Third order)	
Left Lateral Section	*Sg 2,3*	*Left lateral sectionectomy* **OR** *Bisegmentectomy 2,3* (also see Third order)	

Other "sectional" liver resections

Sg 4-8 (+/-Sg1)	*Right Trisectionectomy* *(preferred term)* **or** *Extended Right Hepatectomy* **or** *Extended Right Hemihepatectomy* (stipulate +/-segment 1)	
Sg 2,3,4,5,8 (+/-Sg1)	*Left Trisectionectomy* *(preferred term)* **or** *Extended Left Hepatectomy* **or** *Extended Left Hemihepatectomy* (stipulate +/-segment 1)	

Border or watershed: The borders or watersheds of the sections are planes referred to as the *right and left intersectional planes*. The left intersectional plane passes through the umbilical fissure and the attachment of the falciform ligament. There is no surface marking of the right intersectional plane.

Fig. 3. Nomenclature for second-order division anatomy (sections) and resections.

Third-order division

The third-order division into the numbered *segments* is based on the terminal branching of the sectional arteries and bile ducts (Figs. 1 and 4). Each of the right sectional arteries and bile ducts as well as the left lateral sectional artery and bile duct terminate by dividing regularly into two branches, each of which in turn supplies one segment. Therefore, the right anterior, right posterior, and left lateral sections each contain two segments. However, the left medial sectional artery and bile duct terminate in two or more branches and there is no dominant pattern of division. As a result, by convention, the left medial section has only one segment: segment 4. In other words, the level 2 and level 3 volumes (left medial section and segment 4) are identical.

The right anterior section is divided into two segments, 5 and 8; the right posterior section is divided into segments 6 and 7; and the left lateral section is divided into segments 2 and 3. The planes between these segments are referred to as intersegmental planes. The left medial section is designated as a single segment — segment 4 — as explained

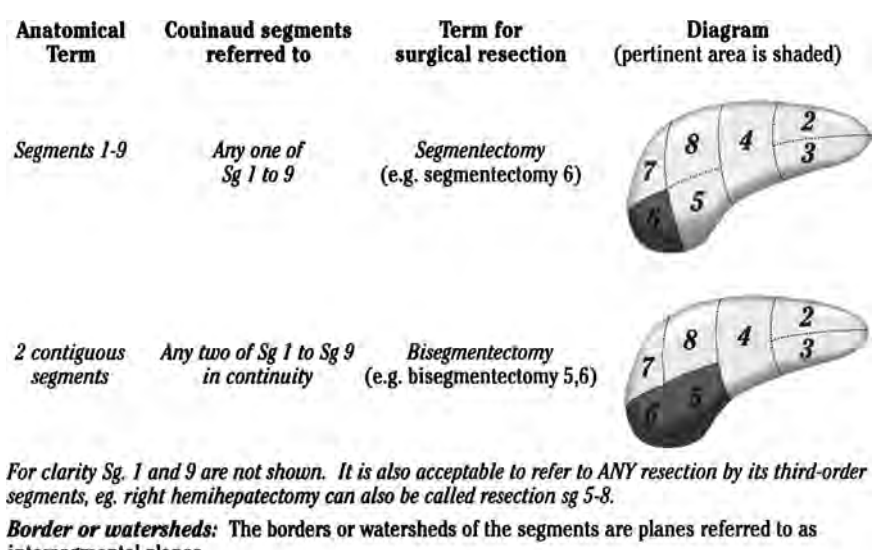

Fig. 4. Nomenclature for third-order division anatomy (segments) and resections.

above; for ease of localization of lesions, it has been arbitrarily divided into Sg 4a (superior) and Sg 4b (inferior) by a plane passing halfway between the superior and inferior limits of the segment.

The caudate lobe is a unique portion of the liver that lies behind the plane of attachment of the major vasculobiliary structures entering the liver at the hilum. It is separate from the right and left hemilivers, and their sections and segments. Its vascular supply and biliary drainage arise from posteriorly coursing branches of the right and left hepatic arteries (and portal veins) and bile ducts, and occasionally the right posterior sectional artery and bile duct. It is appropriately referred to as a lobe, since it is demarcated by visible fissures. The caudate lobe is considered to be segment 1. The more superior portion of the lobe has been described to be a separate segment based on a unique blood supply and vascular drainage (segment 9). This completes the discussion of the anatomical basis of hepatic terminology.

The terminology of hepatic resections is based upon the terminology of hepatic anatomy. Therefore, resection of one side of the liver is called a hepatectomy or hemihepatectomy (Fig. 2). Resection of the right side of the liver is termed right hepatectomy or hemihepatectomy, while resection of the left side of the liver is termed left hemihepatectomy or hepatectomy. Resection of a liver section is referred to as a sectionectomy (Fig. 3). Resection of the liver to the left side of the umbilical fissure is referred to as a left lateral sectionectomy. The other sectionectomies are named accordingly, e.g. right anterior sectionectomy. Resection of the whole right liver plus Sg 4 is referred to as a right trisectionectomy (Fig. 3); it can also be called a right hepatectomy extended to Sg 4. The former is preferred because it implies that all of Sg 4 is resected, whereas the latter may or may not. Similarly, resection of the left hemiliver plus the right anterior section is referred to as a left trisectionectomy (Fig. 3).

Resection of one of the numbered segments is referred to as a segmentectomy (Fig. 4). Resection of the caudate lobe can be referred to as a caudate lobectomy or resection of Sg 1 (and Sg 9). It is always appropriate to refer to a resection by the numbered segments. For instance, it would be appropriate to call a left lateral sectionectomy a resection of Sg 2 and Sg 3. For an understanding of how the consensus on this

terminology was reached (including a discussion on the attributes of the terminology), the reader is referred to the original literature on this subject.[1]

Surgical Anatomy for Liver Resections

The following is an overview on this subject. For detailed discussions of the prevailing pattern and variations of surgical anatomy, the reader is referred to the original literature.[3–8] A key point regarding surgical anatomy of the liver is that there is a prevailing pattern of anatomy (i.e. a pattern which is most commonly found), although variations from the prevailing pattern are frequent. Each surgical patient should be approached with the idea that the prevailing pattern of anatomy may not be present.

The prevailing pattern is the most common anatomical pattern, and it may be present almost always or in less than 50% of patients. *Anomalies* are variations from the prevailing pattern, and may be common or rare. They may be anomalies of position, number, or size of structures. *Aberrancy* refers to abnormal position of a structure. An *accessory* structure is one that is in addition to the normal structures in the prevailing pattern and whose function can be deleted without loss of overall function of the organ. The term *replaced* is used synonymously with aberrant when referring to aberrant arteries in the liver.

Hepatic arteries and liver resections

In the prevailing pattern, the common hepatic artery arises as one of the two terminal branches of the celiac artery in the retroperitoneum near the superior border of the pancreas, about 1–2 cm to the left of the axis of the superior mesenteric vein (SMV)–portal vein axis. It runs anteriorly and to the right for 2–3 cm to divide into gastroduodenal and proper hepatic arteries. The proper hepatic artery normally runs upward toward the liver for 2–3 cm anterior to the portal vein and along the left side of the common bile duct to terminate into the right and left hepatic arteries, the larger right artery immediately passing behind the common hepatic duct. The four sectional arteries described above arise

from the right and left arteries 1–2 cm from the liver and penetrate the liver. Segmental arteries arise within the liver substance.

Variations from the prevailing pattern are very common, and may involve the position or branching pattern of the arteries. For instance, the hepatic artery may arise, albeit rarely, directly from the aorta. The common or proper hepatic artery may either pass under the portal vein and emerge between that structure and the bile duct or even wind around the underside of the bile duct before emerging, although the latter is very rare. The common hepatic artery may be very short and its bifurcation into right and left hepatic arteries may lie very low in the porta hepatis, just a few millimeters from the origin of the gastroduodenal artery; or the common hepatic artery may simply trifurcate into the gastroduodenal artery, right hepatic artery, and left hepatic artery. On rare occasions, the common hepatic artery divides into the left hepatic artery and a common trunk for the gastroduodenal and right hepatic arteries. This situation is more dangerous in pancreatic surgery than in hepatic surgery because the common trunk may be considered to be the gastroduodenal artery and divided, thus depriving the right liver and bile ducts of arterial supply. Probably the most well-recognized variation of hepatic arterial anatomy is that in 20% of patients the right hepatic artery courses in front of rather than behind the bile duct. Another common variation of importance, especially in any split liver surgery, is anomalous division of the right or left hepatic arteries into their sectional branches. For instance, there may be no left hepatic artery — the proper hepatic artery may branch into a left lateral sectional artery and a common trunk artery supplying the right liver and the left medial section (segment 4), with the branch to the latter coming off downstream. The branch to the left medial section arising in this way is sometimes called the "middle hepatic artery" — an imperfect term, since it does not indicate the volume supplied.

One of the most important types of hepatic arterial variation is "replaced" arteries. In many patients, part or all of the liver is supplied by a replaced (or aberrant) artery. The *replaced right hepatic artery* is a structure present in about 20% of patients. It arises from the superior mesenteric artery (SMA) and runs from left to right behind the lower end of the bile duct to emerge and course on its right posterior border.

It may supply a segment, a section, or the whole right hemiliver. This artery sometimes supplies the entire liver and is then called a *replaced hepatic artery*. The *replaced left hepatic artery* arises from the left gastric artery in about 15% of patients, and courses in the lesser omentum in conjunction with vagal branches to the liver (hepatic nerve). Like the right artery, it may supply a segment, a section (usually the left lateral section), a hemiliver, or very rarely the whole liver. Sometimes, left hepatic arteries arising from the left gastric artery are actually accessory arteries, which exist in conjunction with normally situated left hepatic arteries; this is less commonly true of right hepatic arteries arising from the SMA. Transection of the left gastric artery at its origin during gastrectomy has led to devascularization of the left hemiliver in the presence of a replaced left artery, and the same has occurred on the right side as a result of injury to a replaced right artery. In some cases, there is no proper hepatic artery because the entire liver is supplied by right or left replaced arteries or by both; this may be suspected when opening the peritoneum at the base of the left side of the hepatoduodenal ligament, since in these cases the portal vein rather than a hepatic artery is exposed. Replaced arteries occasionally confer an advantage during surgery. For instance, in the case of a replaced left artery supplying the left lateral section, it is possible to resect the entire proper hepatic artery when performing a right trisectionectomy for hilar cholangiocarcinoma.

The preceding is only an overview of possible arterial variations. The interested reader is referred to Michels' classic monograph[5] for a complete description.

When performing hepatectomies using the standard technique, it is important to isolate the arteries going to the side of the liver to be resected. A useful anatomical point is that an artery located to the right side of the bile duct supplies the right side of the liver, but arteries found on the left side of the bile duct may supply either side of the liver. However, the surgeon would be wise not to make assumptions regarding hepatic arteries based on size or position and rely instead on complete dissection, trial occlusions, and radiological support. A trial occlusion of an artery with an atraumatic clamp, such as a bulldog clamp, should always be performed in order to be sure that there is a good pulse to the side of the liver to be retained. When an artery which is to be

ligated appears unusually large, it is especially important to dissect until identification is unquestionable.

Bile ducts and liver resections

Prevailing pattern and anomalies of bile ducts draining the right hemiliver

Normally, only a short portion of the right bile duct, about 1 cm, is in an extrahepatic position. The prevailing pattern of bile duct drainage from the right liver is shown in Fig. 5A. As noted previously, segmental ducts from Sg 6 and Sg 7 (called B6 and B7, respectively) unite to form the *right posterior sectional bile duct*, while the segmental ducts from Sg 5 and Sg 8 (B5 and B8) unite to form the *right anterior sectional bile duct*. These sectional ducts unite to form the *right hepatic duct*, which unites with the left hepatic duct at the *confluence* to form the common hepatic duct. The right *posterior* sectional duct normally hooks over the origin of the right *anterior* sectional portal vein (Hjortsjo's Crook), where it is in danger of being injured if the right anterior sectional pedicle is clamped too close to its origin (Fig. 6).

Two surgically important sets of biliary anomalies exist on the right side of the liver. The first is the anomalous union of a right sectional duct with the left bile duct *to the left of the midplane*; this is a common anomaly. The right posterior sectional duct inserts into the left bile duct in this way in 20% of patients (Fig. 5B), and the right anterior bile duct does so in 6% (Fig. 5C). In both cases, there is no right hepatic duct as both join the left duct, one to the left of the midplane and the other in the midplane. A right sectional bile duct inserting into the left bile duct to the left of the midplane is in danger of injury during left hepatectomy. Therefore, in left hepatectomy, the left bile duct should be divided close to the umbilical fissure so as to avoid injury to a right sectional duct (Fig. 5B, "correct"). If the left duct is divided at its termination at the normal site of confluence of the right and left hepatic ducts, the right sectional duct can be injured (Fig. 5B, "incorrect"). It is good practice to obtain an intraoperative cystic duct cholangiogram when performing a left hepatectomy to detect this anomaly.

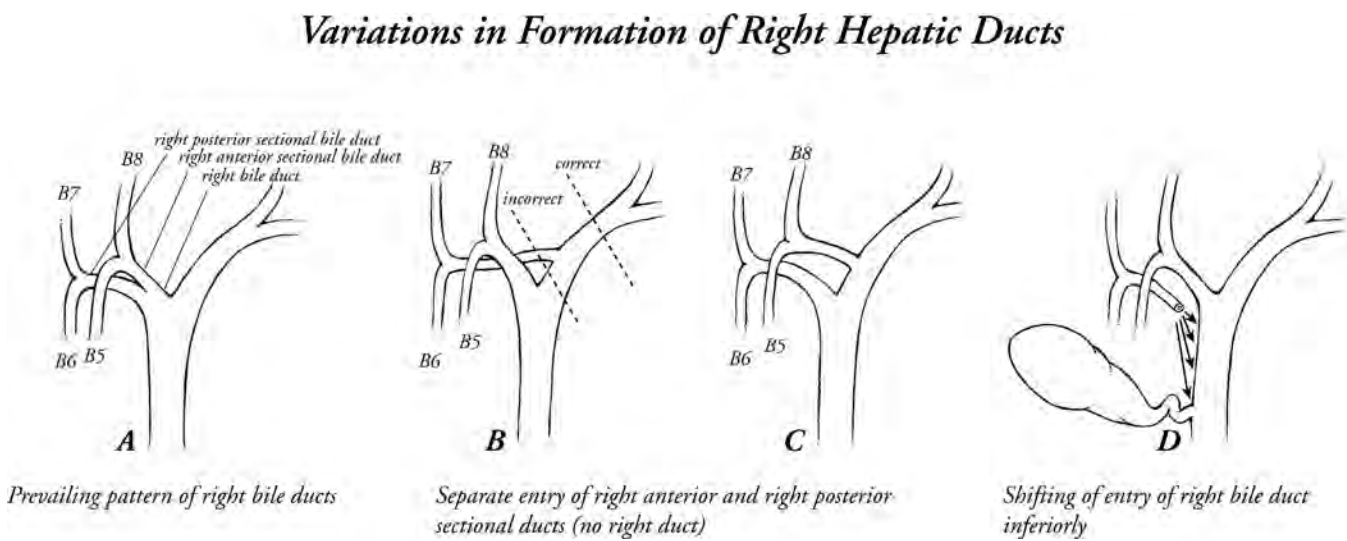

Fig. 5. Prevailing pattern and important variations of bile ducts draining the right hemiliver.

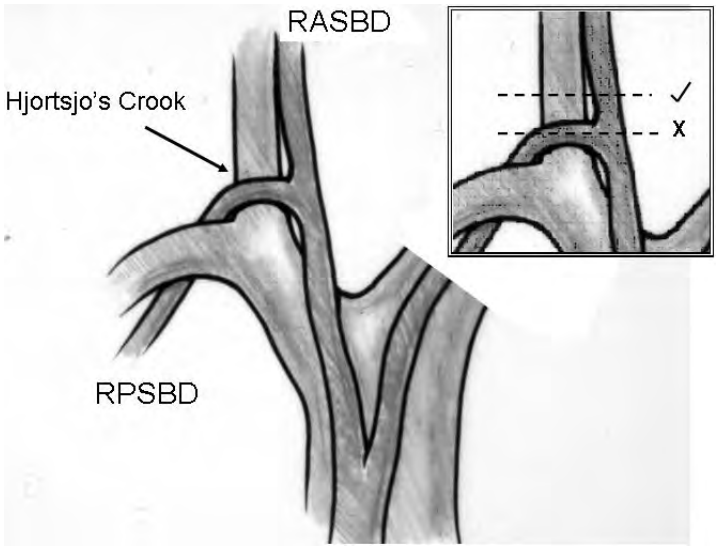

Fig. 6. Hjortsjo's Crook. Note that the right posterior sectional bile duct (RPSBD) crosses the origin of the right anterior sectional portal vein. RASBD = right anterior sectional bile duct.

The second important set of anomalies is insertion of a right bile duct into the biliary tree at a lower level than the prevailing site of confluence (Fig. 5D). Low union may affect the main right bile duct, a sectional right duct (usually the anterior one), a segmental duct, or a subsegmental duct. The duct will unite with the common hepatic duct below the prevailing site of confluence or, in about 2% of patients, unite first with the cystic duct and then with the common hepatic duct. The latter anomaly places the duct at great risk for injury during laparoscopic cholecystectomy.

Prevailing pattern and important variations of bile ducts draining the left hemiliver

The left hepatic duct has a much longer extrahepatic course than the right bile duct. Normally, a 2–3-cm length of the left hepatic bile duct is in an extrahepatic position. This portion of the left duct extends from the confluence of the right and left bile ducts along the base of Sg 4,

two thirds of the way toward the umbilical fissure. The importance of this relates mainly to bile duct reconstruction since this portion of the duct is readily available for this purpose, unlike on the right side.

The prevailing pattern of bile duct drainage from the left liver is shown in Fig. 7A and is present in only 30% of individuals, i.e. variations are present in the majority of individuals. The segmental ducts from Sg 2 and Sg 3 (B2 and B3, respectively) unite to form the *left lateral sectional bile duct.* This duct passes behind the umbilical portion of the portal vein and unites with the duct from segment 4 (B4), also called the left medial sectional duct. The union of these ducts to form the left hepatic duct occurs about one third of the distance between the umbilical fissure and the confluence of left and right bile ducts.

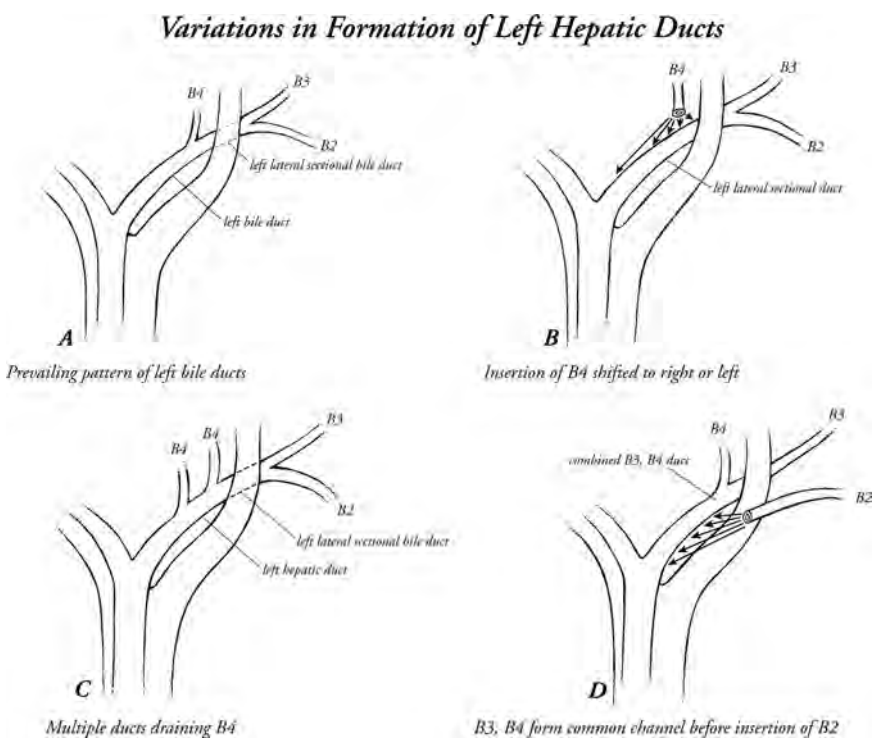

Fig. 7. Prevailing pattern and important variations of bile ducts draining the left hemiliver.

The surgically important anomalies of the left ductal system involve variations in site of insertion of B4 (Fig. 7B), multiple ducts coming from B4 (Fig. 7C), and primary union of B3 and B4 with subsequent union of B2 (Fig. 7D). B4 may join the left lateral sectional duct to the left or right of its point of union in the prevailing pattern (Fig. 7A). In the former case, the insertion of B4 is at the umbilical fissure; while in the latter, the insertion may occur at any place to the right of the prevailing location up to the point where the left lateral sectional duct unites with the right bile duct. In the latter instance, which according to Couinaud[7] is present in 8% of individuals, there is no left hepatic duct; instead, the common hepatic duct is formed by the confluence of three ducts — the right hepatic duct and two left hepatic ducts (B4 and the left lateral sectional duct).

The left hepatic duct runs at a variable angle. In some individuals it is almost horizontal, but in others it runs sharply upward. It is much easier to expose a long length of duct in the former type. The angle of the duct is readily visible on cholangiography, thus helping to prepare the surgeon for the increased difficulty of dissection that may sometimes be present due to this factor.

Prevailing pattern of bile ducts draining the caudate lobe (Sg 1)

Normally, two or three caudate ducts enter the biliary tree. Their orifices are usually located posteriorly on the left duct, right duct, or right posterior sectional duct. This is fortunate as they are less prone to injury.

Portal vein and liver resections

On the right side of the liver, the portal vein divisions correspond exactly to those of the hepatic artery and bile duct and supply the same hepatic volumes. The right portal vein supplies the entire right hemiliver (Fig. 8). It divides into two sectional and four segmental veins, as do the arteries and bile ducts. The left portal vein consists of a *horizontal or transverse portion*, which is located under Sg 4, and a *vertical or umbilical portion*, situated in the umbilical fissure (Fig. 8). The transverse portion of the left portal vein sends only a few small branches to Sg 4. Large branches from

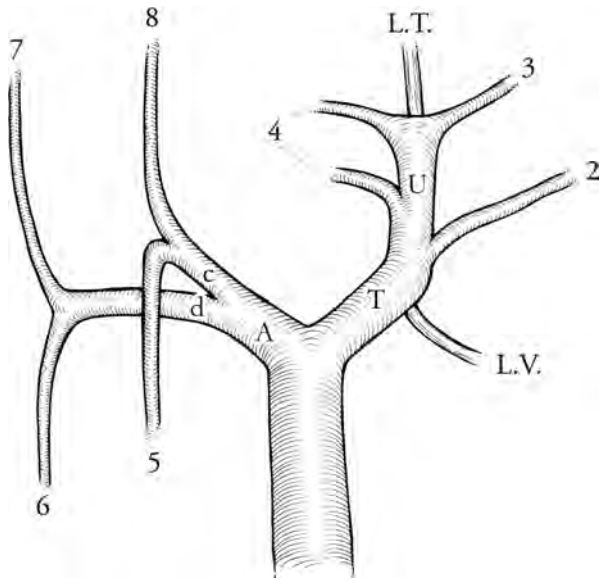

Fig. 8. Ramification of the portal vein in the liver. The portal vein divides into right (A) and left (T) branches. The branches in the right liver correspond to those of the hepatic artery and bile duct (Fig. 1). The branching pattern on the left is unique. The left portal vein has transverse (T) and umbilical portions (U). The transition point between the two parts is marked by the attachment of the ligamentum venosum (L.V.). All major branches come off the umbilical portion (see text). The vein ends blindly in the ligamentum teres (L.T.).

the portal vein to the left liver arise exclusively beyond the attachment of the ligamentum venosum, i.e. from the umbilical part of the vein.[8] These branches come off both sides of the vein: those arising from the right side pass into Sg 4, and those from the left supply Sg 2 and Sg 3. There is usually only one branch to Sg 2, but more than one branch to Sg 3 and Sg 4. The left portal vein terminates where it joins the ligamentum teres at the free edge of the left liver.

Note that the umbilical portion of the portal vein has a unique pattern of ramification. The pattern is similar to an air-conditioning duct that sends branches at right angles from both of its sides to supply rooms (segments), tapering as it does so, finally to end blindly (in the ligamentum teres). Other vascular and biliary structures normally ramify by dividing into two at their termination, not by sending out branches

along their length. The explanation for the unique structure of the umbilical portion of the left portal vein is that it is adapted to a dual function: *in utero*, it acts as a conduit between the umbilical vein and the ductus venosus, a conduit in which blood flows downward toward the ductus venosus; in adult life, it acts as a conduit for portal vein supply to the left liver, and blood flows *in the reverse direction* upward from the ligamentum venosum toward the ligamentum teres. It is for this reason that the umbilical portion of the portal vein is like an air-conditioning duct. It is also because its branching pattern on the left side is so structurally different from the branching pattern on the right side and from the branching pattern of the hepatic artery or the bile duct on either side of the liver that the latter structures were used by the framers of the Brisbane 2000 terminology as the basis of hepatic division.

The junction of the transverse and umbilical portions of the left portal vein is marked by the attachment of a stout cord — the ligamentum venosum. This structure, the remnant of the fetal ductus venosus, runs in the groove between the left lateral section and the caudate lobe and attaches to the left hepatic vein–inferior vena cava (IVC) junction. The umbilical portion of the portal vein may be visible in the umbilical fissure or hidden by a bridge of tissue passing between left medial and lateral sections. This bridge may simply be a fibrous band, but more commonly is composed of liver tissue. The bridge may be divided by passing a blunt instrument behind it and in front of the ligamentum teres and the umbilical portion of the left portal vein. To facilitate passage of an instrument behind the bridge, the peritoneum at the base of the bridge may be opened in a preliminary step. The instrument being passed behind the bridge should never be forced. Care must be taken not to damage the left lateral sectional artery, which lies close to the posterior edge of the bridge.

Although the divisions of the portal vein are unusual for the embryonic reasons described above, it is uncommon to have variations from this unusual pattern. Probably the most common variation is absence of the right portal vein. In this anomaly, the right posterior and right anterior sectional portal veins originate independently from the main portal vein. When this occurs, the anterior sectional vein is usually quite high in the porta hepatis and may not be obvious. An unsuspecting surgeon may divide the posterior sectional vein, thinking that it is the

right portal vein, and will consequently be confused when the anterior sectional vein is come upon during hepatic transection.

A rare, but potentially devastating, anomaly is the absent extrahepatic left portal vein.[7] In this case, the apparent right vein is actually the main portal vein, a structure which enters the liver, gives off the right veins, and then loops back within the liver substance to supply the left side. The vein looks like a right vein in terms of position, but it is larger. Transection results in total portal vein disconnection from the liver. This anomaly should always be searched for on computed axial tomography (CAT) scans, as right hepatectomy is not usually possible when it is present. Identification of the umbilical portion of the left vein in the umbilical fissure on CAT scan precludes the presence of this problem.

The portal vein branches to Sg 4 may be isolated in the umbilical fissure on the right side of the umbilical portion of the left portal vein. The veins here are associated with the bile ducts and the arteries passing to Sg 4. Isolation in this location may provide an extra margin when resecting a tumor in Sg 4 that impinges upon the umbilical fissure. Normally, the branches to Sg 4 are isolated after dividing the parenchyma of the liver of Sg 4 close to the umbilical fissure, an approach used to avoid injury to the umbilical portion of the left portal vein. Injury to this vein would of course deprive Sg 2 and Sg 3, as well as Sg 4, of portal vein supply. However, isolation of these structures does provide an extra margin and can be done safely if care is taken to ascertain the position of the portal vein. Likewise, it is possible to isolate the portal vein branches going into Sg 2 and Sg 3 in the umbilical fissure and to extend a margin when resecting a tumor in the left lateral section. For the same reasons given above, great caution must be taken when doing this so as not to injure the umbilical portion of the portal vein. In order to access the portal vein in this location, it is necessary to divide the bridge of liver tissue between the left medial and lateral sections.

Hepatic veins and liver resections

Three large hepatic veins drain the liver (Fig. 9). These run in the midplane of the liver (middle hepatic vein), the right intersectional plane (right hepatic vein), and the left intersectional plane (left hepatic vein).

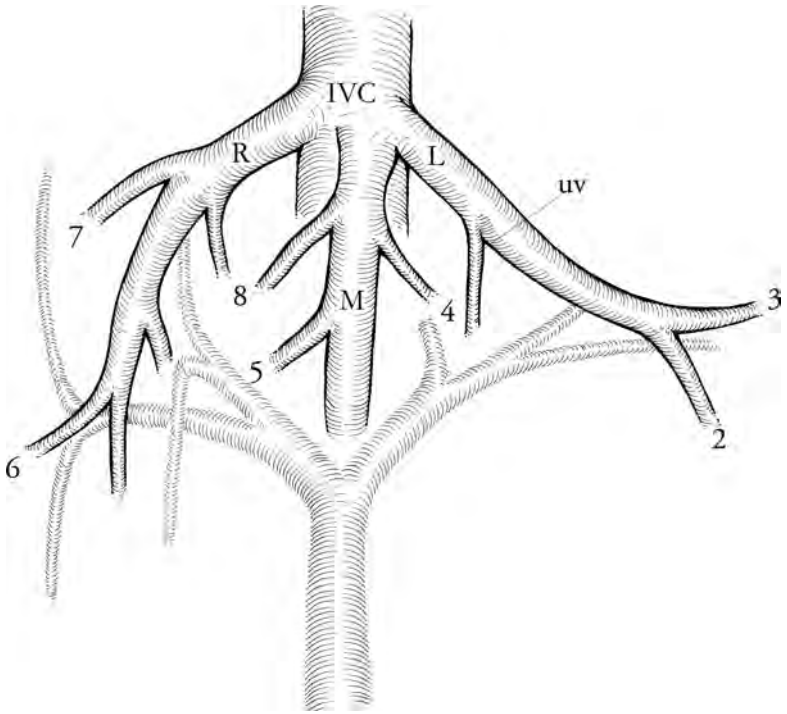

Fig. 9. Hepatic veins. There are normally three hepatic veins: right (R), middle (M), and left (L) hepatic veins. Note the segments drained. UV is the umbilical vein, which normally drains part of Sg 4 into the left hepatic vein. The latter is proof that the terminal portion of the left vein lies in the intersectional plane of the left liver.

The left hepatic vein actually begins in the plane between Sg 2 and Sg 3, and travels in that plane for most of its length. It becomes quite a large vein even in that location. About 1 cm from its termination in the IVC, it enters the left intersectional plane, where it receives the umbilical vein from Sg 4 (Fig. 9). It is important not to confuse the umbilical portion of the left portal vein with the umbilical vein; the latter is a tributary of the left hepatic vein that normally drains the most leftward part of Sg 4 (Fig. 9).[6,9] The length of the left hepatic vein in the left intersectional plane is short. It lies between the point where it receives the *umbilical vein* from segment 4 and the IVC, a distance of only about 1 cm. The left and middle hepatic veins normally fuse at a distance of about 1 cm

from the IVC so that, when viewed from within the IVC, there are only two hepatic vein openings. Rarely, hepatic veins join the IVC above the diaphragm.

In about 10% of individuals, there is more than one large right hepatic vein. In these persons, in addition to the right superior hepatic vein (normally called the right hepatic vein) that enters the IVC just below the level of the diaphragm, there is a right inferior hepatic vein that enters the IVC 5–6 cm below this level. In the presence of this vein, resections of Sg 7 and Sg 8 may be performed (including resection of the right superior vein) without compromising the venous drainage of Sg 5 and Sg 6. There may occasionally also be a large right middle hepatic vein draining Sg 7. This vein enters the vena cava in proximity to the IVC ligament (see below), where it is in danger of injury when the ligament is divided.

The caudate lobe is drained by its own veins, specifically several short veins that enter the IVC directly from the caudate lobe. The number and size are variable. On occasion, they are quite short and wide, and must be isolated and divided with great care. It is usually possible to create a tunnel behind the liver and in front of the vena cava in the midplane between caudate veins. This maneuver is the anatomical basis of the "hanging maneuver" described by Belghiti *et al.*[10]

When performing a right hepatectomy, caudate veins are often divided in the preliminary portion of the dissection. These veins can be thin-walled, wide, and short, and in those cases should be managed by suture ligation rather than by simple ligation. As dissection moves up the anterior surface of the vena cava to isolate the right hepatic vein, one encounters a bridge of tissue lateral to the IVC that connects the posterior portion of the right liver to the caudate lobe behind the IVC. This bridge of tissue prevents exposure of the right side of the IVC at a point just below the right hepatic vein. The bridge of tissue is referred to as the *inferior vena cava ligament*. Its importance was first described by Makuuchi *et al.*,[11] and in Japan is referred to eponymously. This ligament is a point of potential hazard in mobilization of the liver, since it may contain a large hepatic vein. Isolation of the right hepatic vein requires that a passage be created on the anterior surface of the vena cava on the left side of the right hepatic vein, a passage that emerges

superiorly in the space between the right and middle hepatic veins. Formation of this passage is facilitated by first dividing fibrous tissue (from a vantage point above the liver) between the right and middle hepatic veins down to the surface of the vena cava.

The left and middle veins can also be isolated prior to division of the liver in performing hepatectomy. There are several ways to achieve this anatomically. One method is to divide all of the caudate veins as well as the right hepatic vein. This exposes the entire anterior surface of the retrohepatic vena cava and leaves the liver attached to the vena cava only by the middle and left hepatic veins, which are then easily isolated. This is suitable when performing a right hepatectomy or extended right hepatectomy, especially when the caudate lobe is also to be resected. The advantage of having control of these veins during operations on the right liver is that total hepatic vascular occlusion is possible without occlusion of the IVC, and the effect is hemodynamically similar to occlusion of the main portal pedicle (Pringle maneuver). However, in performing a left hepatectomy, the right hepatic vein is conserved and so a different anatomical approach to isolation of the left and middle hepatic veins is required. They may be isolated from the left side by dividing the ligamentum venosum where it attaches to the left hepatic vein, dividing the peritoneum at the superior tip of the caudate lobe and gently passing an instrument along the anterior surface of the vena cava to come out between the middle and right veins and/or between the left and middle veins. Again, great care needs to be applied when performing this maneuver in order to avoid injury to the structures.

Isolation of the vena cava above and below the hepatic veins is also a technique that should be in the armamentarium of every surgeon performing major hepatic resection. It is not always necessary, but surgeons should be familiar with the anatomical technique of doing so. Isolation of the vena cava superior to the hepatic veins is done by dividing the left triangular ligament and the lesser omentum, being careful to first look for a replaced left hepatic artery. Next, the peritoneum on the superior border of the caudate lobe is divided and a finger is passed behind the vena cava to come out just inferior to the fold of the diaphragm next to the IVC on the right. This fold of the diaphragm makes an easily identified column of the right side.

Isolation of the vena cava below the liver is more straightforward, but one should be aware of the position of the adrenal vein; in some cases, it is necessary to isolate the adrenal vein if bleeding persists after occlusion of the vena cava above and below the liver.

Finally, the surgeon should be aware that during transection of the liver large veins will be encountered in certain planes of transection. For instance, the middle hepatic vein enters the left side of the vena cava superiorly, and in its passage along the midplane of the liver it usually receives two large tributaries: one from Sg 5 anteriorly and the other from Sg 8 posteriorly. Both are routinely encountered in performing right hepatectomy (Fig. 8). The venous drainage of the right side of the liver is highly variable, and additional large veins (including one from Sg 6) may also enter the middle hepatic vein.

Liver capsule and attachments

The liver is encased in a thin fibrous capsule that covers the entire organ, except for a large bare area posteriorly where the organ is in contact with the IVC and with the diaphragm to the right of the IVC. The bare area stretches superiorly to include the termination of the three hepatic veins and ends at a point where the attachment of the falciform ligament also ends. The limit of the bare area, where the peritoneum passes between the body wall and the liver, is called the coronary ligament. It is one of three structures that connect the liver to the abdominal wall dorsally, the other two being the right and left triangular ligaments. The liver also has another bare area, best thought of as a bare crease where the hepatoduodenal ligament and the lesser omentum attach on the ventral surface. It is through this crease that the portal structures enter the liver at the hilum (*hilum* = "a crease on a seed"). The other ligamentous structures of interest to surgeons are the ligamentum teres, falciform ligament, and ligamentum venosum.

Portal sheaths and liver plates

As the portal structures approach the liver, they become invested in fibrous sheaths in the region of the hilum.[4,7] These sheaths are carried

into the liver surrounding the portal structures, i.e. portal vein, hepatic artery, and bile duct. The gallbladder rests on a fibrous plate referred to as the cystic plate, which is part of this perihilar system of fibrous tissue. The combined structure consisting of a hepatic artery, bile duct, and portal vein surrounded by its fibrous sheath is referred to as a portal pedicle. There is no *sheathed* main portal pedicle because the main portal vein, proper hepatic artery, and common hepatic duct are not close enough to the liver to be enclosed in a sheath. However, when the right hepatic artery, bile duct, and portal vein approach the liver, they become encased in a tubular fibrous coating, and the combined entity is referred to as the right portal pedicle (*pediculus* = "little foot"). As the right portal pedicle enters the liver, it divides into right anterior and right posterior portal pedicles supplying the respective sections and then into segmental pedicles supplying the four segments. On the left side, the arrangement is somewhat less complete in that only the segmental structures are within sheaths.

The cystic plate attaches directly onto the anterior surface of the right portal pedicle. This is an anatomical point of importance because if the anterior surface of the right portal pedicle is to be visualized, the attachment of the cystic plate to the anterior surface of the right portal pedicle must be divided as we have described.[12] The cystic plate is the fibrous surface encountered during cholecystectomy, deep to which lies the hepatic parenchyma.

Effect of pathological conditions on anatomical structures

Pathological conditions may distort normal hepatic structures. Tumors may invade and occlude or fill vessels. They may cause structures such as bile ducts to dilate to a size many times normal, and may push vessels so that they are stretched and curved over the surface of the tumor. These pathological effects may occur in all organs. However, in the liver there is another important process called atrophy, which affects normal anatomical relationships. Atrophy of a liver volume is induced by processes that occlude either the portal vein or the bile duct. Since the liver undergoes hyperplasia to maintain a constant volume of liver cells, atrophy of one part of the liver is usually accompanied by the

growth of another. This has anatomical consequence of importance to the surgeon. For instance, if the right portal vein is occluded by a tumor, the right liver will atrophy and the left liver will grow. When seen from below, this process will exert a counterclockwise rotational effect on the porta hepatis, rotating the bile duct posteriorly, the hepatic artery to the right, and the portal vein to the left and anteriorly.

Addendum Regarding Liver Anatomy and Terminology

As noted above, the term "lobe" should be reserved for structures that are demarcated by clefts visible in the intact organ. It is a suitable descriptor for the caudate lobe. It can also be used to describe the two parts of the liver demarcated by the umbilical fissure and attachment of the falciform ligament, i.e. the "right lobe" and the "left lobe". However, this usage should be discouraged as it divides the liver on a basis other than internal anatomy, i.e. it divides on surface appearance rather than on vascular supply. Therefore, in the liver, "lobe" should be reserved for the caudate. Similarly, "lobectomy" should be reserved for "caudate lobectomy". Some authors still use right lobectomy and left lobectomy in the sense of right trisectionectomy (Sg 4–8) and left lateral sectionectomy (Sg 2,3). The disadvantage of a surgical term dependent on surface anatomy rather than on vascular supply, which is the basis of resection, is obvious.

"Sector" is a term used to describe a second-order division based on the portal vein rather than the hepatic artery and bile duct. Sectors and sections are anatomically identical in the right liver, where the three elements of the portal triad ramify similarly. But, on the left side, the left medial sector is composed of Sg 3 and Sg 4, whereas the left lateral sector is composed of Sg 2 alone. This division is based upon two contentions. The first is that the transverse portion of the portal vein terminally ramifies into the branch to Sg 2 and the umbilical portion of the portal vein. One might draw this conclusion from corrosion casts in which the ligamentum venosum has been digested away. However, in the intact liver in which the ligamentum venosum is available to demarcate the transition from transverse to umbilical portions of the vein, it becomes clear that there is a smooth transition from transverse to

umbilical portions without branching at this point.[8] The branch to Sg 2 does not originate for about 1 cm beyond this point and is therefore a branch of the umbilical portion, as are the branches to Sg 3 and Sg 4. The other contention is that the left hepatic vein does not run in the plane that separates Sg 4 from Sg 2 and Sg 3, i.e. the plane of the umbilical fissure and the attachment of the falciform ligament. Although the left hepatic vein runs in the Sg 2 and Sg 3 intersegmental plane for most of its course, its terminal portion — which begins where it receives the umbilical vein — must be in the plane between Sg 4 and Sg 2/Sg 3. Therefore, the anatomical basis for "sectorifying" the left liver is suspect. Also, as a practical matter for the surgeon, sections relate much more meaningfully to common resections performed through the umbilical fissure.

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3

Assessment of Liver Function

Darren V. Mann

Introduction

Hepatocellular carcinoma (HCC) generally develops on the background of chronic liver disease, principally cirrhosis, with attendant or latent physiological impairment. Assessment of liver functional status is therefore important for the selection of treatment options for HCC. The therapeutic alternatives when liver status is judged to be poor are different from those when organ functional reserve is intact. An evaluation of liver function should assess not only steady-state physiologic performance, but also, importantly, the regenerative capacity of the organ. The diseased liver regenerates less efficiently than normal parenchyma, and so an evaluation of regenerative potential has important implications for the recovery from therapies in which liver cell mass is lost (for example, resectional surgery).[1] Longitudinal alterations in liver function can also be used to monitor hepatic recovery after treatments; progressive disturbance may be predictive of impending liver failure,

and can be used to judge the timing and selection of hepatic support therapies.[2]

The term "liver function" encompasses a whole host of biologic roles of the liver organ, including not only diverse metabolic tasks, but also the physiological response to injury (acute-phase reaction) and the capability for restoration of lost liver mass (regeneration). Although many of the commonly used traditional biochemical liver function tests do not directly measure actual function, and changes in most are not specific to this organ, these analyses (particularly in combination) have generally proven robust in the prediction of outcomes following hepatectomy.[3]

The assessment of liver physiology can be considered according to the following conceptual framework of four main types of tests (Fig. 1):

1. Passive/Steady-state tests — biochemical analyses of blood reflecting the balance between production and disappearance of bile metabolites, hepatic enzymes, and plasma proteins. These may be combined with clinical evaluations to produce composite clinicobiochemical scoring systems (e.g. Child–Pugh grading).
2. Bioenergetic tests — measures of hepatic energy state (in plasma and at tissue level).
3. Radiological tests — image-based assessments of liver parenchymal quality, performance, and volume.
4. Dynamic tests — assessment of some aspect of liver physiology in a time-dependent manner (e.g. tracer excretion), or repeated measures of any of the above tests used to assess the longitudinal response to a provocation such as metabolic stress or portal vein embolization.

This chapter will describe these tests, with the greatest emphasis on those that have become clinically established in the management of patients with HCC. Emerging technologies that seem most likely to contribute to clinical advancements in the future or that provide new insights with which to interpret currently used tests will also be discussed. The focus will be on the principles underlying the different methods available for evaluation of liver function, touching on their role in clinical decision making. The ways in which clinicians can combine

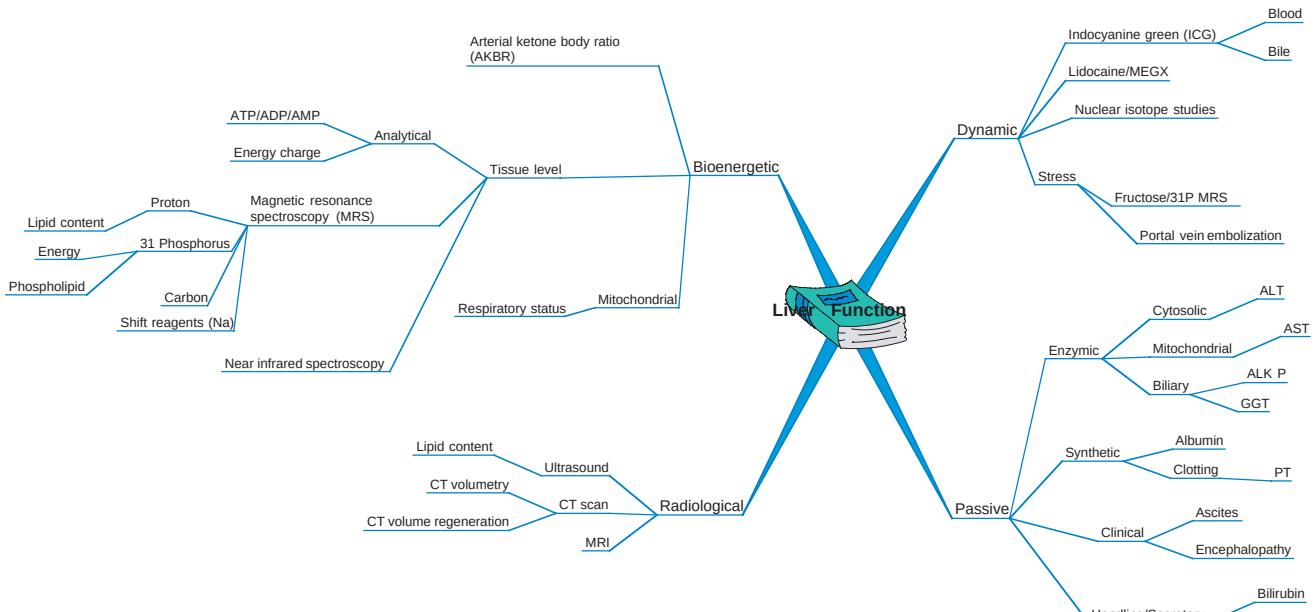

Fig. 1. Outline of scheme of tests for the evaluation of liver function.

these and other relevant clinical data into selection and management options for HCC in the wider clinical context will be dealt with in Chapter 12.

Passive/Steady-State Tests

The term "liver function" is used to describe the sum and spectrum of the physiological duties of the liver organ, namely intermediary metabolism of carbohydrates, protein, and fat; production of bile; synthesis of plasma proteins and clotting factors; metabolic handling and excretion of endobiotics and xenobiotics; and urea synthesis. Cellular integrity of hepatocytes and bile canaliculi is reflected in normally circulating levels of intracellular domain enzymes. A common biochemical panel of liver function tests comprises estimation of the serum level of bilirubin, transaminases, and alkaline phosphatase; estimation of albumin level; and clotting factor analysis. Each of these elements is indicative of a different aspect of liver physiology and its disorder.

Bilirubin

The plasma concentration of bilirubin, the main degradation product of heme protein metabolism, reflects the processes of production (by the reticuloendothelial system), hepatic extraction, conjugation, and excretion. When production is constant, the circulating level is taken to represent overall bile pigment handling by the liver. Bilirubin levels may be influenced by nonhepatic factors (e.g. increased production by hemolysis and sepsis) and/or by mechanical obstruction to bile flow, and therefore may not accurately reflect function in these instances. Although independently predictive of morbidity following hepatic resection,[4] plasma bilirubin concentration is most commonly combined with other laboratory and clinical factors such as the Child–Pugh scoring system or the Model for End-stage Liver Disease (MELD) (see below). A pattern of progressive increase in bilirubin after liver resection may herald the onset of organ dysfunction, although sepsis, biliary obstruction, and portal vein thrombosis may also present in this way.

Transaminases

Serum activities of aminotransferase enzymes are reflective of hepatic cellular injury, although specificity may be reduced by contributions from other organs, particularly striated muscle. Alanine transferase (ALT) is cytosolic in origin (and more specific), whilst aspartate transferase (AST) is of mixed mitochondrial and cytosolic source. Elevated preoperative transaminase levels have been found to be associated with increased risk of complications and death after liver resection in cirrhotic patients.[5] A markedly elevated transaminase level is suggestive of ongoing hepatic necrosis, for example active viral or alcoholic hepatitis, and cautions against surgery. The relative weighting of these enzymes for risk is comparatively weak, and does not routinely feature in composite preoperative scores.

Alkaline phosphatase

Alkaline phosphatases are a group of hydrolase enzymes responsible for removing phosphate groups in the 5- and 3-positions from many types of molecules, including nucleotides, proteins, and alkaloids. They are distributed in liver, bile ducts, bone, kidney, and placenta. Hepatic-origin alkaline phosphatase levels are elevated in the presence of liver disease with hepatic cell injury or biliary obstruction, due to increased enzyme synthesis. Preoperative serum activity of alkaline phosphatase may be predictive of risk of hepatic failure following hepatectomy.[6] Liver regeneration following hepatectomy is associated with an elevation of alkaline phosphatase levels, and failure of regeneration may be presaged when levels of this enzyme do not increase in the posthepatectomy period.

Albumin

This plasma protein is synthesized exclusively by the liver. The circulating half-life is 20 days, and an assay can be used to interpret steady-state synthetic function (although starvation and protein-losing conditions also influence levels). Acute reduction in plasma concentration more

likely reflects a change in the volume of distribution due to capillary leakage rather than diminished synthesis. Albumin has prognostic value for risk of liver surgery as part of the Child–Pugh score.

Prothrombin time

The liver is the predominant site for the manufacture of clotting factors. Derangements in liver function may therefore be detected by disturbed laboratory measures of clotting times or reduced amounts of individually assayed clotting factors. The most common measurement is that of prothrombin time, which is indicative of the extrinsic pathway of coagulation involving factors II, V, VII, and X and fibrinogen. The prothrombin time is predominantly affected by factor VII, which has the shortest half-life (4–6 hours) and is vitamin K–dependent; therefore, abnormalities may arise from vitamin K insufficiency states or protein synthetic deficits. Prothrombin time is a component of the Child–Pugh score. Levels of factor V and fibrinogen have also been used in combined scoring systems (see below).

Prognostic clinicolaboratory scoring

A common method for the evaluation of hepatic function is the use of a combined prognostication system based on several laboratory criteria and some clinical contributions. These elements reflect different core aspects of liver physiology — including endobiotic handling and excretion, protein synthesis, and clinical estimates of the degree of established portal hypertension — that can be combined into an overall score. In general, the score components are formulated by multivariate logistic regression methods. The advantages of such a score are that a greater degree of overall liver function is represented (parallel testing enhances sensitivity) and the predictive power goes beyond that of any individual component test. Such scores are predictive of the natural history of cirrhotic liver disease in general, and may stratify the risk of therapeutic interventions (e.g. portosystemic shunt surgery and liver resection) and prioritize selection for transplantation.

Child–Pugh score

The Child score (Pugh modification) is the most widely used system and is composed of albumin (synthetic function), bilirubin (excretion), prothrombin time (synthesis), ascites (portal hypertension), and encephalopathy (portosystemic shunting).[7] Components of the system and the point allocation for scoring are given in Table 1.

Individuals are grouped into classes according to the number of points as follows: class A, 5–6; class B, 7–9; and class C, 10–15 (there is some variation in the literature among authors on class allocation). In the management of HCC, the Child–Pugh score is used mainly to evaluate operative risk. In particular, the outcomes of liver resectional surgery are numerically related to the Child–Pugh score, with mortality rates being lower and survival rates higher in Child–Pugh class A patients compared to those in classes B and C.[8,9] Well-compensated Child–Pugh class A cirrhosis does not negatively impact on survival after hepatectomy for HCC.[10]

Model for End-stage Liver Disease (MELD)

The MELD score was originally developed to predict short-term survival in patients undergoing transjugular intrahepatic portosystemic shunt procedures, and has subsequently become a key determinant of

Table 1. Child–Pugh score.

Measure	1 point	2 points	3 points	Units
Bilirubin (total)	<34 (<2)	34–50 (2–3)	>50 (>3)	μmol/L (mg/dL)
Serum albumin	>35	28–35	<28	g/L
International normalized ratio (INR)	<1.7	1.71–2.20	> 2.20	No unit
Ascites	None	Suppressed with medication	Refractory	No unit
Hepatic encephalopathy	None	Grade I or II (or suppressed with medication)	Grade III or IV (or refractory)	No unit

ranking for patients awaiting liver transplantation.[11] Scores are calculated according to the following formula:

$$\begin{aligned}\text{MELD} = {} & 0.957 \times \log_e(\text{creatinine, mg/dL}) \\ & + 0.378 \times \log_e(\text{bilirubin, mg/dL}) \\ & + 1.120 \log_e(\text{INR}) + 0.643.\end{aligned}$$

MELD has been examined as an alternative to the Child–Pugh score for prediction of liver failure posthepatectomy. Although the MELD score is correlated with the risk of liver failure after resection, it is unclear whether the discriminant function is superior to Child–Pugh class.[3,12]

Okuda score and Calvet system

These systems incorporate the degree of underlying cirrhosis and related functional impairment as well as tumor stage. In general, they prognosticate negatively with respect to complications (liver failure) after surgery and overall survival. The Okuda score is based on tumor size (as a proportion of the liver area), ascites, jaundice, and albumin.[13] The Calvet model comprises bilirubin, ascites, toxic syndrome (weight loss, malaise, anorexia), blood urea nitrogen, tumor size, gamma-glutamyltranspeptidase level, age, serum sodium, and presence of metastases.[14]

Bioenergetic Tests

Individual passive tests of hepatic function are used to identify an abnormality in one of many possible biologic roles of the liver. Because results may be influenced by nonhepatic factors, there is often variation in the degree of disturbance of different tests in the same patient. A limitation common to these evaluations is that they are indirectly representative of underlying liver physiology.

At the most fundamental level, the key determinant of hepatic functional status and reserve is the energy state of the organ, which in turn is determined by the aggregate energy balance of individual hepatocytes.

Energy transduction for the maintenance of cellular integrity and function is achieved through the adenylate high-energy phosphate system, the principal currency being adenosine triphosphate (ATP). In the liver, each individual hepatocyte may be thought of as a self-recharging battery in which energy status is controlled according to energy charge (ATP + 1/2 ADP) / (ATP + ADP + AMP) or phosphorylation potential (ATP / ADP × Pi).[15] These key metabolic parameters govern the balance between energy-producing and energy-consuming processes, thereby maintaining the biochemical poise of the energy system.

A fall in energy state produces a curtailment of endergonic (synthetic, secretory, and storage) reactions while favoring energy-producing ones (and vice versa), thereby tending to restore equipoise when energy demands and supply (temporarily) dissociate (Fig. 2). When net energy consumption exceeds supply, whether due to increased physiologic demands or to limitations of ATP-generating ability secondary to disease (or some combination of the two), then a fall in energy state is produced. By the action of feedback modification, a compensatory suppression of ATP-consuming processes results. This has widespread and varied consequences for liver function, but not all aspects of hepatocyte biology are necessarily affected to the same degree for any given magnitude of

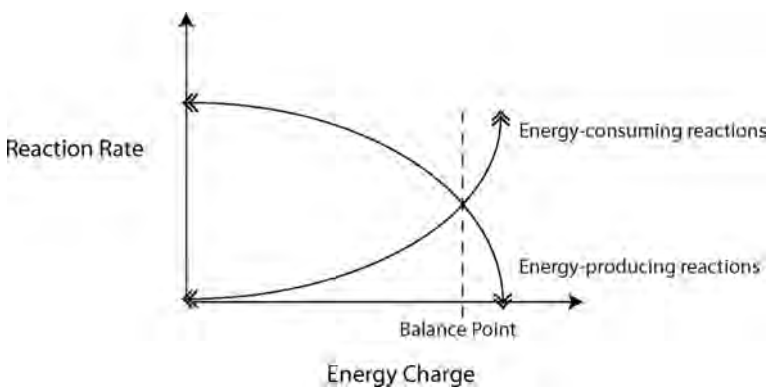

Fig. 2. Energy charge and metabolic control. The graph shows how a reduction in energy state results in a decrease in energy-consuming reaction rates (secretion, synthesis, storage) and an increase in energy-producing reaction rates, thereby restoring energy balance.

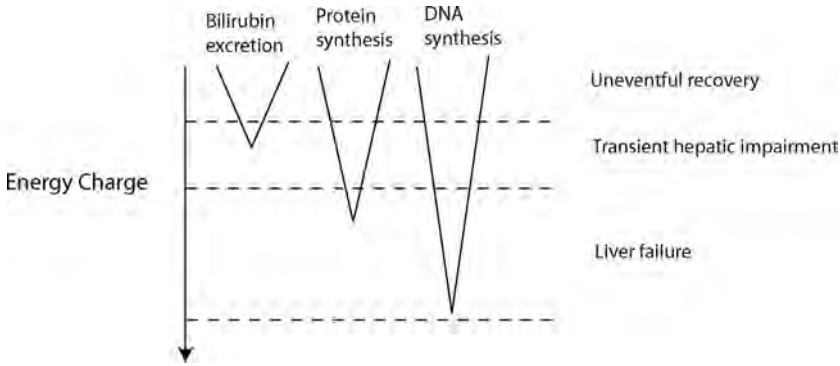

Fig. 3. Energy state and liver function. A fall in energy charge necessarily results in some limitation of energy-consuming processes such as those for excretion of bilirubin, production of proteins, and nucleic acid synthesis. The relative impairment varies, as does the tolerable degree of disturbance, which is clinically reflected in the different patterns of liver recovery after partial hepatectomy.

energy-state depression (Fig. 3). Active anionic transport and protein synthesis are typical of energy-consuming processes that are curtailed during conditions of energy-state depression; hence, plasma bilirubin levels tend to rise, whilst prothrombin and albumin levels fall. Other important energy-dependent processes such as nucleic acid synthesis may also be suppressed, with important implications for mitotic capacity and regeneration. More extreme deviations from energy balance may result in metabolic decompensation and organ failure.

Estimations of energy state may more accurately reflect global liver function and physiologic reserve than the individual indirect tests outlined above. A variety of different methods are available with which to gauge hepatic energy status, and tests may be performed on peripheral blood or alternatively on the liver itself (by both invasive and noninvasive means).

Peripheral blood redox state

The hepatic mitochondrial redox state can be estimated by measurement of the relative abundance of ketone bodies. The ratio of acetoacetate to hydroxybutyrate is in equilibrium with that of oxidized

to reduced nicotinamide adenine dinucleotide (NAD^+/NADH) in mitochondria[16]:

$$\text{Acetoacetate} + \text{NADH} + H^+ \rightarrow \text{3-hydroxybutyrate} + NAD^+.$$

The balance between these states of NAD reflects the ATP-synthesizing potential of the mitochondria. When electron acceptor (oxygen) availability is limited, the ratio of NAD^+/NADH falls, ATP generation is reduced, and the energy state declines — these changes are also reflected in a decrease in the acetoacetate/hydroxybutyrate ratio (and for biochemically analogous reasoning, a decrease in the pyruvate-to-lactate ratio).

In the liver, acetoacetate is produced via the formation of 3-hydroxy-3-methylglutaryl–CoA (HMG-CoA) and also by the deacylase reaction from acetoacetyl-CoA. When conditions leading to the accumulation of reducing equivalents prevail, conversion to hydroxybutyrate increases.

The liver is the predominant source of ketone bodies, although other tissues are involved in their subsequent metabolism. The ratio of acetoacetate to hydroxybutyrate in arterial blood (the arterial ketone body ratio, AKBR) has been shown to be related to the hepatic mitochondrial redox state. A fall in AKBR can be taken to represent a decline in hepatic mitochondrial redox (phosphorylating) potential, and hence attenuation of those aspects of liver function that are dependent on energy supply. In the setting of HCC, serial estimates of AKBR are predictive of the postoperative course and development of complications, principally identifying the risk of development of hepatic failure.[17] Single preoperative measures of AKBR are of limited use in predicting outcomes, although refinements based on dynamic response to glucose loading have been described (see below).[18]

Tissue adenine nucleotide and mitochondrial analysis

Because of the requirement for tissue biopsy, these measurements have principally been used in a research setting. Nevertheless, the information is valuable for proof of concept in the application of novel, noninvasive methods for estimating energy state (see below). Biochemical assays of tissue-level metabolism are commonly based on chemical analyses of

biopsy specimens for high-energy phosphate compounds, the key reactive species in energy transduction. The principal compounds measured are adenosine monophosphate (AMP), adenosine diphosphate (ADP), and adenosine triphosphate (ATP). The relative concentrations of these compounds determine the cellular energy charge (or equivalently, the phosphorylation potential).

As discussed earlier, these parameters are central to the regulation of metabolism by constraining the balance between exergonic (energy-producing) and endergonic (energy-consuming) reactions. Alternative techniques involve analysis of mitochondrial phosphorylative activity and of cytochrome chain component redox state. In general, the cirrhotic liver displays altered cytochrome chain activity with a negative influence on ATP-synthesizing ability — these findings are predictive of complications after liver resection as a consequence of decreased functional reserve.[19,20]

Magnetic resonance spectroscopy

Spectroscopy describes the interaction of electromagnetic radiation with matter, and in this context the resonating exchange of energy by nuclei in a magnetic field. This is an emerging technique that allows noninvasive assays of hepatic intracellular metabolism *in vivo*. Formerly called nuclear magnetic resonance (NMR), it should be emphasized that no radioactivity is involved. The measurements can be performed on standard clinical magnetic resonance imaging (MRI) systems after suitable adaptation, and consequently are increasingly being used in the modern clinical domain. The basis of the technique is similar to that of magnetic resonance (hydrogen nucleus) imaging, except that the information is obtained from a different chemical nucleus (usually 31-phosphorus, but also 13-carbon and 23-sodium amongst others).

The principle of the measurement is that atomic nuclei have electrical charge and spin, and hence a magnetic moment (by Faraday's laws). If a sample of the tissue to be studied (or indeed, a whole organ *in vivo*) is placed within an external magnetic field, nuclei with odd-quantum spin numbers align themselves in one of a number of possible quantum states with a slight preponderance of nuclei aligned along the

field (low-energy state) according to the Boltzmann constant. Within this field, the nuclei precess at a specific rotational rate, the Larmor frequency (analogous to the way in which a spinning gyroscope precesses in the earth's magnetic field). When a radiowave pulse oscillating at the same (Larmor) frequency is applied perpendicular to the original field, the nuclei absorb energy (the resonance condition) and change their quantum state: a greater proportion is now in the higher energy condition, which can be measured by electromagnetic induction of current in a detector. Different nuclei can be assayed by varying the frequency of the radiowave probing pulse. The signal obtained is mathematically treated (Fourier transformation) to produce a spectrum of concentration against frequency, with nuclei of the same type but within different chemical species being resolved.

A typical spectrum obtained by resonating on the 31-phosphorus nucleus (31-phosphorus magnetic resonance spectroscopy, ^{31}P-MRS) is shown in Fig. 4. ^{31}P-MRS is particularly appealing for the study of liver metabolism *in vivo* because this naturally occurring phosphorus isotope is central to biological energy transduction and is ubiquitous in cell membrane phospholipids. Using ^{31}P-MRS, it is possible to measure the energy state of the liver and appreciate changes in cell membrane composition.

With respect to hepatic energy balance, two relevant phosphate compounds are assayed: ATP and its hydrolytic breakdown product, inorganic phosphate (Pi):

$$\text{ATP} \longleftrightarrow \text{ADP} + \text{Pi}.$$

The ratio of ATP/Pi is an estimate of energy state, analogous to cellular energy charge or phosphorylation potential.[21] Serial measurements of ATP/Pi energy state in the regenerating human liver after partial hepatectomy have revealed patterns of high-energy phosphate depletion and recovery.[22] In the setting of obstructive jaundice, measurements of liver energy status may be used to determine the optimum timing of surgery following biliary decompression.[23] This is important because the risks of liver resection are greater when biliary obstruction is present, since this is associated with deficient regeneration (probably due to impaired ATP production).[24]

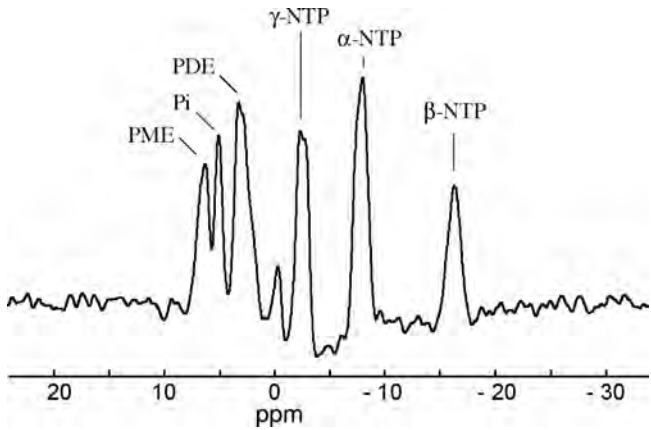

Fig. 4. 31-phosphorus magnetic resonance spectrum of human liver. The peak area is proportional to the amount of metabolites. Peaks labeled on scan: PME, phosphomonoester (mainly phospholipid precursors and sugar phosphates); Pi, inorganic phosphate (product of adenosine triphosphate hydrolysis, which yields adenosine diphosphate and inorganic phosphate: ATP ↔ ADP + Pi); PDE, phosphodiester (principally phospholipid catabolites with some contribution from cell membranes); and γ-, α-, and β-phosphates of nucleotide triphosphate (NTP; high-energy phosphate compounds). By convention, the [β-P] NTP peak is taken practically to represent adenosine triphosphate (ATP). The unlabeled peak at zero parts per million (ppm) is phosphocreatine contamination from muscle. Data are conventionally presented as ratios of peak areas, comprising energy status (ATP/Pi) and phosphoester metabolites (PME/PDE), respectively; alternatively, individual peak areas may be expressed as a function of total visible phosphate (TP). These measures are independent of the volume of liver from which the signals are obtained.

The relative proportions of phospholipid compounds detectable by ^{31}P-MRS are reflective of hepatocyte membrane composition. Two broad peaks representing phospholipid metabolites are generally observed: the phosphomonoester (PME) peak mainly consists of phospholipid precursors, while the phosphodiester (PDE) peak comprises phospholipid catabolites. Changes in the relative abundance of these compounds, characterized by a relative excess of phospholipid precursors with respect to catabolites, has been interpreted to reflect amplification of membrane synthesis. In the human liver, this has been observed in neoplasia, in the maturing neonatal organ, and also in

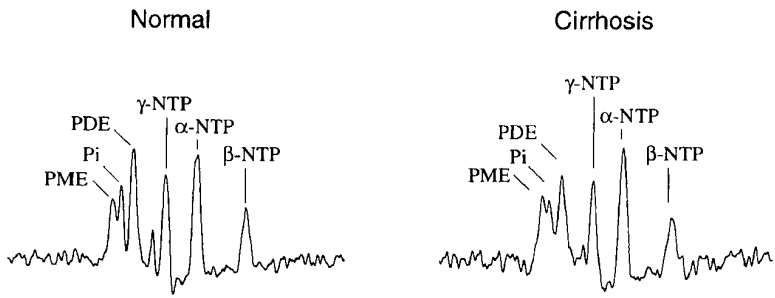

Fig. 5. 31-phosphorus magnetic resonance spectra from normal and cirrhotic human liver. There are visible differences in the relative amount of phospholipids in the PME and PDE peaks, which are reflective of injury and ongoing cellular regeneration in the cirrhotic liver.

benign parenchymal disease (including cirrhosis and hepatitis) — all conditions in which accelerated cell renewal can be anticipated.[25–27] In general, disturbance of phospholipid balance correlates with the grade of parenchymal disease in hepatic fibrosis and cirrhosis, and it is likely that such measurements will play a role in the assessment of hepatic status in the future (Fig. 5 illustrates the differences between normal and cirrhotic liver spectra).[28] Changes in hepatic membrane phospholipid composition can also be detected after nonhepatic surgery, and so these alterations appear to also represent hepatocyte activation and acute-phase physiology rather than hepatic cell division *per se*.[22]

A major advantage of MRS is the ability to perform repeated assessments of *in vivo* liver function noninvasively (see the section below on "Longitudinal Evaluation after Hepatectomy").

Radiological Imaging and Qualitative Assessments

Volumetric analysis of the liver parenchyma forms an integral component of the assessment of functioning liver cell mass and physiological reserve in the management of HCC. Computed tomographic liver volumetry is used to assess the respective volumes of liver and tumor, and to estimate the parenchymal resection rate and thus judge the suitability for resectional surgery.[29,30] Estimates of postoperative liver volume can be

used to guide the selection of therapies for HCC, within the context of the condition of the underlying liver.[31] For example, when inadequate parenchymal volume is anticipated, measures to increase hepatic cell mass (such as portal vein embolization) may be indicated or nonresectional alternatives (transplantation, local ablation, chemo-embolization, etc.) may be considered. Volumetric estimations can be combined with other analyses of liver function, such as indocyanine green retention, to provide composite scores of high accuracy for predicting complications of liver surgery.[32]

Hepatic steatosis (fatty liver) is a risk factor for complications and death after liver resection, and some authors advocate efforts for preoperative identification prior to major hepatic resection. The fat content of the liver can be assessed by ultrasound, computed tomographic, or magnetic resonance imaging.[33]

Dynamic Tests

Dynamic tests generally examine one or more aspects of liver physiology in a time-dependent manner or in response to some provocation such as metabolic stress. The advantages of these assessments are that they can quantify hepatic function and can be used repeatedly to obtain a longitudinal appreciation of changes in functional status. Traditionally, the most common techniques are tracer excretion studies (clearance tests), although metabolic and bioenergetic measurements and volumetric/receptor mass estimations are also available to the clinician.

Clearance tests

These test estimate the hepatic extraction, handling, and excretion of test substances. Depending on the test substance selected, the process examined is variably specific, but generally reflects the number of hepatocytes (liver cell mass), the functional ability of those hepatocytes, and — for very high-efficiency elimination — some dependence on hepatic blood flow. The most commonly used tests are the indocyanine green (ICG) test which measures an energy-dependent excretion mechanism, and the aminopyrine test which is reflective of microsomal function. Some

tests of metabolic function such as galactose elimination capacity are of practical and theoretical interest.

Indocyanine green (ICG) test

This is probably the most common quantitative liver function test in clinical use. ICG is a tricarbocyanic green-colored dye which, when administered into the circulation, rapidly combines with plasma proteins (albumin, lipoproteins, etc.); the volume of distribution is therefore the blood volume. ICG is taken up selectively by the liver, and is excreted unaltered into the bile by an energy (ATP)-dependent carrier-mediated mechanism. The carrier is a member of the canalicular multiple organic anion transporter (cMOAT) group, which is also responsible for the excretion of bilirubin. The disappearance of ICG from the blood is therefore a measure of an energy-dependent process.

ICG exhibits a maximum absorbance at a wavelength of 805 nm (near-infrared region of the electromagnetic spectrum) and the principle of the measurement is one of photoabsorbance, using pulse densitometry based on pulse oximetry. In its modern form, the test is performed by administering ICG intravenously at a dose of 0.5 mL/kg and by monitoring blood concentration through a noninvasive transcutaneous probe (with diodes emitting in the near-infrared 805-nm and 905-nm wavelengths) and photocell sensor. Since 805 nm also comprises an isosbestic point at which absorption of oxyhemoglobin intersects with that of deoxyhemoglobin, the measurement of ICG is independent of oxygen saturation of the blood. ICG distributes uniformly in the blood within 2–3 minutes after intravascular injection, and the blood level then falls exponentially for about 20 minutes thereafter, by which time about 97% is excreted.

Because the physical nature of clearance is a natural exponential function, the measurements can be mathematically interpreted to produce values for the plasma half-life ($t_{1/2}$), decay constant, and time constant, and thus the plasma disappearance rate and derived retention rate. An example of a typical ICG clearance test elimination curve is shown in Fig. 6. The exponential decay function of ICG concentration is converted by logarithmic transformation into a straight line to derive

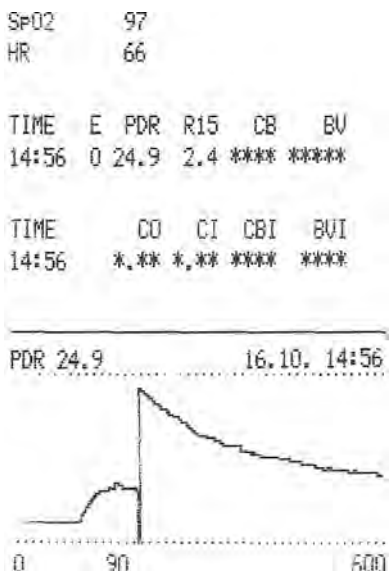

Fig. 6. Indocyanine green (ICG) elimination curve in a human subject. The graph shows an exponential decay curve. The derived values are plasma disappearance rate (PDR) = 24.9 and retention rate at 15 mins (R15) = 2.4%.

a half-life and decay constant (or its inverse, the time constant). The plasma disappearance rate (PDR, which equates to the decay constant of units 1/time) of the dye in the plasma is calculated as

$$\mathrm{PDR} = \ln 2/t_{1/2} \times 100 = 0.693/t_{1/2} \times 100$$

and is expressed as %/min with a normal range of 18%–25%. The ICG retention rate is conventionally measured after 15 minutes (ICGR15) and is calculated by measurement of the plasma concentration after 15 minutes, expressed as a ratio of that at time zero (calculated by backward extrapolation of the transformed decay curve) according to the formula

$$\mathrm{ICGR15} = [\mathrm{ICG\ at}\ t = 15\ \mathrm{min}]/[\mathrm{ICG\ at}\ t = 0\ \mathrm{min}] \times 100\,(\%),$$

with a normal range of the order of 0%–10%.

The ICG test has been shown to be of value in predicting the risk of surgery, specifically of liver failure and death, in patients with cirrhosis.[34,35] Discriminant function analysis has shown an ICGR15 of

14% to be a useful predictor of risk, conferring a threefold relative risk for mortality.[36] Refinements in the estimation of the extent of tolerable parenchymal resection can be made on the basis of ICG testing.[37]

Postoperative (remnant liver) recovery of ICG elimination has been shown to be predictive of the development of complications.[38] ICG testing can be combined with volumetric assessment of the parenchymal hepatic resection rate (PHRR), given by Okamoto's formula,

$$\begin{aligned} \text{PHRR} &= \text{resected volume} - \text{tumor volume} \\ &\text{or} \\ &= \text{liver volume} - \text{tumor volume}, \end{aligned}$$

and with patient age to produce a predictive score for the likelihood of developing liver failure after hepatectomy.[29,32] The appeal of this approach is that it permits an estimation of hepatic parenchymal volume (and hence postoperative liver cell mass) together with an evaluation of the functional status of those hepatocytes (by an energy-requiring process), which can be interpreted as a surrogate marker for physiological reserve and, by extension, regenerative potential. Combined evaluation systems of this type have the potential to reduce deaths related to excessive resection in individuals with impaired liver function.

An interesting area of ongoing research is in the use of near-infrared spectroscopy for direct measurement of ICG clearance from hepatic parenchyma.[39] Measurement of ICG excretion in bile may more accurately reflect the underlying liver energy state, since this has been shown to correlate more closely with hepatic ATP levels than plasma ICG clearance.[40]

Microsomal capacity tests

These evaluations probe the capacity of the microsomal cytochrome P450 system, and are in essence an assessment of liver cell mass. This system of mono-oxygenases is responsible for the metabolism of a wide range of xenobiotic (and endobiotic) compounds using enzymatic hydroxylation. For any given compound R, the reaction catalyzed is

$$\text{R} + \text{O}_2 + \text{NADPH} + \text{H}^+ \rightarrow \text{R-OH} + \text{H}_2\text{O} + \text{NADP}.$$

A number of test substances can be used for the purpose of testing liver microsomal function, including aminopyrine, caffeine, lidocaine, and the lidocaine metabolite monoethylglycinexylidide (MEGX). A significant limitation of these tests is that the enzyme system is inducible by ethanol and is influenced by many commonly used drugs such as phenytoin (inductive potentiation) and omeprazole (inhibition).

Aminopyrine

The aminopyrine (dimethyl aminoantipyrine) test is the most commonly used one, since the progress of metabolic conversion (*N*-demethylation) can be measured after oral administration by a breath test. The principle of the assay is that a dose of aminopyrine with radioactive isotope (^{14}C)- or stable heavy isotope (^{13}C)-labeled methyl groups is administered. The labeled methyl groups are cleaved by the hydrolytic action of microsomal P450 and subsequently converted to labeled carbon dioxide, which is exhaled. The breath may then be analyzed by radiation counter or isotope ratio mass spectrometry accordingly, and the result is expressed as a percentage of the dose expired within a given time. Despite the potential for confounding as outlined above, the aminopyrine breath test has been shown to be a sensitive and quantitative indicator of liver dysfunction, with the ability to stratify surgical risk in patients with liver disease.[41]

A composite score, the liver resection index (LRI), has been devised that combines the aminopyrine breath test (ABT) with volumetric measures of the parenchymal hepatic resection rate (PHRR) and tumor volume–to–liver volume ratio to formulate a preoperative risk assessment for fatal posthepatectomy complications:

$$\text{LRI} = \text{ABT (\%)} \times 100/\text{PHRR} \times \text{age (years)} \times \text{tumor volume/liver volume ratio.}$$

The LRI has a reported sensitivity of 75% and a specificity of 83%.[42]

Lidocaine and MEGX

Lidocaine is a commonly used local anesthetic and antiarrythmic agent. Lidocaine is metabolized in the liver by the cytochrome P450 pathway,

with the formation of monoethylglycinexylidide (MEGX). In the setting of chronic liver disease, the hepatic clearance of lidocaine is reduced with prolongation of its half-life, and the generation of MEGX (a build-up or positive exponential process) is consequently reduced — it is the determination of this metabolite that forms the quantitative basis of the liver function test. Clinical studies indicate that this test is of value in assessing the likelihood of development of complications for cirrhotic patients undergoing liver resection.[43]

Hexose sugar metabolic capacity

The handling and metabolism of hexose sugars (glucose, galactose, and fructose) by the liver involves energy-dependent processes. Dynamic liver function tests using galactose and fructose have been described, together with the effect of glucose loading on the ketone body ratio.

Galactose elimination capacity

The rate-limiting step in the metabolism of galactose within the liver is that catalyzed by galactokinase, which phosphorylates galactose to galactose-1-phosphate. The reaction is an energy-dependent one, consuming ATP, and the phosphorylated galactose is converted to glucose which is then oxidized in the standard way. The test is performed by administering galactose and then monitoring serial blood levels, or alternatively by a breath test that measures the conversion of either radioactive ^{14}C or mass spectrometric detection of ^{13}C, in expired carbon dioxide. The test has been shown to predict complications and survival after hepatic resection.[44]

Glucose load: redox tolerance test

The redox tolerance test quantifies the potentiation of hepatic mitochondrial energy metabolism (measured by the arterial ketone body ratio) in response to an oral glucose loading. The redox tolerance index is derived from the change in ketone body ratio as a function of the change

in blood glucose level: the lower the index, the higher the postoperative morbidity and mortality associated with major hepatic resections.[18]

Fructose tolerance test

Fructose is phosphorylated in the liver by fructokinase, a reaction that consumes ATP. A bolus dose of fructose can deplete the liver of inorganic phosphate by trapping within fructose-1-phosphate and thereby limiting the regeneration of ATP from ADP within the cell. These changes can be followed by 31-phosphorus magnetic resonance spectroscopy (^{31}P-MRS), which can measure the accumulation of fructose-1-phosphate, the depletion of inorganic phosphate, and the decline in ATP levels.[45] When the liver is diseased, a reduced rate of fructose-1-phosphate formation is found following fructose loading; this may be explained by impaired fructose delivery to, transport into, and handling by hepatocytes. These findings are of interest in view of the noninvasive manner in which detailed bioenergetic information is obtained. However, the theoretical risk of precipitating lactic acidosis warrants caution in the application of such tests outside of carefully controlled environments.

Hepatobiliary uptake and excretion scintigraphy

Isotope-labeled organic anions such as technetium-99m–iminodiacetic acid permit simultaneous evaluation of total and regional hepatocyte uptake (cell mass estimate) as well as excretory kinetics (functional evaluation). The biliary excretion mechanism is common to that of the energy-dependent organic anion transporter system, and hence the findings of dynamic testing correlate with those of ICG clearance studies.[46]

Asialoglycoprotein receptor scintigraphy

Asialoglycoproteins (ASGPs) such as ceruloplasmin are removed from the circulation by a mechanism that involves adherence to specific hepatic protein receptors in the sinusoidal membrane of hepatocytes (asialoglycoprotein receptors, ASGPRs). When the liver is diseased,

the number of such receptors is reduced; this is associated with accumulation of the glycoprotein in the blood. A manufactured scintigraphy agent that binds to ASGPRs on hepatocytes, technetium-99m-diethylenetriamine-pentaacetic acid–galactosyl-human serum albumin (^{99m}Tc-GSA), can be used to probe the receptor complement in the setting of chronic liver disease. Using a radiopharmacokinetic model that incorporates the hepatic uptake and blood disappearance rates, a quantitative index for receptor binding can be obtained.[47,48] This value has been shown to be useful for the prediction of liver failure in high-risk patients. The measurement is of value because it appears to be independent of other measures of liver function, such as organic anion–, hexose sugar–, or microsomal-based clearance tests, and appears to more accurately reflect histological findings.

Regenerative capacity: portal vein embolization

When a tumor is technically suitable for resection but there are concerns about the adequacy of residual hepatic parenchyma (and its functional reserve), one possibility that may be considered is portal vein embolization. Typical indications for portal vein embolization are when the predicted remnant liver volume is 25% or less of the total liver volume for normal liver, and 40% or less when the liver function is compromised.[49] The principle of the technique is that when one lobe of the liver is deprived of portal blood flow, it undergoes relative atrophy, and a hypertrophic (regenerative) compensatory response is induced within the contralateral lobe. In essence, this represents a therapeutic trial of regenerative potential: if the hypertrophic response is adequate, then formal resectional surgery may be entertained. However, if the augmentation of hepatic cell mass is deficient, surgery would likely result in decompensation of an inadequate liver remnant with failure of regeneration.

The growth of the nonembolized lobe is usually monitored by serial computed tomographic volumetry. In the most common setting, a right portal vein is embolized to produce left lobe hypertrophy for the subsequent treatment of a right lobe tumor encroaching variably onto the left side. The average growth of nonembolized tissue that can be anticipated

is of the order of 30%, with a mean increase of the order of 10%–15% in total liver volume.

In addition to volumetric measurement (which is a surrogate for liver cell mass), the functional response of the nonembolized lobe can also be assessed. After a successful regenerative response, biliary excretion of ICG by the nonembolized lobe is increased and energy charge is maintained within normal limits.[50,51]

Longitudinal Evaluation After Hepatectomy

The express purpose of preoperative evaluation of liver status is to avoid surgery on those individuals whose liver function is likely to deteriorate to the point of liver failure after resection. Recovery of liver cell mass following hepatectomy requires a metabolic compromise between differentiated function and organ regrowth. The likelihood of liver failure ensuing is based on complex interrelationships involving liver-specific and general clinical parameters (the latter will not be further addressed here). Liver-specific factors include the current state of liver physiology, the presence and degree of underlying liver disease (and the inherent regenerative potential), the magnitude of parenchymal resection, and the size of the remnant liver.[1]

Postoperative liver failure has not been uniformly defined. Clinical features include jaundice, ascites, hepatorenal syndrome, and onset of encephalopathy. Derangements in commonly used biochemical tests, plasma proteins, and coagulation profiles are characteristic, but there is no standardized definition of when these constitute liver failure; moreover, similar patterns (albeit with less extreme deviations) are noted after liver resection when the recovery proves to be uneventful. Clinical and laboratory experience has shown that events pivoting around the fifth postoperative day are of predictive value for the eventual outcome.[2,52] What is happening to hepatocytes at this critical time after liver resection, and what types of measurement may we employ to refine our interpretations and make therapeutic decisions?

If liver function is to be preserved after hepatic resection, the remaining hepatocytes must meet the inherited demands of baseline-differentiated activity. The average cellular workload is, however,

increased in mathematical proportion to the number of liver cells lost. The remnant liver is also required to coordinate and host an acute-phase reaction characterized by a major redirection of protein synthesis designed to restore bodily homeostasis. The metabolic burden on hepatocytes is increased further when endeavoring to replenish lost cell mass by widespread mitosis. Indirect measures of cell cycling in humans have confirmed the regenerative process to be maximal 4–5 days after hepatectomy.[53]

At the hepatocyte level, the metabolic kinetics underlying these events can be studied in a number of direct and indirect ways according to the techniques discussed earlier in this chapter. Liver regeneration following hepatic resection is associated with a decline in cellular energy charge (with a compensatory increase in net hepatocyte ATP production), which produces a fall in both ketone body ratio and ICG clearance; these changes normalize when volume recovery is complete.[54–58] Figure 7 illustrates the time course of these events. The development of liver failure is reflected in increasing derangements of metabolic indices, and can be shown by serial measurement of ketone body ratio and ICG elimination rates.[17,59]

In the modern clinical arena, ^{31}P-MRS has been used for the noninvasive study of hepatic metabolism and regeneration after liver resection. The technique has appeal because it can provide noninvasive monitoring of intracellular metabolism and simultaneous measurement of liver volume (a surrogate indicator of liver cell mass). Let us examine some clinical magnetic resonance study data that compare the metabolic response of normal and cirrhotic livers during the regenerative process.[22,60] As shown in Fig. 8, the patterns of recovery are very different. In the remnant normal liver, metabolic balance appears to be initially achieved by diverting energy away from quiescent hepatic functions (excretory and synthetic) whilst also rechanneling resources for acute-phase requirements. During the maximal growth phase between the fourth and sixth days after hepatectomy, energy expenditure exceeds ATP availability, inducing a decline in energy state; accordingly, derangements in differentiated function tend to reach their extremes at this time when energy charge is at its nadir, around the fourth postoperative day. As organ regrowth progresses, the distribution of cellular metabolic load becomes

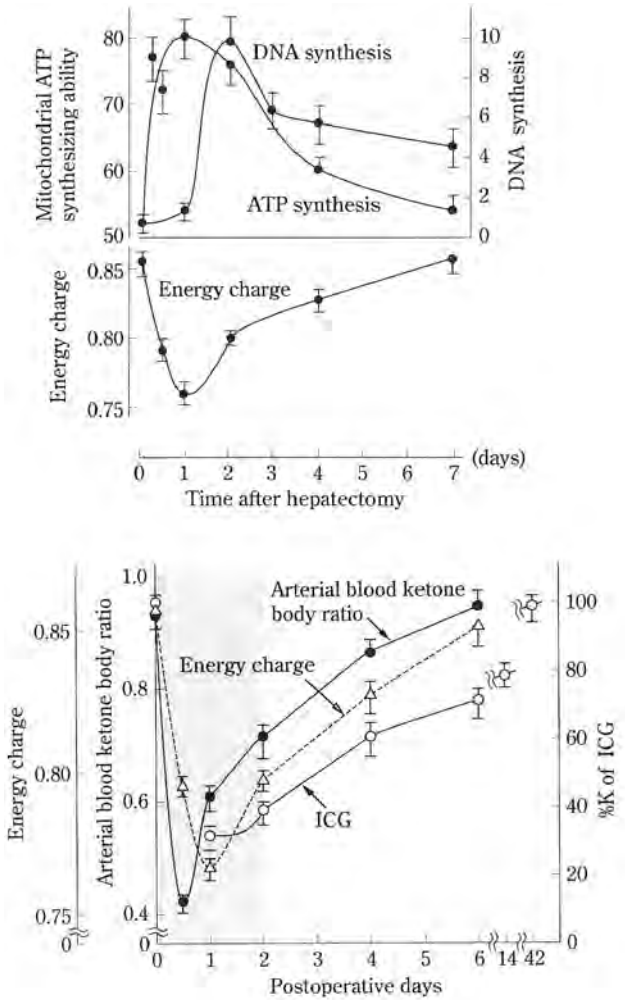

Fig. 7. Serial changes in ATP production, energy charge, DNA synthesis, ketone body ratio, and ICG clearance after hepatectomy. Modified after Ozawa K (*Liver Surgery Approached Through the Mitochondria: The Redox Theory in Evolution*, Tokyo, Japan, 1992) and reproduced with kind permission from the publisher Medical Tribune, Inc.

more equitable so that energy balance and organ function are restored. The pattern of recovery is different in the diseased liver. In the cirrhotic liver, the early demands of inherited workload and stress reaction are not matched by compensatory changes in energy usage and supply,

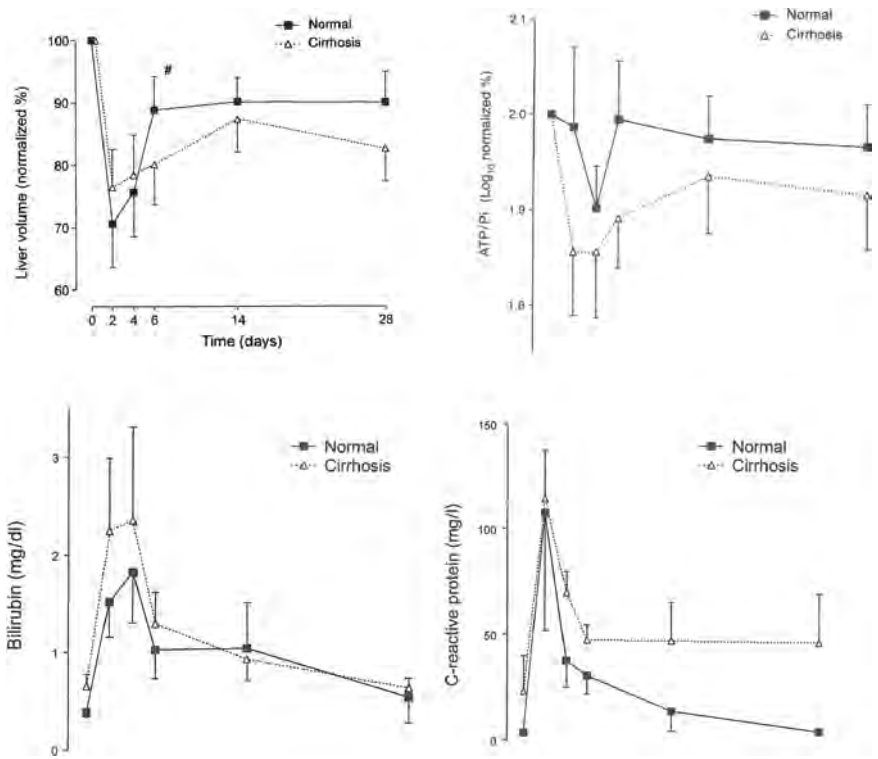

Fig. 8. Changes in liver volume (by MRI), energy state (ATP/Pi by ^{31}P-MRS), and function (bilirubin level), and acute-phase reaction (C-reactive protein) after liver resection: comparison of normal and cirrhotic livers (data are mean ± SE, $n = 9$ in each group). Reproduced after Mann *et al.*[60] with permission.

and a sustained fall in energy state occurs, evident in greater degree of dysfunction. The regenerative response is retarded (most volume regain occurring between the 6th and 14th days) and incomplete because the depressed energy state restricts protein and nucleic acid synthesis.

How can these findings be interpreted to explain the mechanisms of metabolic control and maintenance of hepatic function during liver regeneration, and to predict the development of postresectional liver failure? A helpful analogy here is the concept of a liver energy economy, which is comprised of the sum and distribution of exergonic (income-generating) and endergonic (consumption/expenditure) reactions. The

metabolic demands on the remaining hepatocytes after liver resection can be apportioned into three vectors: (1) maintenance of differentiated function, (2) activation and acute-phase reactions, and (3) cellular regeneration. These synchronous competing factors can be combined to produce a representation of hepatic energy economy after partial hepatectomy (Fig. 9).

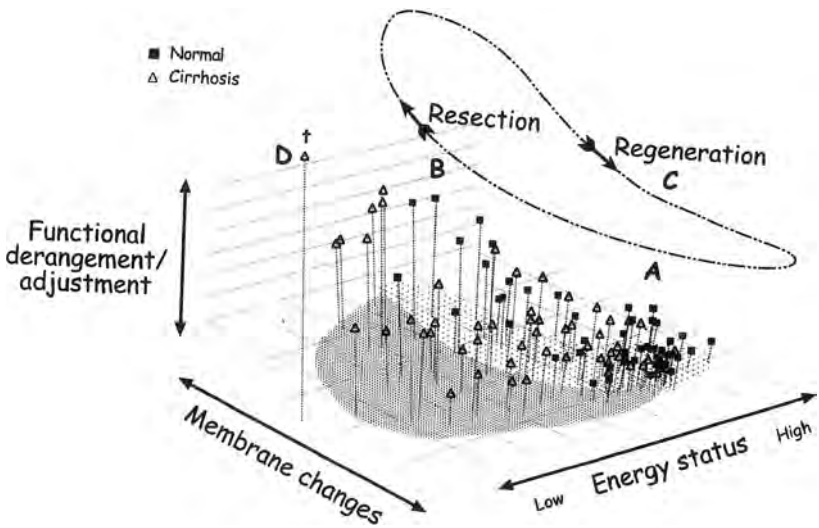

Fig. 9. Hepatic energy economy after partial hepatectomy: three-dimensional plot for patients undergoing hepatectomy with normal and cirrhotic livers. (A) Starting conditions. (B) Resection: liver cell mass is lost and the alteration in membrane phospholipid metabolism (*x*-axis) reflects hepatocyte activation, acute-phase reaction, and onset of proliferative response. This condition is associated with a fall in energy state (*z*-axis) and compensatory adjustment (permissible derangement) in differentiated function (shown here as prothrombin time prolongation on the *y*-axis) (C) Regeneration: recovery of liver cell mass as well as restitution of energy balance and functional status occur within the framework of the integrated response loop shown here for survivors. The trajectory coordinates for cirrhotic liver (darker shading) are more extreme, indicating greater departure from the equilibrium and strain on homeostatic recovery mechanisms when the organ is diseased. (D) Departure of an individual from these physiologic boundaries, as a result of inadequate energy production, will result in decompensation of liver function and failure of the organ. This is evident from the coordinates of a patient who died of postoperative liver failure. Reproduced after Mann *et al.*,[60] with permission.

Successful regeneration of the human liver after partial hepatectomy involves modulation of the hepatic energy economy in response to changing work demands. The efficiency of this process is influenced by the histopathologic state of the organ, which in turn governs physiologic reserve. The mechanism and timing of posthepatectomy liver failure can be conceptually explained by an inability to maintain organ energy balance during recovery. This concept can also account for the well-known clinical phenomenon of postoperative sepsis precipitating liver failure after hepatectomy.[32] In this instance, the infection induces a second-hit acute-phase stress on the liver that, if it occurs at or around the critical regenerative growth spurt, may be sufficient to induce metabolic decompensation.

Organ monitoring based on intracellular metabolism after hepatectomy has the potential to provide new insights for the early detection of impending liver failure, and has clinical promise to guide the development and application of novel hepatic support strategies.[61]

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4

Prevention

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Is There a Need to Prevent Hepatocellular Carcinoma?

Hepatocellular carcinoma (HCC) is regarded as one of the major malignant diseases in the world today. Among the several reasons for this, two are especially germane in considering the need to prevent this tumor. The first is the high incidence of HCC, and the second is its extremely poor prognosis.

HCC is the fifth most common global cancer (fifth in males, eighth in females),[1–3] and is either the most common tumor or among the three most common tumors in many of the most populous regions of the world.[1–4] Approximately 550 000 new cases of HCC occur worldwide each year, accounting for about 6.0% of all new cancers (7.5% among men, 3.5% among women).[1,3] The incidence of the tumor varies considerably in different geographical regions, with more than 80% of all cases occurring in resource-poor (low-income) countries in the Asian-Pacific region and sub-Saharan Africa.[1–4]

HCC ranks fourth in annual global cancer mortality rates,[1,3,4] with a rate that is virtually the same as its annual incidence (annual fatality ratio, 0.97).[3,4] The prognosis is especially grave in Chinese and black African populations with a high incidence of the tumor. In these populations, HCC may be responsible for as much as two thirds of cancer deaths[1,5]; and average survival times from the onset of symptoms may be as short as 11 weeks, and from the time of diagnosis, 6 weeks.[6]

Because of the often rapid growth of HCC (especially in black African and Chinese populations) and the absence of symptoms during the early stages of the disease, the tumor is usually at an advanced stage when the patient is first seen. Symptomatic HCC is seldom amenable to, and has a high recurrence rate after, surgical resection or ablation by other means. Recurrences may also occur after liver transplantation. Moreover, the tumor almost always responds poorly to nonoperative forms of treatment.

Attempts at early detection and resection or ablation of small presymptomatic tumors in population-screening or case detection and surveillance programs conducted during the past three decades have not significantly improved the survival rates of patients with HCC. Thus, so prevalent is HCC (especially in many populous poor-resource countries), so poor are the results of treatment when the tumor is symptomatic, and so grave is the prognosis that prevention of HCC is an urgent priority.

Definition of Cancer Prevention

Cancer prevention can be attempted at three levels[7]:

1. ***Primary prevention*** is preventing an etiological agent from initiating the carcinogenic process. This premier strategy is achieved by eliminating, avoiding, or neutralizing the carcinogen, or by preventing the *in vivo* conversion of a precarcinogen into a carcinogen.
2. ***Secondary prevention*** is rendering a carcinogen innocuous either by interfering with its metabolism or by preventing it from reaching its target or interacting with tissue nucleophiles, especially DNA.

3. ***Tertiary prevention*** is preventing precancerous lesions from progressing to cancer.

Prevention of HCC includes prevention of tumor recurrences after apparently successful surgical resection, ablation by other means, or transplantation of the liver. The term "secondary prevention" is sometimes loosely used to describe this form of intervention. This term has also, in the past, been incorrectly used to refer to the early detection and resection or ablation of small presymptomatic tumors. Intervention by this means is a commendable attempt to improve the dismal prognosis of patients with symptomatic HCC, but it is not (by definition) prevention.

HCC is multifactorial in etiology and has a complex multistep pathogenesis. Primary prevention of a tumor depends upon knowing its cause or causes; while secondary and tertiary prevention require, in addition, an understanding of the mechanisms involved in its pathogenesis. These mechanisms differ, in part, in the different etiological forms of the tumor. Primary prevention of HCC has become possible because a number of potentially preventable environmental causes of the tumor have been identified. There is at present less chance of secondary or tertiary prevention because much remains to be learnt about the pathogenesis of the tumor. Nevertheless, the increased necroinflammation resulting from the immune response of the host to viruses or oxidative damage as well as the preneoplastic nature of cirrhosis lend themselves to these interventions, as does knowledge of the metabolic pathways of a number of environmental carcinogens and of the changes caused by the mutations responsible for some of the inherited metabolic disorders complicated by HCC.

Etiology of Hepatocellular Carcinoma

The most common and geographically most widely distributed of the recognized causes of HCC are chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections as well as chronic necroinflammatory hepatic disease (usually in the form of cirrhosis), whatever its cause. Other risk factors are important only in specific geographical

regions: dietary exposure to aflatoxins in parts of sub-Saharan Africa, the People's Republic of China, and Taiwan; dietary iron overload in parts of sub-Saharan Africa; nonalcoholic steatohepatitis (NASH) mainly in resource-rich industrialized countries; ditch, pond, or river water contaminated by blue-green algae that produce tumor-promoting microcystins in parts of the People's Republic of China; and membranous obstruction of the inferior vena cava in Nepal, South Africa, Japan, the People's Republic of China, and Korea. Additional etiological associations, with varying geographical distributions, are a number of inherited metabolic disorders, the most common of which is hereditary hemochromatosis. The risk posed by oral contraceptive usage and cigarette smoking is uncertain.

The principal thrust of a prevention program in a particular region should be directed against the more important etiological forms of HCC in that region.

Chronic hepatitis B virus infection

Approximately 45% of the world's population live in regions endemic (or hyperendemic) for HBV infection,[8] and more than two billion people are estimated to have been exposed to the virus.[4,9] Some 360 million of these (approximately 6% of the global population) are chronically infected with HBV.[4,9]

HBV is classified by the International Agency for Research on Cancer (IARC) as being carcinogenic to humans.[10] Chronic HBV infection is the predominant global environmental cause of HCC, and is responsible for as much as 80% of the tumor in the Asian-Pacific region and sub-Saharan Africa. Of those individuals chronically infected with the virus, 25% or more will develop HCC (in some hyperendemic regions of the virus, such as Taiwan, the figure may be as high as 40%[11]).[1–4,11] Each year, between 500 000 and 700 000 people chronically infected with HBV die from HCC, cirrhosis, or both diseases[8]; and the virus is today believed to be second only to tobacco in importance as an environmental carcinogen to which humans are exposed.[12]

In East and Southeast Asia, several of the Western Pacific islands, and sub-Saharan Africa, with HBV carrier rates as high as 15% or more

and with a very high incidence of HCC, the infection is predominantly acquired in infancy or early childhood. The principal route of infection in Chinese populations is perinatal transmission from highly infectious HBV e antigen (HBeAg)-positive carrier mothers, with fewer infections occurring later as a result of horizontal spread of the virus.[13] In contrast, relatively few infections in black African children are the result of perinatal transmission, most infections instead being acquired a short time later by horizontal spread.[14] Young (less than 5 years of age) recently infected, and hence highly infectious, siblings or playmates are the major source of horizontal transmission, although the exact routes remain uncertain. HBV infections acquired during the first year of life have a 90% chance of becoming chronic, and those acquired between 1 and 5 years have a 30%–50% chance.[15] These early-onset carriers are at very high risk of HCC development later in life, with lifetime relative risks as high as 100 or more.[11] The risk of malignant transformation is even greater when cirrhosis is present.[10]

Because the majority of the older population in these countries is already immune to HBV infection, other routes of viral transmission later in life play a relatively minor role in the overall acquisition of the infection. These include, most importantly, blood donations not screened for pathogenic blood-borne viruses (as many as 45% of blood transfusions in sub-Saharan Africa are estimated to be unscreened[16]); the use of unsterilized needles, syringes, and surgical instruments by medical, paramedical, and dental practitioners and lay persons; and unsafe sex. Furthermore, HBV infections acquired at these ages seldom become chronic.[15]

In resource-rich countries, the screening of blood donors, the widespread use of disposable needles and syringes, and safer sex practices have curtailed the spread of blood-borne hepatitis viruses. HBV infection is rare or uncommon in these countries, and is acquired predominantly in late adolescence or adulthood. The main sources of spread of the virus at present are infected illicit drug users and sexual partners. Practices such as ear piercing, tattooing, and acupuncture account for a small number of infections, as do needlestick injuries. Because infections acquired at these ages seldom become chronic,[15] HBV-induced HCC is rare in these countries. Nevertheless, the future impact of large numbers

of immigrants from HBV-endemic to non–HBV-endemic countries on the incidence of chronic HBV infection and the occurrence of HCC must not be underestimated.[17]

Factors that increase the risk of HCC supervention in chronic HBV carriers differ, to a degree, between high- and low-incidence regions of the tumor. These factors are male gender, longer duration of infection (older age), cirrhosis, HBeAg positivity and high viral loads, HBV genotype (and perhaps subgenotype), certain HBV mutations, exposure to aflatoxin B_1 (AFB_1), alcohol and tobacco, and coinfection with HCV.[18–20] Whether or not coinfection between HBV and hepatitis D (HDV) increases the hepatocarcinogenic potential of HBV is uncertain.[21]

Although HBV is known to be both directly and indirectly carcinogenic (the latter by causing chronic necroinflammatory hepatic disease), much remains to be learnt about the precise mechanisms involved.

Chronic hepatitis C virus infection

Chronic HCV infection is another important global cause of HCC. Some 170 million people (approximately 3% of the global population) are currently estimated to be chronically infected with this virus.[4,22,23] The infection is predominantly acquired in late adolescence or adulthood, mainly as a result of the illicit use of intravenous drugs or the transfusion of contaminated blood. Eighty percent or more of individuals acutely infected with HCV become chronic carriers, and about 60% develop chronic hepatitis. Of the latter, approximately 20% progress to cirrhosis over a period of 20–25 years, and a proportion of these develop HCC.[22,23] With rare exceptions, HCV-induced HCC occurs in patients with established cirrhosis or chronic hepatitis with advanced or moderate fibrosis.[22,23] The annual risk of tumor formation in those chronically infected ranges from 8%–9% in Japan to 1.9% in the United States, and the risk is at least four times greater in those with cirrhosis.[22,23] Other risk factors for HCC supervention are increasing age, male gender, a high viral load, possibly genotype 1, and more severe degrees of hepatic fibrosis.[23] After resection of HCV-induced HCC, 70% to 80% of tumors will recur within 5 years.[24] Recurrences

may also occur after liver transplantation. The tumor is more likely to recur in patients with persistent viremia.

In recent decades, the incidence of HCV-related HCC has increased markedly in Japan[23] and Egypt,[4] and to a lesser extent the United States[25] and some western European countries including the United Kingdom.[4] HCV (often in association with alcohol abuse) is now the major cause of HCC in Japan (which has a high incidence of HCC); Spain, Italy, and Egypt (with intermediate incidences of the tumor); and a number of industrialized countries with a low incidence of the tumor.[4] The reservoir of HCV infection in the general population of many industrialized countries raises concerns that an increasing incidence of cirrhosis and HCC is likely in these countries in the coming decades.

The hepatocarcinogenic potentials of HCV and HBV are synergistic.[26] HCC formation in patients with persistent HCV infection was initially thought to be exclusively the result of chronic virally induced necroinflammation of the liver. However, more recent evidence suggests that the virus may also be directly carcinogenic.[27]

Cirrhosis

With almost all of the known causes of HCC and in most geographical regions, the majority of the tumors occur in association with chronic necroinflammatory hepatic disease, commonly in the form of cirrhosis,[28–30] less often chronic hepatitis,[28–30] and occasionally reversed hepatic lobulation complicating prolonged hepatic venous outflow obstruction.[31] Moreover, all forms of cirrhosis, whatever their cause, may be complicated by HCC. Although chronic necroinflammatory hepatic disease may itself be hepatocarcinogenic, it far more often acts in concert with other known, or as yet unidentified, causes of the tumor. This association explains the observation that the frequency with which HCC complicates cirrhosis ranges from as high as 30% with chronic HCV infection to as low as 4% with Wilson's disease and primary biliary cirrhosis.[27,29]

The main causes of cirrhosis complicated by HCC are habitual alcohol abuse, chronic HCV infection, and chronic HBV infection. In industrialized countries, the first two risk factors often occur

together, although the exact nature of their interaction remains to be determined.[29] Apart from the etiology of the cirrhosis, the major factors predisposing to malignant transformation in cirrhotic patients are increasing age and duration of cirrhosis as well as male sex.[28–30] Chronic necroinflammatory hepatic disease is characterized by continuous or intermittent necrosis of hepatocytes followed by regenerative proliferation that can, for reasons not yet known, trigger the conversion of regulated proliferation to unconstrained (constitutive) proliferation.[27] In addition, reactive oxygen and nitrogen species generated by the chronic necroinflammatory process are mutagenic and carcinogenic.[27]

Aflatoxins

Aflatoxins are structurally related difuranocoumarin derivatives produced mainly by certain species of *Aspergillus flavus* and *A. parasiticus.* These fungi are ubiquitous, but because humidity and moisture content of plants are important factors in determining the growth of (and toxin production by) the molds, contamination of crops occurs particularly in resource-poor tropical and subtropical countries with warm, humid climates. Certain staple foodstuffs, such as maize, ground nuts, and fermented soy beans, are prone to contamination.[32–34] The extent of aflatoxin contamination of growing crops is a function of ecology and is not entirely preventable. Contamination occurs not only during the growth of the crops, but also as a result of their improper storage.

Of the aflatoxins B_1, B_2, G_1, and G_2, aflatoxin B_1(AFB_1) is most often found in contaminated human foodstuffs and is the most potent hepatocarcinogen in both humans and experimental animals.[32–34] When high levels of dietary exposure to AFB_1 occur in regions highly endemic for HBV infection, the importance of the toxin as a human hepatocarcinogen is enhanced. The carcinogenic effects of the two risk factors are synergistic, with multiplicative relative risks for HCC development.[35]

The liver is the primary site for biotransformation of ingested aflatoxins. Although the parent molecule is harmless, it is converted by members of the cytochrome P450 superfamily into electrophilic intermediates that are mutagenic.[30–32] During phase I metabolism, the

parent molecule undergoes a two-electron oxidation by CYP3A4 and CYP1A2 to form AFB_1-8,9-*exo*-epoxide and AFB_1-8,9-*endo*-epoxide. AFB_1-8,9-*exo*-epoxide is the more highly reactive of the two. Other metabolites are formed from AFB_1, including AFQ_1, AFM_1, and AFP_1. These are poorer substrates for epoxidation and, consequently, are less mutagenic than AFB_1. CYP3A4 is the predominant cytochrome P450 in the human liver and forms *exo*-epoxide and AFQ_1, whereas CYP1A2 forms some *exo*-epoxide but also a high proportion of *endo*-epoxide and AFM_1.

The *exo*- and *endo*-epoxides are detoxified in a number of phase II pathways. The principal route is by glutathione *S*-transferase–mediated conjugation with reduced glutathione to form AFB_1-*exo*- and AFB_1-*endo*-epoxide–glutathione *S*-transferase conjugates.[32–34] The AFB_1-*exo*-epoxide–glutathione *S*-transferase conjugate is converted to AFB_1–mercapturic acid, which is excreted in the urine. Both AFB_1-*exo*- and AFB_1-*endo*-epoxides can also undergo rapid nonenzymatic hydrolysis to AFB_1-8,9-dihydrodiol.[32–34] If the quantity of AFB_1 ingested in the diet exceeds the capacity of the phase II pathways to detoxify the AFB_1-8,9-*exo*-epoxide (and, of lesser importance, the AFB_1-8,9-*endo*-epoxide) formed or if, for any reason, the activity of these pathways is decreased (for example, by polymorphisms of the glutathione *S*-transferase gene), the highly reactive metabolite accumulates and binds with high affinity to guanine bases in cellular DNA to form the 8,9-dihydro-8-(N^7-guanyl)-9-hydroxy–AFB_1 DNA (AFB_1–N^7-guanine) adduct.[32–34] This adduct can give rise to guanine-to-thymine transversions in cellular DNA. AFB_1-induced promutagenic changes can result in the activation of proto-oncogenes and the inactivation or loss of tumor suppressor genes. AFB_1 and AFG_1 dialdehydes do not bind to DNA, but form Schiff bases with primary amine groups (e.g. lysine) to form protein adducts such as the AFB_1–albumin adduct.[30]

Iron storage diseases

Although iron is essential for the growth of cells, in excessive amounts it is toxic. The liver is especially subject to this toxic effect because it is the major site of iron storage. Iron storage disease occurs in two

main forms: hereditary hemochromatosis (HH) and dietary iron overload in the black African (formerly called Bantu visceral siderosis). HH is an autosomal recessive metabolic disorder that results in increased absorption of elemental iron from a diet containing normal amounts of the metal. Portal fibrosis, cirrhosis, and HCC are frequent complications of the resulting iron accumulation.[36] HCC is responsible for as many as 45% of deaths in patients with HH, with a relative risk of greater than 200; the longer the patient survives, the greater the risk.[36] A substitution of tyrosine for cysteine at amino acid 282 of the $\alpha 3$ loop (C282Y) of the HFE protein is the mutant most often responsible for HH.

Cirrhosis was thought to be an essential precursor of malignant transformation of hepatocytes in HH. However, in recent years, about 30 patients with the disease but without cirrhosis have been reported to develop HCC, raising the possibility that excess hepatic iron may be directly carcinogenic in addition to causing HCC indirectly by way of chronic necroinflammatory hepatic disease.[37] Moreover, the risk of HCC in patients with cirrhosis complicated by HH is greater than that in patients with cirrhosis attributable to other causes.[38,39] Further evidence for a direct hepatocarcinogenic effect of excess hepatic iron is provided by reports of a few patients with other iron-loading conditions (such as thalassemia, sideroblastic anemia, and spherocytosis) who have developed HCC in the absence of cirrhosis.[37]

HCC has occurred after therapeutic iron depletion in some patients with HH.[40] This sequence of events should not discount a direct role of excess iron in hepatocarcinogenesis. The carcinogenic effects of chemicals may become evident only 20 or more years after exposure, and it may be argued that the pathogenic mechanisms responsible for malignant transformation were irreversibly underway before iron depletion was accomplished.

Increased levels of hepatic iron on a par with those present in HH are found in black Africans with dietary iron overload.[41,42] This condition occurs in some rural regions of sub-Saharan Africa, where as many as 15% of the men may be iron-overloaded.[43] This is due to the consumption of large quantities of traditional alcoholic beverages with

a high iron content as a result of being brewed in iron drums or pots. During the process of fermentation, the pH of the ferment drops to a very low level, causing iron to leach out of the container into the contents. Large quantities of the beverage are consumed because it has a low alcohol content.

Fibrosis and cirrhosis complicate dietary iron overload, although in fewer patients than occurs in HH.[41,42] HCC develops with a relative risk of 10.6 (95% confidence interval, 1.5–76.8) and a population-attributable risk of 29.[44] Support for a direct hepatocarcinogenic effect of excess dietary iron was provided by a recent report of the formation of iron-free preneoplastic foci and HCC in the absence of cirrhosis or portal fibrosis in an animal model of dietary iron overload.[37] Malignant transformation in this model appeared to be induced as a result of the generation of reactive oxygen species by the increased hepatic iron.[37]

Nonalcoholic steatohepatitis (NASH)

Obesity, type 2 diabetes mellitus, and NASH have in recent years been shown to be associated with the development of HCC.[45] Because obesity and type 2 diabetes cause fatty infiltration of the liver and predispose to NASH, the carcinogenic potential of NASH has come under scrutiny. Although not proven, it is likely that the association between NASH and HCC reflects the progression of NASH to cirrhosis and hence to malignant transformation, although other mechanisms are certain to contribute.[45]

Microcystins

In most rural regions with a high incidence of HCC in the People's Republic of China, the population drinks primarily pond or ditch water. Drinking water from these sources or, to a lesser extent, river water rather than deep-well water is a risk factor for HCC in some of these regions, with relative risks of 1.9 (95% confidence interval, 1.01–4.74) and 2.9 (95% confidence interval, 2.59–3.27) being recorded in Haimen and Fusui, respectively.[46] Microcystins derived from blue-green algae have been identified in pond and ditch water in these high-incidence

regions of HCC, and differences in the microcystin content of the drinking water have been recorded between HCC patients and controls.[46] Microcystins also act as a tumor promoter in experimental studies of aflatoxin-induced liver cancer in rats.[47]

Membranous obstruction of the inferior vena cava

This rare abnormality of the inferior vena cava (IFC), in the form of either a membrane across the lumen or a fibrotic occlusion of variable length, is situated at or just below the level of the diaphragm.[31] Controversy exists as to whether membranous obstruction of the IFC is a developmental anomaly or the end result of organization of a thrombus in the hepatic portion of the IFC. Although rare in most countries, the lesion occurs more frequently in Nepal, South Africa, Japan, India, the People's Republic of China, and Korea. Long-standing obstruction to hepatic venous flow causes severe centrolobular fibrosis. HCC occurs in 40%–48% of black South African and Japanese patients with membranous obstruction of the IFC, but less often in other populations.[31]

Inherited metabolic disorders

Alpha-1 antitrypsin deficiency

Homozygous PIZZ α1 antitrypsin deficiency (α1ATZ) is the most common metabolic liver disease in children. α1AT is the archetype of the serine protease inhibitor (serpin) supergene family, and is an acute-phase reactant with the principle function of inhibiting neutrophil elastase. α1ATZ results from a glutamate-to-lysine mutation at position 342 of the gene, which alters the conformation of the resulting protein in such a way that it is retained in the endoplasmic reticulum of hepatocytes.[48] This accumulation triggers a series of events that are eventually hepatotoxic and may be carcinogenic. The mechanisms by which retention of the aggregated protein in the endoplasmic reticulum leads to malignant transformation are not fully understood, although the predilection for

HCC in homozygotes for the Z allele is significantly greater than that attributable to cirrhosis alone.[49]

Hereditary tyrosinemia type 1

Hereditary tyrosinemia type 1 (HT1), the most common and severe disturbance of the tyrosine catabolic pathway, is an autosomal recessive metabolic disorder caused by a deficiency of fumarylacetoacetate hydrolase, the final enzyme in the tyrosine catabolism pathway. Deficiency of fumarylacetoacetate hydrolase results in the accumulation of metabolites that are highly toxic because of their alkylating potential.[50] One of these metabolites, fumarylacetoacetate, has been shown to have mutagenic activity as well as to induce both cell cycle arrest at G_2/M and apoptosis.[51,52] Patients with the chronic form of HT1 are at high risk for the development of cirrhosis and HCC,[50] as well as for renal tubular dysfunction.

Glycogen storage diseases

Glycogen storage diseases, a group of inherited metabolic disorders characterized by the accumulation of glycogen in the liver and other tissues, are often complicated by hepatic adenoma formation and less often by HCC. HCC has been reported to occur in types Ia, III, IV, and VI of these diseases. Patients with glycogen storage disease Ia (von Gierke disease) usually present with HCC between 8 and 20 years after hepatic adenoma is diagnosed.[53,54] In glycogen storage disease type III, hepatic fibrosis and cirrhosis rather than adenomas precede HCC formation.[55]

Glycogen storage disease type Ia, the most common type, is caused by a deficiency of glucose-6-phosphatase resulting from mutation of the *G6PC* gene, which encodes the phosphatase of the microsomal glucose-6-phosphatase system.[53,54] Many mutations have been described in these patients, although a homozygous G727T mutation is commonly present in Japanese patients, and HCC develops in 22%–75% of these patients. In type III disease, the affected enzyme is amylo-1,6-glucosidase, 4-α-glucanotransferase, which is responsible for the debranching of the glycogen molecule during catabolism. A number of

mutations have been described in these patients.[55] Type IV disease is caused by a deficiency of the glycogen branching enzyme.[56]

Type II hypercitrullinemia

Hypercitrullinemia is a rare hereditary metabolic disease caused by the deficiency of citrin, a liver-type mitochondrial aspartate–glutamate carrier encoded by the *SLC25A13* gene on chromosome 7q21.3, causing a decreased activity of argininosuccinate synthetase.[57] Three types of mutations are described; of these, only type II, which presents in adulthood, is associated with the development of cirrhosis and HCC, the latter occurring in 15% of patients.[57] Type II hypercitrullinemia occurs particularly frequently in Japan. In this form of the disease, argininosuccinate synthetase is reduced in liver tissue only. There is no mutation of the gene, and the mRNA level of the enzyme is normal. The decreased levels are thought to be the result of increased degradation of the enzyme or inhibited translation of its mRNA.[58] The molecular mechanism responsible for malignant transformation is not known.[57] Possible explanations include promotion of hepatocyte proliferation by citrulline and enhancement of DNA synthesis by polyamine.

Wilson's disease

Wilson's disease is a rare autosomal recessive disorder characterized by impaired biliary copper excretion and defective incorporation of the metal into ceruloplasmin, resulting in progressive accumulation of copper in hepatocytes and other tissues. Copper overload causes pathological changes in the liver and neurological tissue. The three main complications of copper accumulation in the liver are chronic active hepatitis, cirrhosis, and fulminant hepatic failure.[59,60] HCC is a very rare and late complication[59,60] — so much so that it has been suggested that excess hepatic copper might have a protective effect against cancer development. The gene responsible for Wilson's disease encodes a cation-transporting P-type ATPase.[59,60] A great many mutations of Wilson's gene have been described,[61] but most of them occur only in a few families or individuals.

Prevention of Hepatocellular Carcinoma

Attempts at preventing HCC are of relatively recent origin, but there is every prospect that the prevention of most cases of this common and devastating tumor will be possible in the not-too-distant future. For the immediate future, the emphasis should be on practical and economical interventions in countries with high incidences of HCC, especially resource-poor countries. Because of the varying patterns of etiological associations in different geographical regions, strategies for prevention will need to be tailored for each region.

Primary prevention

Primary prevention is, at least theoretically, the most effective form of cancer prevention. It lends itself particularly well to intervention in viral, chemical, and physical causes of cancer. Given that oncogenic hepatitis viruses contribute to the development of 80% or more of global HCC, the prevention of these chronic infections alone would have an immense influence on the global occurrence of the tumor. Primary prevention could most effectively be accomplished by universal immunization against the viruses. This approach became possible, in part, when an effective and safe vaccine against HBV became available in the 1970s.

Immunization against hepatitis B virus infection

Since 1991, the World Health Organization (WHO) has recommended that the HBV vaccine be included in the routine immunization services in all countries.[62] The vaccine is currently incorporated into the Expanded Program of Immunization (EPI) in 147 countries. In those countries where HBV infection is endemic and universal infant immunization is in place, 80%–90% of babies are now receiving the vaccine. This accomplishment has already resulted in a decrease from 90% to 15% in the percentage of chronically infected babies born to highly infectious carrier mothers, and a 10-fold or more decrease in the rate of chronic HBV carriage in the age groups that have been immunized.[63,64]

Because of the long interval between the initial infection with HBV and the development of HCC, it will take 30–50 years for a decrease in the incidence of HBV-induced HCC in adults to be realized in these countries. Nevertheless, in Taiwan, where immunization of babies against HBV began in 1984 and universal coverage was achieved by 1986; coverage of all preschool children by 1987; and extension to older school children, teenagers, and adults by 1990; the prevalence of HCC among recipients of the vaccine has decreased by 70% in comparison with those in the nonvaccinated age groups.[63,65] In early reports, the response was greater in boys than in girls[66]; but in later studies based on larger numbers of children, this difference was not evident (70% decrease in boys, 62% in girls).[67] In addition, the beneficial effect on the occurrence of the tumor in young adults in Taiwan should soon become evident. These findings augur well for the eventual elimination of HBV infection and HBV-induced HCC in the Asian-Pacific region.

Regrettably, in sub-Saharan Africa, for a number of reasons — principally because of financial constraints, competing healthcare priorities (HIV/AIDS, malaria, tuberculosis, measles, and diarrheal illnesses), and poor delivery services not able to access large parts of the countries — only 10% of babies were until quite recently being immunized against the virus. However, with the provision of financial backing from the Global Alliance for Vaccines and Immunization (GAVI), the Vaccine Fund, and other governmental and nongovernmental sources, the dismal picture in sub-Saharan Africa is set to change.[68] Approximately 35% of infants are now being immunized. The encouraging results achieved in the Far East give promise that the universal incorporation of the HBV vaccine into the EPI in those countries and in sub-Saharan Africa will prevent hundreds of thousands of deaths per year from HCC and cirrhosis in future birth cohorts,[69] and that with global immunization HBV-induced HCC could ultimately be completely prevented.

Because of the early acquisition of HBV infection that becomes chronic in highly endemic regions, immunization should be performed at or shortly after birth. In populations where perinatal transmission from highly infectious HBeAg-positive mothers to their babies predominates, the highest level of protection against the virus is achieved when the first dose of the vaccine is given as soon after birth as

possible, together with hepatitis B hyperimmune globulin as passive prophylaxis[63,64]; the second and third doses of the vaccine are given at 1 and 6 months, respectively.[63,64] In practice, because of its high cost, hyperimmune globulin is seldom given, thus decreasing the rate of protection by 5%–10%. In spite of the success of HBV immunization in Taiwan, a significant number of Taiwanese children are still being infected with HBV.[69] The main reasons for this are failure to complete the vaccination schedule and failure of children infected perinatally to receive hyperimmune globulin at the time of birth in spite of otherwise receiving the full immunization schedule. Children born during the HBV immunization era who become infected with the virus (breakthrough infections) have a higher incidence of HCC than those born before immunization commenced,[69] although the tumor is not occurring in children successfully protected against later horizontal infection. Serious consideration will have to be given to ensuring that children born to highly infectious HBeAg-positive mothers, and hence very likely to be infected perinatally, receive hyperimmune globulin in addition to the first dose of the vaccine at the time of birth.

Active immunization with three or four doses of the vaccine without hyperimmune globulin is immunogenic in 90% of neonates born to HBeAg-negative carrier mothers or noncarrier mothers.[63,70] In regions where the majority of the infections that become chronic are acquired a little later in life by the horizontal route, the first dose of the vaccine can be given slightly later and without passive immunization. Three injections are normally given. The aim should be to reach vaccine coverage levels of 95%.[71] The need for a booster dose at the time of entering school has not yet been resolved. Novel HBV vaccine strategies are being explored, including the use of epidermal powder immunization[72] and oral administration of hepatitis B surface antigen (HBsAg)-transgenic plants.[73,74]

The introduction of the HBV vaccine into the EPI in most countries, and the beneficial effect that this has already achieved in reducing viral carriage rates and the occurrence of HCC in vaccinated children and adolescents, is undoubtedly the most promising and far-reaching development in the prevention of this tumor and indeed, indirectly, other

virally induced tumors. The HBV vaccine is the only vaccine currently in use that prevents cancer.

The universal inclusion of the HBV vaccine in the EPI of all countries has already required and will continue to require considerable investment of resources and time. Regrettably, health workers and epidemiologists concerned with the prevention of cancer are still largely unaware of this momentous development in global cancer control.[54] Healthcare workers who are at risk of being exposed to blood or other body fluids should be vaccinated against HBV.

Immunization against hepatitis C virus infection

Despite considerable research over many years into the development of a vaccine against HCV, there appears to be little likelihood of such a vaccine becoming available in the near future. Difficulties impeding the development of this vaccine include the extreme variability of the genomic structure of the virus (especially in the hypervariable region), the large number of quasispecies in the blood of infected individuals at any one time, and the lack of evidence for an effective neutralizing antibody against the virus.

Because immunization against HBV is still not universally practiced and the ultimate beneficial effects of immunization against HBV on the occurrence of HCC will not be felt for many years, and there is still no early prospect of a vaccine against HCV, other methods of preventing the spread of these viruses must continue to be rigidly enforced in an attempt to prevent HCC induced by these viruses.

Other forms of primary prevention against hepatitis B and C virus infections

These forms of primary intervention are potentially more effective in preventing HCV-related than HBV-related HCC. Persistent infection with HCV occurs predominantly in late adolescence and adulthood as a consequence of intravenous drug abuse and transfusion of contaminated blood[22,23,75] — routes that are, in the absence of vaccination, more amenable to intervention than those responsible for the great majority

of the chronic HBV infections acquired in early childhood in endemic regions of the virus.[13,14]

Despite recent advances in treating patients with chronic HCV infection, the overall impact of therapy is relatively small because the majority of chronically infected individuals are unaware that they are infected.[76] Accordingly, prevention of the spread of and infection with this virus by means other than vaccination and antiviral treatment will continue to be an important strategy for the foreseeable future. Efforts to prevent infection should focus on identifying persons at increased risk of HCV infection and providing them with counseling and testing for the presence of the virus, as well as reducing both the incidence of new infections and the risk of progression to chronic liver disease. The following practices should be introduced on as wide a scale as possible[76]:

1. Safe injection practices

These are based on the education of medical, paramedical, and dental practitioners to avoid the use of unnecessary injections and to improve the safety of their injection and infusion techniques. The latter includes the rigid adherence to the use of needles and syringes on a single occasion only or, if this is not possible, the unfailing use of fool-proof methods of sterilization of needles or syringes that have to be reused. Also important is avoiding the use of, or employing the correct use of, multidose vials; and lessening the risk of nosocomial infections resulting from needlestick injuries by the proper disposal of used needles and, and whenever possible, the use of disposal-proof needles.

Preventing HCV and HBV infections in illicit drug users remains a difficult and sometimes contentious issue. Changes in injection practices that will minimize the sharing of contaminated equipment by providing needle and syringe exchange programs (which should include the exchange of not only needles and syringes, but also all other drug paraphernalia) on as wide a scale as possible is a pivotal part of any program to prevent the spread of HCV or HBV among drug addicts.

2. Screening of donated blood for the presence of hepatitis viruses

Transfusion-associated hepatitis C and B virus infections have been virtually eliminated in industrialized countries by screening all donated blood with very sensitive assays for detecting these viruses. Regrettably,

the screening of donated blood for blood-borne viruses is not performed in many resource-poor countries, especially in Africa. Rectifying this hazardous practice is an essential step in preventing HCV-induced and, to a much lesser extent, HBV-induced HCC in these countries.

3. The rational use of viral inactivation steps in the manufacture of blood products

4. Passive immunization

Passive immunization with hepatitis B hyperimmune globulin (HBIG) is useful in preventing infection with HBV, but it is expensive and its effect is of limited duration. The value of immune globulin in preventing HCV infections has yet to be ascertained.

5. Antiviral agents

Treatment with currently used antiviral agents has limited efficacy in the sustained eradication of hepatitis B and C viruses, and so achieves relatively little in preventing the spread of these viruses. Nevertheless, in those patients with HCV infection who respond to treatment with interferon-α (IFN), the risk of HCC development is reduced or delayed (see the section on "Tertiary Prevention"). This may also be true of patients at risk from HBV-induced HCC who respond to lamivudine (see "Tertiary Prevention").

Prevention of exposure to aflatoxin B_1 (AFB_1)

Contamination of staple foodstuffs by AFB_1 does not occur in industrialized countries because those foodstuffs that might be affected are screened for their aflatoxin content by governmental agencies and do not enter the commercial market if unacceptably high levels are found. The problem occurs in resource-poor countries where the crops are consumed by the subsistence farmer's family and neighbors or are sold locally or regionally without ever coming under the scrutiny of a governmental agency, or where appropriate governmental agencies do not exist. Because contamination by *A. flavus* or *A. parasiticus* takes place both during the growth of the crops and as a result of their improper

storage, attempts at primary prevention must be directed at minimizing both sources of contamination.[32–34,77,78]

One possible intervention is to alter agricultural practices in regions of high dietary AFB_1 intake by replacing crops that are highly susceptible to fungal contamination with others, such as rice, at lower risk. This approach has been successfully used in one limited study in the People's Republic of China, where a change to a rice-based diet resulted in an appreciable decrease in AFB_1 intake.[32–34] Unfortunately, for most communities in low-income countries, a change in diet is not feasible. Relatively simple preharvest prevention could involve spraying with fungicides and, because damaged plants are more susceptible to fungal contamination, increasing the resistance of the plants to fungal infection by ensuring adequate irrigation and spraying with insecticides.[32,34,77,78] In the longer term, contamination of growing crops might be prevented by the introduction of nonaflatoxigenic strains of *Aspergillus* to compete with the aflatoxin-producing strains, or by genetically engineering foodstuffs that are resistant to infection with *Aspergillus* species. These methods may, however, not be affordable or feasible in those countries with the greatest need to prevent dietary exposure to AFB_1.

The likelihood of contamination during storage is increased by excessive moisture and any form of damage to the crops. Methods of combating this include sun drying of the crops before storage and drying on cloth rather than directly on the earth; well-ventilated, rainproof storage facilities; storage in jute rather than plastic sacks and in wooden containers rather than on the earth; removal of visibly moldy plants by hand sorting; and use of insecticides to control insect damage and fungicides in order to prevent the spread of fungal spores.[32–34] A study confirming the effectiveness of postharvest intervention in significantly reducing AFB_1 intake has recently been performed in a rural region of Guinea.[78] For these interventions to be successful on a wide scale in resource-poor countries, the education of subsistence farmers in their use and the provision of the means to improve storage facilities, as well as the monitoring of levels of contamination, are required.

Dietary iron overload in the African

Dietary iron overload has virtually disappeared from urban black Africans as a result of a change in their drinking habits from home-brewed traditional beverages with a high iron content to commercially available iron-free varieties of alcohol. However, the pattern of alcohol consumption in rural areas remains largely unchanged. Attempts at intervention will require education about the health hazards of alcohol brewed in iron drums or pots, backed up by the provision of suitably sized aluminum or other iron-free containers in which to prepare the beverage. Such a program has yet to be attempted on a large scale.

Nonalcoholic steatohepatitis (NASH)

A weight-reducing diet, an appropriate exercise program, and long-term administration of drugs that increase insulin sensitivity (e.g. metformin, troglitazone, or the thiazolidinediones) have been suggested to prevent the progression of NASH to cirrhosis and HCC.[79] These measures have not yet been introduced on a wide scale, and insufficient time has elapsed to ascertain their efficacy.

Blue-green algae and microcystins

Since 1973, the government of the People's Republic of China has been urging rural populations to drink deep-well water instead of pond, ditch, or river water.[80] This policy has resulted, for example in the Qidong county, in 80% of the population now drinking deep-well water compared with 20% in the 1970s.[80] In addition, in some regions the drinking water is treated by granular-activated carbon filtration. The effect of these interventions on the occurrence of HCC has yet to be published.

Membranous obstruction of the inferior vena cava

If the presence of membranous obstruction of the IFC is recognized early in life, primary prevention of the complicating HCC is possible. When the obstruction is membranous, prevention can be achieved by balloon

angioplasty with or without stenting. With more substantial obstruction to longer sections of the IFC, surgical correction is required.[31] If the condition is recognized only later in life when long-standing hepatic venous outflow obstruction has resulted in severe portal fibrosis with reversed lobulation of the liver, surgical correction might still prevent this preneoplastic lesion from progressing to malignant transformation (tertiary prevention).

Secondary prevention

Secondary prevention of HCC currently provides only a limited number of opportunities. These include early treatment of acute hepatitis C with interferon to prevent the progression to chronic hepatitis,[81–83] modulation of phase I and II AFB_1 metabolism, and early diagnosis and treatment of certain inherited metabolic diseases to prevent the complicating tumor. In addition, some of the genetic and epigenetic changes involved in the complex pathogenesis of HCC have been unraveled, and these may lend themselves to secondary prevention of the tumor. For example, the prevention of HCC in individuals already chronically infected with HBV might in future be accomplished with the use of either small interfering RNAs (RNAi) to prevent HBV replication[84] or appropriately designed ribozymes to prevent the expression of the HBV X gene, which has been incriminated in the pathogenesis of HBV-induced HCC.[27] Another future possibility might be the use of DNA vaccination, which has been shown in animal models to induce antibodies against HBsAg/anti-HBs.[85–87]

Chemoprevention entails the use of natural or synthetic chemicals to block, retard, or reverse the carcinogenic process. Effective strategies need to be safe, inexpensive, and mechanistically simple. There are currently two etiological forms of HCC in which preliminary evidence indicates that chemoprevention might be possible. These are AFB_1-induced and alcohol-induced HCC.

Chemoprevention of aflatoxin B_1-induced hepatocellular carcinoma

Chemoprevention of AFB_1-induced malignant transformation is based on the principle of attenuating the consequences of currently

unpreventable dietary exposure to the toxin. This is attempted by modulating the balance between metabolic activation and detoxification of the reactive AFB_1 metabolites, particularly AFB_1-8,9-*exo*-epoxide and to a lesser extent AFB_1-8,9-*endo*-epoxide. AFB_1-induced malignant transformation in experimental animals can be inhibited by many chemopreventive agents and in a variety of ways; however, very few of these agents are suitable for use in humans. One possible agent is chlorophyllin.

1. Chlorophyllin

Sodium copper chlorophyllin — a water-soluble derivative of natural chlorophylls — has been used as a food colorant; in a number of over-the-counter medicines for controlling body, fecal, and urinary odor in geriatric and osteomy patients; and as an accelerant in wound healing.[32,88] It is a potent anticarcinogen in a number of experimental models,[89] including AFB_1-induced HCC. Chlorophyllin acts as an interceptor molecule, forming tight molecular complexes with a number of chemical carcinogens (including aflatoxins), thereby reducing their bioavailability and hence their carcinogenic capability.[90] It is also a potent *in vitro* inhibitor of cytochrome P450 enzymes involved in the bioactivation of several environmental carcinogens.[91] Thus, chlorophyllin affects AFB_1 metabolism at two or more levels. It is most effective if given in molar excess to the carcinogen at or around the time of exposure.[92] Chlorophyllin also acts as an antioxidant.[93]

A single randomized, double-blind, placebo-controlled trial in the Qidong county, the People's Republic of China, has thus far been conducted.[88] It found that 100 mg of chlorophyllin, administered three times a day for 4 months, caused a 55% reduction in the median level of urinary excretion of the AFB_1 DNA adduct, AFB_1–N^7-guanine, when compared with placebo. No toxic side effects were observed and compliance to the drug was good. Further trials are needed to ascertain whether the long-term administration of this drug will be feasible and safe. Supplementation of the diet with foods that are rich in chlorophylls, such as spinach and other leafy green vegetables, might be a more practical alternative.

2. Oltipraz

A second approach is to modify the phase II detoxification pathway of AFB_1 in such a way as to render its reactive metabolite innocuous. The antischistosomal drug oltipraz (a substituted 1,2-dithiole-3-thione) is structurally similar to the dithiolethiones found in cruciferous vegetables that may play a role in cancer prevention.[34,94] Oltipraz is a potent inducer of the expression of glutathione-*S*-transferase, and also regulates the transcription of genes encoding other conjugating or antioxidative enzymes; therefore, it may be effective in the secondary prevention of AFB_1-induced HCC.[95,96] Keap1 (Kelch-like ECH-associated factor 1) sequesters Nrf2, a member of the nuclear factor erythroid-derived 2 family, in the cytoplasm by binding to its amino-terminal regulatory domain.[94] Treatment with oltipraz disrupts the interaction between KEAP1 and Nrf2, allowing Nrf2 to translocate to the nucleus, where it forms heterodimers with small MAF-family proteins to activate the expression of glutathione-*S*-transferase and other genes,[34] enhancing the phase II inactivation of the AFB_1-8,9-epoxides. More recent studies of the pharmacodynamic effects of oltipraz have shown that the drug also has an inhibitory effect on certain phase I enzymes, including CYP3A4 and CYP1A2.[97] It therefore reduces the oxidation of AFB_1 to AFB_1-8,9-epoxides. Like chlorophyllin, oltipraz affects AFB_1 metabolism at two levels.

A randomized, placebo-controlled, double-blind trial conducted in adults with detectable serum levels of an aflatoxin–albumin adduct in the Qidong county showed a 2.6-fold increase in the urinary excretion of the AFB_1-8,9-*exo*-epoxide metabolite, AFB_1-mercapturic acid, and lesser increases in the excretion of other AFB_1 biomarkers.[98] In another study, 1 month of therapy with weekly oltipraz administration led to a significant decrease in aflatoxin M_1 excretion in the urine, and sustained low-dose oltipraz increased the conjugation of AFB_1.[99]

Because of cost and safety considerations, it is doubtful whether oltipraz could be used on a wide scale in the secondary prevention of HCC. A whole host of chemicals have been shown in animal models or tissue culture experiments to prevent cancer formation or to have properties suggesting that they might have chemopreventive potential. However, until the use of these substances can be shown to be effective,

safe, and feasible in humans, they cannot be considered to have a role in the secondary prevention of human HCC. The same is true of a number of molecular maneuvers performed in transgenic animal models, and of dietary changes in animals known to spontaneously develop liver cancers.

The bigger question of whether the modulation of carcinogen metabolism, either by enzyme inhibition or by enzyme induction, can substantially reduce the risk of cancer individuals at high risk for exposure to environmental carcinogens remains open.[34]

Polyprenoic acid

Retinol and its derivatives (retinoids) have important roles in controlling cell growth and differentiation.[100] Retinoids have been shown to inhibit the activation of hepatic stellate cells[101] and to suppress the proliferation of malignant hepatocytes.[102] Retinol also inhibits the formation of AFB_1–DNA adducts in hepatocytes.[103] In addition, retinoids inhibit the production of proinflammatory cytokines, thereby reducing inflammatory reactions, and can neutralize reactive oxygen species.[103,104] A statistically significant interaction between low serum retinol levels and HBsAg positivity on the risk for HCC has been demonstrated.[104]

Crucial events in alcohol-induced hepatic damage are an altered homeostasis and the depletion of retinoids (retinyl esters, retinol, and retinoic acid),[105] as well as the proliferative activation of hepatocytes — changes that may provide a promoting environment for hepatocarcinogenesis. Malfunction of the retinoid nuclear receptors may do likewise.[104] Possible mechanisms for these actions may involve crosstalk with the alcohol-activated Jun N-terminal kinase (JNK)-dependent signaling pathway, inhibition of c-Jun and c-Fos activity, and induction of apoptosis. The restoration of retinoids and their homeostasis by either dietary supplementation or the use of an inhibitor of retinoid metabolism might thus have a secondary preventive effect on hepatocarcinogenesis caused by chronic alcohol abuse and perhaps a number of other risk factors.

Polyprenoic acid, an acyclic retinoid, was originally shown to have chemopreventive properties in experimental models of liver cancer.[105]

In addition, the agent suppresses cell growth and induces differentiation and apoptosis in human cancer cell lines.[105] Clinical trials of polyprenoic acid have been confined to attempts to prevent the recurrence of HCC after surgical resection (see the section on "Prevention of Recurrence of Hepatocellular Carcinoma").

Other chemoprevention possibilities

A lessened risk of HCC correlates with an increased consumption of leafy, green vegetables.[106] These vegetables contain a range of biologically active phytochemicals. Plants belonging to the family *Cruciferae* and the genus *Brassica* (including broccoli, cauliflower, and Brussel sprouts) contain large quantities of isothiocyanates, mostly in the form of their glycosinolate precursors. Some of these isothiocyanates have been shown to inhibit tumor formation in rats.[107] Trials of the use of glycosinolates and isothiocyanates from broccoli sprouts in preventing HCC in cohorts of subjects at high risk for the tumor are in progress. One such trial in the Qidong county, the People's Republic of China, showed no difference in urinary aflatoxin–N^7-guanine levels between volunteers receiving infusions of broccoli sprouts and those receiving placebo.[107]

Iron storage diseases

Whether or not excess hepatic iron is proved to be directly hepatocarcinogenic, the deironing of patients with HH by repeated venesection would be expected to have a secondary preventive effect against HCC formation, both by reversing the accumulation of iron and by preventing the development of cirrhosis. Deironing aims to lower the serum ferritin concentration to a normal level and to maintain it there. Studies have shown that removing the excess iron dramatically improves prognosis: life expectancy reverts to normal, the number of cases of HCC decreases if cirrhosis is not present, and survival improves considerably in those with cirrhosis.[108] This intervention is preferably commenced as soon as the diagnosis of HH is made and should be continued for life.

Secondary prevention or reduction of excess hepatic iron by repeated venesection has not been attempted on a large scale in dietary iron overload.

α1 antitrypsin (α1AT) deficiency

Although the repeated infusion of purified α1AT obtained from pooled human plasma may have a protective effect against the development of emphysema in patients with α1AT deficiency, there is at present no evidence that this or other approaches to intervention prevent the development of HCC.

Glycogen storage disease

Minimizing the metabolic consequences of the glycogen storage diseases, especially increased lactate production, by administering glucose in the form of corn starch may decrease the risk of long-term complications, including HCC.[109] In addition, experimental evidence indicates that early adeno-associated virus vector–mediated gene therapy could reduce the risk of long-term complications of glycogen storage disease type 1a, including HCC.[110]

Hereditary tyrosinemia type 1

A diet restricted in both tyrosine and phenylalanine can ameliorate the symptoms in these patients. However, this diet alone does not prevent the development of chronic liver disease or HCC.[111] If the tyrosine- and phenylalanine-restricted diet is, starting in infancy, accompanied by the long-term administration of 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione) (NTBC; nitisinone), then chronic liver dysfunction and disease and HCC may be prevented.[111] But, if the nitisinone is started after 2 years of age, the development of HCC is not prevented.[111,112]

Type II hypercitrullinemia

At present, no forms of secondary prevention are helpful in this disorder.

Wilson's disease

The current secondary intervention of choice in preventing the hepatic complications of Wilson's disease is oral administration of zinc, with or without the copper chelator, trientrine.[113,114]

Tertiary prevention

Chronic necroinflammatory hepatic disease is a premalignant condition.[27–30] The three most common causes of cirrhosis complicated by the development of HCC are alcohol abuse as well as chronic HBV and HCV infections. In the last two, long-term suppression of viral replication could be expected to reduce inflammation as well as hepatocyte necrosis and proliferation, and hence lessen the risk of progression to dysplasia and malignant transformation.[27,30] Interferon has been most widely used in the treatment of both chronic HCV- and HBV-induced diseases,[75,115–117] and glycyrrhizin has long been used in chronic HCV infection in Far Eastern countries. These agents may be regarded as being immunopreventive by functioning as biological response modifiers.

Use of interferon-α in preventing hepatitis C virus–induced hepatocellular carcinoma

The development of HCV-induced HCC is closely related to the duration and progression of chronic hepatitis and cirrhosis. A large number of studies on the use of interferon (IFN) treatment in preventing the supervention of HCC in patients with chronic HCV-related hepatitis or cirrhosis have now been reported, particularly from Japan and Europe.[75,115,116,118–125] Most, but not all, of them have shown that this treatment has a small but significant effect on reducing the risk of HCC or, at least, delaying the development of the tumor. However, many of the published analyses, particularly among the earlier ones, have had defects in design, some of which have been difficult to avoid because of ethical and logistical considerations. Particularly important among the defects have been relatively small numbers of

patients studied, heterogeneity of the patients, poor matching of treated and untreated patients, and insufficient length of patient follow-up. Ideally, it takes at least 5 years to show a statistically significant difference between rates of HCC development in IFN-treated and IFN-untreated patients. Another difficulty in proving a beneficial effect of IFN treatment is the high rate of tumor development in the treated patients.

IFN-induced prevention or delay in HCC formation has been shown to be likely in patients with chronic HCV hepatitis, but conflicting results were obtained when cirrhosis was present. However, recent analyses of pooled data have confirmed that IFN significantly reduced the risk of HCC even when cirrhosis was present.[75,115,118,119] A number of studies have shown that the reduction in rates of malignant transformation complicating both chronic hepatitis and cirrhosis has been far greater in patients in whom a sustained response to IFN was obtained[75,115,118–122]; however, this group represents a relatively small proportion of the cirrhotic patients. In some studies, the beneficial effect of IFN was confined to patients with sustained viral clearance; whereas in others, it also accompanied a sustained biochemical response (normalization of serum transaminase levels)[75,115.3,118–122] or perhaps even no response provided that fibrosis was mild (F1).[123]

HCC is more likely to develop in the presence of severe hepatic fibrosis,[118] and the likelihood of IFN preventing HCC formation is proportional to the degree of hepatic fibrosis.[123] Fibrosis has been shown either to progress more slowly or to regress in patients in whom IFN induces a sustained virological response and normalization of serum transaminase levels, indicating that the antifibrotic effects of IFN may contribute to its chemoprevention capability.[124,125] Despite these encouraging results, it should be remembered that the tumor may still develop even with complete elimination of the virus and normalization of the serum transaminase levels.

The relatively recent innovation of combining pegylated IFN and ribavirin in the treatment of patients with chronic HCV infection has improved the sustained virological clearance rates. However, the effectiveness of this combination in preventing supervention of HCC has not yet been reported. A preventive effect of IFN is supported by studies

showing that this treatment prevents recurrences of HCC after initial surgical resection or ablative treatment.[126,127] Further carefully controlled trials are needed to put this observation beyond doubt.

The mechanism or mechanisms by which IFN reduces the risk for HCC are uncertain. Clearance of the virus as well as reduction in hepatic inflammation and its consequences are obvious factors, but another mechanism may be upregulation of the function of tumor suppressor genes.[128] In support of this mechanism is the observation that IFN has a tumor-inhibiting effect on HCC cell lines.[129]

Use of interferon-α in preventing chronic hepatitis B virus–induced hepatocellular carcinoma

Most of the factors known to increase the risk of HCC in chronic HBV carriers are irreversible.[18,19] Recent studies have, however, shown that patients who have persistently high levels of HBV replication — as shown by the presence of HBeAg in serum — are at higher risk of HCC, and that chronic HBV carriers with low serum HBV DNA levels seldom progress to tumor formation.[130–133] Theoretically, antiviral treatment that results in viral clearance or sustained suppression of HBV replication should prevent the development of HCC. However, in contrast to the many studies on the effect of IFN in preventing the development of HCC in patients with HCV-induced chronic hepatitis or cirrhosis, fewer studies have addressed this issue in patients with HBV-related disease and the findings have been conflicting. In addition, the majority of the trials were performed in patients without advanced fibrosis or cirrhosis, making the transferability of the results to the whole spectrum of chronic liver disease caused by HBV questionable.[115–117] Most of the studies failed to provide convincing evidence that treating patients with HBV-related cirrhosis or chronic hepatitis with IFN would lessen the risk of malignant transformation.[115–117] A recent meta-analysis of the available literature concluded that consistent results were observed only with studies emanating from European countries, and these did not indicate a protective effect of IFN.[115] It is possible that IFN protects against the development of HCC only in those patients with very high levels of viral replication.

Two recent studies have, however, shown a protective effect of lamivudine treatment in patients with chronic HBV infection. In the first, a randomized, double-blind, placebo-controlled trial, HCC occurred in 3.9% of Taiwanese patients in the lamivudine-treated group compared with 7.4% in the placebo-treated group (hazard ratio, 0.49; $p = 0.047$).[134] In the second, a case/control study of a large number of Japanese patients with chronic hepatitis B showed that those who received lamivudine treatment had an annual incidence of HCC of 0.4%/patient compared with 2.5%/patient in the control group.[135] The main disadvantage of the long-term administration of lamivudine is the emergence of resistant strains of the virus as a result of the development of YMDD mutations in the reverse transcriptase (polymerase) gene. Newer drugs of a similar sort, adefovir and entecavir, have a far lower risk of developing resistant strains, and future trials should examine their efficacy in preventing HCC. In addition, future trials need to address the questions of whom to treat and for how long treatment should be administered.

The development of more effective and cost-effective treatments for B and C viral hepatitis remains a major challenge.

Glycyrrhizin

Glycyrrhizin, the active principle of licorice, has a chemical structure similar to cortisone. It is composed of one molecule of glycyrretinic acid and two molecules of glucuronic acid. Glycyrrhizin enhances IFN-γ production, has immune-modulating activity, and stimulates natural killer cells.[136,137] The compound also has antioxidative properties and suppresses hepatic inflammation.[136,137] It has been used for over 30 years in Japan, partly in the form of the Chinese herbal medicine Shosaikoto, of which glycyrrhizin is one of the main ingredients, in the treatment of chronic hepatitis (of which the most common cause by far in Japan is HCV).

Daily intravenous injections of glycyrrhizin reduce the levels of the serum aminotransferases in a dose-dependent manner in these patients, although antiviral activity *per se* is not evident.[138] In a prospective trial performed in Japan over 15–20 years, a 2.5-fold lower risk of HCC

formation was reported in patients receiving parenteral glycyrrhizin compared to those who did not.[136] HCV-RNA titers did not decrease, and the beneficial effect of the drug was attributed to controlling or retarding necroinflammatory and fibrotic processes in the liver. These conclusions were supported by two further studies.[139,140] In addition, glycyrrhizin reduced the risk of HCC recurrence after surgical resection.[141] Daily intravenous injections of glycyrrhizin would appear to be a drawback of this approach to prevention.

Another chemopreventive approach is with polyphenols derived from green teas. These agents have been effective in preventing liver tumors in animal models, and a clinical study is underway in Guanxi, the People's Republic of China.[142]

Inherited metabolic diseases

Liver transplantation, with or without lung transplantation, at present offers the only way to prevent HCC in patients with α1ATZ.[143] Liver transplantation should be considered in patients with glycogen storage disease type 1a when dietary treatment fails or when hepatic adenomas develop.[144] In patients with hereditary tyrosinemia, liver transplantation is curative both for HCC and for the metabolic disturbance.[145] In Wilson's disease with severe liver pathology, liver transplantation is the only option to prevent HCC.[111,112] Liver transplantation would seem to be the sole option to intervene in preventing HCC in hypercutrillemia, although no reports to this effect have been published.

Prevention of Recurrence of Hepatocellular Carcinoma

The recurrence of HCC or a second *de novo* tumor after apparently successful resection or ablation of HCC is not infrequent,[146] and strategies to prevent this occurrence are needed to improve the overall survival of these patients. If the risk factor for the initial tumor (such as chronic HBV or HCV infection, aflatoxin exposure, or iron overload) is still present, attempts to eradicate the cause should, if possible, be instituted.

Three agents have been reported to reduce the risk of recurrence: IFN; the acyclic retinoid, polyprenoic acid; and glycyrrhizin. Two randomized

control trials in Japan have evaluated the effect on recurrence of HCV-induced HCC of IFN-α and one of IFN-β. All three trials showed a lower recurrence rate in those treated, with the benefit being greatest in those achieving a sustained virological response.[126,127,147] A single trial showed that glycyrrhizin reduced the risk of HCC recurrence after surgical resection.[141]

Oral administration of polyprenoic acid over 12 months has been reported in a double-blind, placebo-controlled trial in Japanese patients to delay and perhaps prevent a second HCC after resection of the initial tumor or its eradication using percutaneous ethanol injection, and to significantly improve survival rates.[148–150] Serum leactin–reactive α-fetoprotein (AFP-L3), which indicates the presence of transformed hepatocytes in the remnant liver, disappeared after 12 months of administration in the polyprenoic acid group but not in the placebo group. This observation suggests that the AFP-L3–producing latent malignant clones were eliminated from the remnant liver by the polyprenoic acid and prevented the recurrence of HCC.[150] The findings in this trial will need to be confirmed in further studies with a prolonged follow-up period before its use for this indication can be advocated.

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5

Screening

Morris Sherman

Introduction

Hepatocellular carcinoma (HCC) continues to be one of the more common malignancies in the world. In many parts of the world, the incidence is rising[1–6]; and in most countries the incidence and mortality rates are identical, indicating that most patients who acquire the disease die from it. To be sure, curative treatments do exist. Unfortunately, most patients still present with advanced disease, despite the fact that the background risks for HCC are well known and that patients most likely to get HCC can be easily identified. Early detection of other cancers — such as colon cancer, cervical cancer, and in some women breast cancer — has been shown to reduce mortality. Screening methods for the early detection of HCC are also available, and have been shown to reduce mortality from the disease. This chapter describes these methods and the application of a screening program.

Screening Tests

Screening tests fall into two categories: serological and radiological. The serological tests that have been most intensively investigated are the alpha-fetoprotein (AFP) test, the des-gamma-carboxy prothrombin (DGCP) test, and the ratio of the L3 fraction of AFP to total AFP (AFP-L3) test. None are very useful as screening tests. Receiver operating curve analysis of AFP used as a diagnostic test suggests that a value of about 20 ng/mL provides the optimal balance between sensitivity and specificity.[7] However, at this level, the sensitivity is only 60%, i.e. AFP surveillance would miss 40% of HCC if a value of 20 ng/mL is used as the trigger for further investigation. This is inadequately sensitive for use as a screening test. If a higher cut-off is used, a progressively smaller proportion of HCCs will be detected; if the AFP cut-off is raised to, e.g., 200 ng/mL, the sensitivity drops to 22%. Conversely, reducing the cut-off means that more HCCs would be identified, but at the cost of a progressive increase in the false-positive rate. This and other data[8–11] have led the American Association for the Study of Liver Diseases (AASLD) to recommend that screening with AFP no longer be performed. Although serum AFP is an inadequate screening test,[8] measurement of AFP still has a role in the diagnosis of HCC. In cirrhotic patients, the association of a mass in the liver and an AFP greater than 100 ng/mL has a very high positive predictive value for HCC.[8]

Another serological test used to diagnose HCC is the des-gamma-carboxy prothrombin (DGCP) test, also known as prothrombin induced by vitamin K absence II (PIVKA II).[11–15] Most reports on the use of DGCP have evaluated the use of this test in a diagnostic mode rather than for surveillance. Although there are reports of its use in a surveillance mode, these do not yet provide sufficient justification for the routine use of this marker. There are also reports that DGCP is a marker for portal vein invasion by tumor.[16] If confirmed, this would also suggest that DGCP is not a good screening test. A screening test should be able to identify early disease, not late disease.

Alpha-fetoprotein exists in serum as a series of molecules with different degrees of glycosylation. The L3 fraction is reported to be more specific for HCC than total AFP concentration. The ratio of the L3 fraction of AFP to total AFP has been investigated as a screening test

for HCC.[17–23] Although in some patients the AFP-L3 may be elevated prior to the demonstration of a mass in the liver, it cannot be recommended for general use. The test requires special equipment and is expensive.

The radiological test most widely used for surveillance is ultrasonography. A small HCC on ultrasound may take on one of several different appearances. The smallest lesions may be echogenic because of the presence of fat in the tumor cells; other lesions may be hypoechoic or show a target-lesion appearance. None of these appearances is specific. Ultrasound has been reported to have a sensitivity of between 65% and 80%, and a specificity greater than 90% when used as a screening test.[24] However, the performance characteristics have not been as well defined in nodular cirrhotic livers undergoing surveillance.[25–27] These performance characteristics, although not ideal, are considerably superior to any of the serological tests. The major drawback to using ultrasound for HCC surveillance is that it is very operator-dependent. In addition, scanning is difficult in obese subjects. Periodic ultrasound examinations have become the recommended screening test for HCC.

Strategies such as alternating AFP and ultrasonography at intervals have no basis in theory. The guiding principle should be that the best available screening test is chosen and applied regularly. Combined use of AFP and ultrasonography increases detection rates, but also increases costs and false-positive rates.[28] Some reports suggest the use of computed tomography (CT) scanning as a screening test for HCC.[29–31] This is problematic for several reasons. The performance characteristics of CT scanning have been developed in diagnostic studies, but the performance characteristics of CT scanning in HCC surveillance are unknown. If the CT scan is to be used as a screening test, i.e. every 6–12 months over many years, there is a significant radiation exposure to be considered. Practical experience suggests that the false-positive rate will be very high.

Surveillance Interval

The ideal surveillance interval is not known.[32,33] A surveillance interval of 6–12 months has been proposed based on tumor doubling times.[18]

The surveillance interval is determined by the tumor growth rates, not by the degree of risk. This is an important concept because it means that the surveillance interval need not be shortened for patients who are thought to be at higher risk. However, it is important to make the distinction between patients undergoing surveillance (i.e. those who, although high risk is recognized, do not have any *a priori* reason to suspect HCC) and those in whom surveillance tests have been abnormal and there is a concern that HCC is already present. Such patients are, strictly speaking, not candidates for surveillance, but should be receiving enhanced follow-up (see later).

Target Populations

The only randomized controlled study in which screening has been shown to reduce HCC mortality was undertaken in a population of hepatitis B carriers[34]; however, the characteristics of the screened population were not well described. Decision analysis has allowed us to define the circumstances under which screening could theoretically be beneficial.[35,36] To be considered effective, screening has to prolong the life expectancy of the screened population by at least 3 months.[37] For practical purposes, these are cirrhotics in whom the incidence of HCC exceeds about 1.5%/year. The decision analyses did not stratify patients according to severity of liver disease at the start of screening, so it is not clear whether the benefits of screening apply equally in patients. Thus, younger hepatitis B carriers, who are at lower risk of HCC, may not require screening.

Populations in whom screening is likely to be beneficial in reducing HCC-related mortality include male hepatitis B carriers over the age of 40 years, female hepatitis B carriers over the age of 50 years, and patients with cirrhosis from any cause.[35,36,38] The latter includes patients with cirrhosis due to chronic hepatitis C, steatohepatitis, alcoholic liver disease, genetic hemochromatosis, alpha-1 antitrypsin deficiency, and primary biliary cirrhosis. The benefits of screening in patients with cirrhosis due to autoimmune hepatitis or Wilson's disease are less clear.

Who Should Not Be Screened?

Screening should only be offered to patients for whom therapy is available. With the availability of noninvasive methods of treating small HCC (primarily radiofrequency ablation), the contraindications to screening are few. Age is probably the major contraindication. The survival after diagnosis of a small HCC will vary, although most patients can expect to live 2 years and some will live 5 or more years. Only those whose expected survival from age or concomitant disease is longer than the expected survival from HCC should undergo screening. Patients with advanced liver disease, who are unlikely to receive a liver transplant, may not benefit from screening because their life expectancy from their liver disease may be shorter than the life expectancy from the tumor.

Does Screening Reduce HCC-related Mortality?

The objective of screening for any disease is to institute treatment early and thereby reduce mortality from the disease. As mentioned above, screening has been shown to reduce HCC-related mortality in a single randomized controlled trial.[34] In this study, conducted in China, patients with hepatitis B were screened with alpha-fetoprotein and ultrasound every 6 months; those who developed HCC underwent hepatic resection, if possible. Over the 5 years of the study, the mortality in the screened group was 37% lower than that in the unscreened group — this was despite a record of compliance in the screened group that was less than optimal. There is no equivalent study showing the benefit for any other cause of liver disease; furthermore, it is not certain that the results of this study can be generalized to other causes of liver disease. In patients with chronic hepatitis B, HCC can develop in a liver that is not cirrhotic; thus, fewer patients would have liver disease that is too advanced to allow resection. In contrast, in other causes of liver disease, HCC occurs almost universally in the presence of cirrhosis, so a larger proportion of patients will have liver disease too far advanced to allow resection.

The study referred to above was conceived and designed in an era when AFP screening was thought to be valuable. Subsequent investigation has shown that screening with AFP alone is not highly

effective.[7] In addition, the Chinese hepatitis B study showed that combined screening with AFP and ultrasound was associated with a higher false-positive rate and higher costs, although the detection rate did increase slightly.[39] However, if AFP detects a lesion that is too small to be seen on ultrasound or other imaging techniques, such lesions cannot be treated; therefore, there is no advantage to adding alpha-fetoprotein to the screening regimen. Likewise, combined screening with alpha-fetoprotein and ultrasound is also not recommended. The recommended regimen, therefore, is to screen at-risk individuals with ultrasound only at 6-month intervals.[36]

Dealing with Abnormal Screening Test Results

An essential component of screening is the algorithm developed to deal with abnormal screening test results. Not all abnormal test results are due to HCC, since all tests are associated with a measurable false-positive rate. Furthermore, the smaller the lesion that is detected, the closer the lesion is to the premalignant state and the less certain it is that the lesion will progress to behave in a malignant fashion, i.e. develop independent growth. Not all dysplastic lesions in the liver develop into cancer.[40] Therefore, it is important to develop an algorithm that allows rapid and accurate investigation and clearly distinguishes a false-positive result from a true-positive one. Unfortunately, this aspect of the management of abnormal screening test results has not been well investigated.

The AASLD has issued guidelines to help separate cancers from non-malignant lesions.[38] The guidelines are based mostly on expert opinion, and take into consideration the following:

- Liver biopsy of lesions smaller than 1 cm is technically difficult and may be inaccurate.
- Histological interpretation of the earliest changes of HCC in these small lesions is also challenging.
- The radiological features of HCC (see below), when present, are highly specific.
- Large lesions (>2 cm) exhibit typical radiological features in the majority of lesions.

- In smaller lesions (1–2 cm), the typical radiological features are less often present and the specificity of these features may be lower.

The diagnostic algorithm in Fig. 1 suggests that lesions smaller than 1 cm are too small to investigate and generally have a low likelihood of being malignant. These should be followed at 3–4-month intervals. Lesions between 1–2 cm have a higher likelihood of being malignant. If the typical radiological features are present in two dynamic contrast studies, the specificity of these findings is sufficiently high that the diagnosis can be made without a biopsy[41,42]; if the two radiological examinations are discordant or atypical, a biopsy is required to confirm the diagnosis of HCC. If the lesion is larger than 2 cm, a single contrast radiological examination is sufficient to make the diagnosis if the findings show the typical features; if the features are not typical, a biopsy is necessary.

A workup of an abnormal screening test result that does not convincingly show cancer requires additional or enhanced follow-up. Since the possibility of a false-negative cannot be easily ruled out, further testing is required. The algorithms shown in Figs. 1–3 indicate the nature of

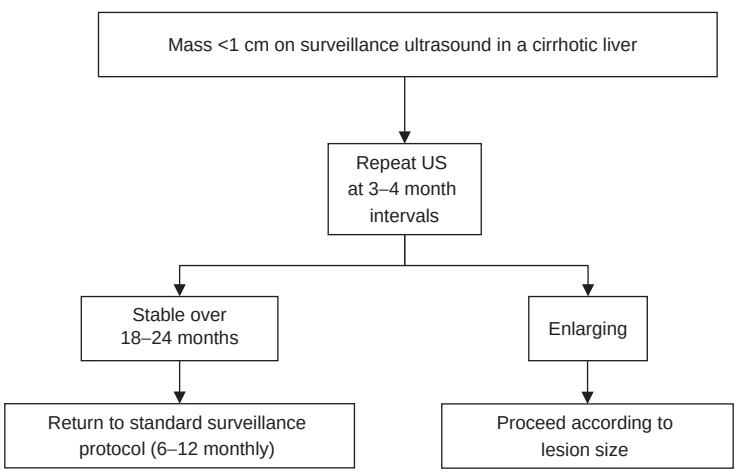

Fig. 1. Diagnostic algorithm for lesions found on ultrasound (US) that are smaller than 1 cm in diameter.

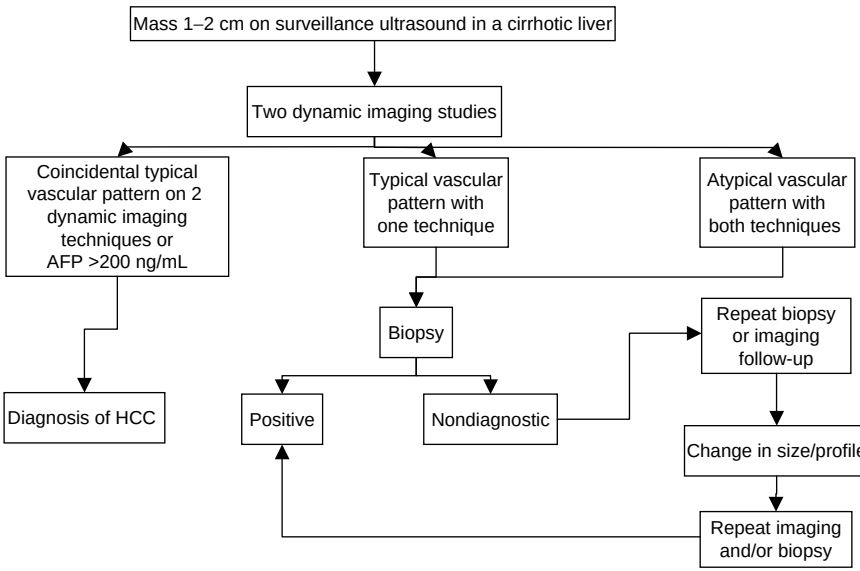

Fig. 2. Diagnostic algorithm for lesions found on ultrasound that are between 1–2 cm in diameter.

additional follow-up, which should be conducted at 3–4-month intervals. If the lesion has been stable for 18–24 months and no tests are convincingly positive for HCC, then the lesion is likely benign and the patient can be entered into routine screening again.

A Screening Program

Much attention has been focused on screening tests, both AFP and ultrasound. However, the process of screening involves more than just the application of a test or tests. A screening program includes identification of the population likely to benefit right through to definitive diagnosis and treatment; and includes application of the screening test(s), evaluation of abnormal test results, and application of the appropriate treatment. In particular, it is important to establish quality assurance standards, and to have the proper management structures in place in order to ensure that these standards are maintained and that corrective

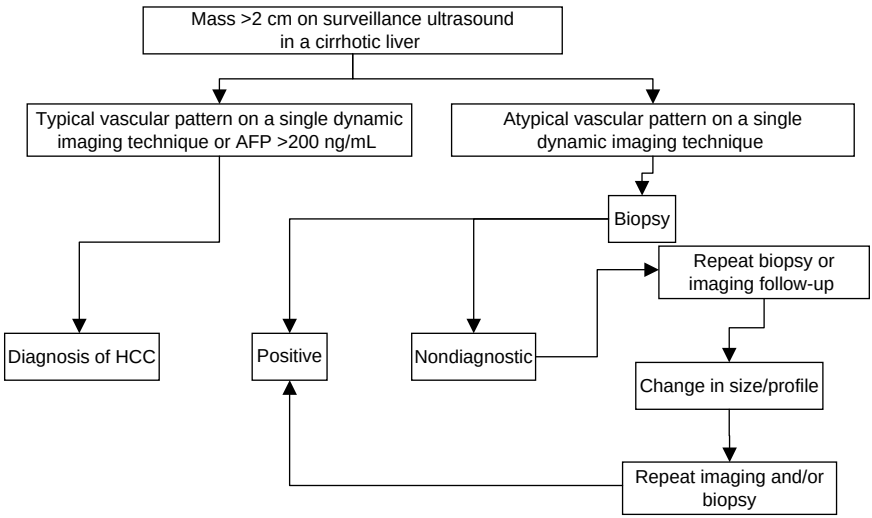

Fig. 3. Diagnostic algorithm for lesions found on ultrasound that are larger than 2 cm in diameter.

action is taken if they are not. This is particularly important since ultrasound is such an important component of the screening process. In many parts of the world, high-quality ultrasound is available and has allowed the establishment of screening programs, in which patients rarely present with tumors larger than 3 cm. Unfortunately, in the USA, high-quality ultrasound for HCC screening is seldom available, and there is no structure in place to ensure that this deficiency is corrected. Under these circumstances, screening is likely to be less than optimal.

Summary

Patients at risk for the development of HCC should undergo screening with ultrasonography at 6-month intervals. Abnormal ultrasound results should be investigated according to the algorithm outlined above. Patients in whom HCC is not identified are nonetheless at risk (false-negative workup) and should be followed at shorter intervals (3–4 months).

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6

Presentation and Diagnosis

Dario Ribero, Gareth Morris-Stiff and Jean-Nicolas Vauthey

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common neoplasm worldwide and the third most common cause of cancer-related mortality, with as many as 600 000 new cases diagnosed annually and a similar number of deaths each year.[1] Signs and symptoms at presentation, as well as clinical features such as age and the presence and severity of accompanying liver cirrhosis, differ among the various regions of the globe as a result of epidemiologic differences in etiologic factors and medical interventions devoted to surveil high-risk populations. The purpose of this chapter is to provide an overview of the clinical presentation of patients with HCC.

Clinical Presentation: Epidemiologic Differences

The incidence of HCC varies greatly among different ethnic groups and geographic regions of the globe, with the highest incidence of cases in Eastern and Southeastern Asia and sub-Saharan Africa at 50–150 cases

per 100 000 population.[2] In Latin America and developed countries, the incidence of HCC has traditionally been low, with less than 10 cases per 100 000 population, with the exception of those countries bordering the Mediterranean basin where the cancer occurs with intermediate frequency. However, recent evidence from the United States has shown that the prevalence of HCC is increasing rapidly, with data from the National Cancer Institute indicating a twofold rise in overall incidence between 1980 and 1998 as well as a 37% increase in mortality between 1997 and 2001.[3] This trend has also been observed in the United Kingdom and France.[4,5]

The epidemiologic differences are largely explained by differences in the prevalence of hepatitis B virus (HBV) infection worldwide, with endemic areas being those with the highest HCC incidence. In low-incidence countries, hepatitis C virus (HCV) infection and alcoholic cirrhosis are the leading etiologies. It would appear that the increasing prevalence of HCC in the Western world is following 20–30 years after the HCV epidemic in the 1960s and 1970s.[3]

Clinical features and presenting symptoms differ markedly between subjects diagnosed with HCC from endemic HBV areas and those from low-prevalence zones (Tables 1 and 2). This heterogeneity is the result of several factors such as differences in HBV- and HCV-related tumorigenesis, and the age at which patients acquire the infection. Up to 90% of patients with perinatal HBV infections, from vertical transmission from the mother to the newborn, follow a chronic course of infection and have a higher risk of HCC compared to those who acquire HBV later in life through sexual or parenteral routes in whom more than 90% of acute HBV infections resolve spontaneously.

Beside these biologic differences, the time that elapses between the appearance of the tumor and the diagnosis is critical in determining the clinical pattern. Disappointingly, the growth of HCC is typically silent during the early course of disease and becomes symptomatic only in advanced stages because of several reasons. The tumor must reach a substantial size before it invades adjacent organs or structures. The functional reserves of the liver ensure that hepatic decompensation does not appear until a large portion of the parenchyma has been replaced by the tumor, thus delaying the development of clinical symptoms related to a

Table 1. Clinical features of HCC according to prevalence zone and geographic location.

Prevalence zone	Geographic location	Etiology	Age of onset (years)	Presence of cirrhosis	Diagnosis at an asymptomatic stage	Male gender
High						
	Rural South Africa	HBV	46	60%	16%	86%
	China	HBV	50	70%–80%	30%	68%
	Japan	HCV > HBV > EtOH	65–68	85%	n/a	74%
Intermediate						
	Italy	HCV > HBV ≥ EtOH	61	∼80%	38%	75%
	France	HCV > HBV ≥ EtOH	55	∼80%	n/a	76%
Low						
	North America	NSCirr > EtOH > HCV > HBV	65	∼80%	n/a	74%

HBV: hepatitis B virus; HCV: hepatitis C virus; EtOH: alcohol; NSCirr: nonspecific cirrhosis; n/a: not available.
Adapted from Szilagyi A, Alpert L (1995), *Am J Gastroenterol* **90**:15–23 (with permission), with data pooled from Refs. 3, 7, 50–54.

Table 2. Clinical signs and symptoms of HCC in different geographic regions.

Clinical data	Black South Africa[48] (%)	Japan[49,50] (%)	China[17,51] (%)	Italy[7,23] (%)
Asthenia	—	60.5	8.6	15
Abdominal pain	95	46.2	51	38
Anorexia	25	44.7	6.7	13
Weight loss	34	28.9	—	8
Ascites	51	26.5	17.5	12
Palpable mass	92	23.3	4.7	—
Hepatomegaly	—	—	53.8	90
Ankle edema	—	16.8	14	—
Jaundice	28	16.7	9	14
Fever	35	16.7	1.7	12
Nausea/Vomiting	8	15.6	—	3
Diarrhea	—	—	0.9	3
Variceal bleeding	2	7.6	—	4
Hemoperitoneum	—	7.4	2.9	3
Others	3	—	—	3
Asymptomatic	—	—	29.9	38

functional disturbance of the liver. Moreover, none of the symptoms or signs attributable to HCC are pathognomonic. Fortunately, advances in imaging technology and the recent implementation of aggressive surveillance programs in high-risk patients over the past decades have increased the likelihood of discovering small tumors, thereby precipitating a shift in the clinical presentation with an increase in the number of patients diagnosed at an early, asymptomatic stage. Indeed, Inagaki *et al.*[6] reported a decrease in the frequency of all presenting symptoms of HCC in the late 1980s as compared with that seen until 1981. Recent reports indicate that the incidence of asymptomatic patients in areas with active screening programs is 43%–60%.[7,8]

HCC is usually diagnosed during the fifth and sixth decades of one's life as a consequence of the time needed to first develop liver cirrhosis and subsequently the tumor. HBV-positive patients who develop HCC appear to be younger than those with HCV,[9] and the age at diagnosis

of HCC in high-incidence areas is 10–20 years earlier than in low-incidence areas. Notably, whereas HCC in HCV patients arises mostly in the setting of cirrhosis, liver cirrhosis is not an essential prerequisite for HBV-related HCC; and in 12%–50% of these latter patients, there is no cirrhosis associated with the HCC.[10] For most etiologies, HCC has a male predominance and is reported to be four to eight times more common in males than females in low- and high-prevalence regions, respectively.

The majority of patients with HCC, at least in the West, have coexisting cirrhosis with estimates of approximately 80% (Table 1). Exceptions to this rule are fibrolamellar variants in young adults and *de novo* HCCs in the elderly. There is a great deal of variation in the prevalence of HCC in relation to the etiology of the cirrhosis. The presence of HBV and HCV cirrhosis carries a high risk of 3%–5% per year.[11] Another chronic liver disease at high risk for HCC is genetic hemochromatosis, with an annual risk of 7%–9%.[12] This risk may be reduced, but does not disappear, with optimal medical management of the condition. Other genetic conditions such as tyrosinemia and $\alpha 1$ antitrypsin deficiency also have a risk for the development of HCC. For alcoholic cirrhosis amongst males, the risk is placed at 1%–4% per annum[13]; the risk for female alcoholics appears to be less. For other causes of cirrhosis such as autoimmune hepatitis, primary biliary cirrhosis, and Wilson's disease, there is less accurate epidemiological data. Of recent concern is the increased documentation of HCC amongst patients with nonalcoholic steatohepatitis (NASH).[3,14]

In addition to cirrhosis, a number of other factors have been linked to the development of HCC, the most conclusive of which has been aflatoxin B_1 (AFB_1).[15] Aflatoxins are mycotoxins from *Aspegillus flavus* and *Aspergillus parasiticus*, and are amongst the most common naturally occurring carcinogens. They are seen in African and Asian countries, where grain is stored in hot and humid conditions. There is also some evidence in relation to the long-term use of oral contraceptives and anabolic steroids. In addition, smoking has been identified as a risk factor for HCC amongst patients with chronic liver disease.[11] Obesity and diabetes are also believed to be important, and may be linked to the presence of fatty liver disease and subsequent NASH.[3,16]

Clinical Presentation: Signs and Symptoms

The coexisting presence and severity of cirrhosis strongly impacts on the clinical pattern of presentation (Fig. 1), with a clear relationship between the symptoms and signs and both the functional hepatic reserve and tumor volume. In the presence of moderate or severe cirrhosis, signs and symptoms of liver failure and portal hypertension such as progressive jaundice, ascitis, tremors, confusion and disturbances of consciousness, and frank encephalopathy are the predominant factors. Peripheral stigmata of liver insufficiency, such as ankle edema, palmar erythema, and caput meduseae, are accompanying signs. Hepatomegaly can be recognized on physical examination and is more frequently appreciated in noncirrhotic patients,[17] being largely related to the volume of the tumor. In such patients, hepatomegaly can cause an asymmetry of the upper abdomen and, as a result of tumor compression, the edge of the right costal margin may be projected forward. Voluminous tumors may also cause appreciable elevation of the right

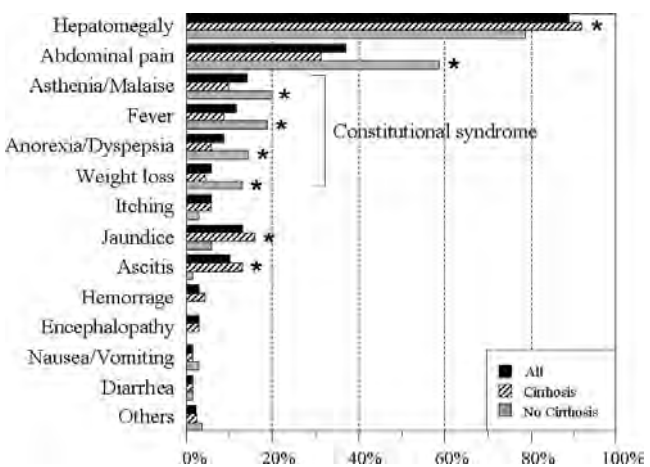

Fig. 1. Clinical presentation of 475 Italian patients according to the presence or absence of liver cirrhosis. The constitutional syndrome was more common in noncirrhotic patients, whereas symptoms of liver failure and portal hypertension were more frequent in those with cirrhosis. *Significant difference between cirrhotic and noncirrhotic patients. (Modified with permission from Trevisani *et al.*[7])

hemidiaphragm,[18] leading to mild respiratory symptoms, and can be clinically diagnosed through the identification of dullness to percussion in association with absent breath sounds at the right lung base. In such cases, a pleural effusion is sometimes present, as is the finding of linear atelectasis in the right lower lobe of the lung on a chest radiograph.

Palpation of the abdomen may reveal a mass, and an arterial bruit can be heard in 25% of patients due to the presence of an arteriovenous fistula.[19] This bruit can be differentiated from one transmitted from the aorta because it can be heard throughout the liver; is independent of patient position; and is louder, rougher, and longer than an aortic bruit. In Southeast Asian and African populations, the underlying liver cirrhosis appears to be milder and often does not produce symptoms, being discovered coincidentally during the diagnostic workup. Indeed, in these high-incidence areas, symptoms related to tumor growth and features of advanced malignancy — such as weight loss, dysphagia, fever, anorexia, and malaise (the so-called constitutional syndrome) — are the usual findings, and abdominal distension is a common coexisting feature.

One of the most frequent manifestations in patients with HCC is right upper quadrant pain, which can be referred to the shoulder and is reported to vary in intensity from a simple sensation of discomfort through a mild dull ache to a severe unrelenting pain, although the latter is a rare presentation. Pain was reported as a feature in 46% of Japanese and 90%–95% of African patients with HCC (Table 2), and is frequently associated with the presence of advanced disease or when the tumor is noted to be stretching the liver capsule. The onset of acute pain may also be triggered by complications related to the tumor, such as intratumoral hemorrhage or acute necrosis. Acute onset pain may also reflect intraperitoneal bleeding secondary to the rupture of a tumor located on the liver surface, in which case presentation is that of an acute abdomen — this is one of the most dramatic and life-threatening presentations of HCC. Rupture is usually spontaneous, but it may follow mild blunt abdominal trauma[20] or abnormal muscular exertion. Forceful palpation by a physician has also been described as a cause of tumor rupture (see Chapter 35).[21]

In sub-Saharan Africa and Southeast Asia, spontaneous rupture of HCC is the most common cause of spontaneous hemoperitoneum, with an incidence of approximately 10% of patients with HCC.[22] In contrast, this pattern of presentation is rare in the West, with an incidence of only 3%.[23] The patient is typically distressed and restless, and reports a sudden onset of severe upper abdominal pain in association with abdominal distension. The abdomen rapidly becomes rigid with involuntary guarding, and rebound tenderness is identified on palpation. Pale conjunctivae, cold and clammy skin, and a rapid feeble pulse are signs of hemodynamic instability and commonly precede full-blown hypovolemic shock. Less acute bleeding is much more common in patients with advanced HCC; and at the time of autopsy, more than 50% of patients have blood-stained ascites.[21]

Variceal bleeding, generally regarded as a complication of advanced cirrhosis and portal hypertension, can also be the first clinical manifestation of a previously silent HCC. The incidence of individuals with a variceal bleeding episode as the presenting symptom of HCC is approximately 3%.[24] Although it is difficult to demonstrate a direct causal relationship between the HCC *per se* and the bleeding episode, 33% to 76% of the patients presenting with gastrointestinal bleeding have radiological evidence of tumor invasion of the portal venous system, which may contribute to aggravate the underlying portal hypertension associated with cirrhosis. A reduced portal venous return also has the potential of making the bleeding varices more difficult to control and favoring bleeding from hypertensive gastropathy. The reported in-hospital and 1-year mortality rates after variceal bleeding in patients with HCC are 20% and 80%, respectively. These poor survival outcomes are related to initial uncontrollable hemorrhage, rebleeding after endoscopic sclerotherapy, and development of liver failure, as a direct consequence of the hemodynamic instability accompanying the hemorrhagic episode on a pre-existing impaired liver function. Of note, Yeo *et al.*[25] reported that varices represent the source of bleeding in only half of the HCC patients presenting with gastrointestinal bleeding; in those patients with nonvariceal bleeding, duodenal ulceration is the most common cause. A rare cause of gastrointestinal bleeding is direct invasion of the gastrointestinal tract, mainly the stomach and duodenum by tumor.[25,26]

Jaundice, which is described in 5%–44% of patients, represents an important clinical presentation of HCC and assists in the differentiation of potential etiologies. Based upon its pathophysiology, jaundice complicating HCC has been classified into one of two types.[27] The hepatocellular type, which accounts for 90% of icteric patients, is a sign of hepatic parenchymal insufficiency, most commonly related to extensive tumor infiltration of a cirrhotic liver. These patients have a grim prognosis, with 90% of them dying within 10 weeks of their first clinical presentation.[27] Other rare causes of jaundice of hepatocellular type include reactivation of the underlying viral hepatitis, and alcohol- or drug-induced hepatitis. In contrast, in those with an obstructive picture, jaundice results from neoplastic obstruction of bile ducts. The typical features of cholestasis, with unremitting and progressive jaundice, overshadow or accompany other symptoms and signs. The reported incidence of obstructive jaundice varies from 0.5% to 13% of patients with HCC. Based on the mechanism of obstruction and cholangiographic appearances, Lau *et al*.[28] classified those patients presenting with obstructive jaundice into three different types. In type 1, the primary tumor erodes into a branch of the biliary tree and propagates toward the porta hepatis, reaching as far as the common hepatic duct. Patients with type 1 obstructive jaundice have an intrahepatic or extrahepatic intraluminal obstruction due to either a tumor thrombus or a free-floating tumor fragment. Patients with a free-floating tumor plug in the extrahepatic biliary tree may present with intermittent jaundice, which can be accompanied by a colicky pain. Biliary obstruction due to clot formation secondary to hemobilia arising as a result of tumor ingrowth into the wall of a branch of the biliary tree is typical of a type 2 obstruction. Type 3 obstruction is characterized by extraluminal neoplastic compression of the biliary tree. In this instance, tumor compression or encasement of the major intrahepatic ducts causes a localized stricture with proximal duct dilatation. Less frequently, type 3 obstruction is related to compression of the common hepatic duct in the region of the porta hepatis by metastatic lymph nodes.

Intermittent fever of unknown origin[29] (accompanied by leukocytosis) may characterize the clinical presentation of a patient with HCC, and has been reported in 6%–54% of patients. The cause of the fever

is not clear, although tumor necrosis has been invoked as a possible explanation.

Hepatic venous system invasion is a frequent complication of HCC. Through the hepatic veins, the tumor may propagate into the inferior vena cava, causing partial or complete obstruction and features typical of the Budd–Chiari syndrome.[30] Clinical signs include the sudden appearance of severe pitting edema extending up to the inguinal region, tense ascitis, and tender hepatomegaly. The extension of caval thrombus to the right atrium may be responsible for acute episodes of dyspnea, and can also be the cause of sudden death in this patient cohort. Compression of the superior vena cava by metastatic nodes in the mediastinum, with signs and symptoms of the superior mediastinal syndrome, has also been reported.[31]

The clinical presentation of HCC may also be related to extrahepatic manifestation of the tumor resulting from distant metastases or paraneoplastic syndromes. Si *et al.*[32] reported a prevalence of extrahepatic metastases at the time of initial presentation of 42%. Metastatic spread — via the lymphatic or hematogenous route — to abdominal and thoracic lymph nodes, lung, bone, adrenal glands, meninges, and brain have the potential to produce a wide range of symptoms. These can, on rare occasions, completely overshadow those of the primary lesion in the liver, and may even be the only manifestation of otherwise asymptomatic liver cancer.[33] Osteolytic bone metastases often produce pain and may cause pathologic fractures.[34] The bones most frequently affected are the neck of the femur, ribs, vertebrae, skull, and sacrum. Destruction of vertebrae may cause nerve root compression with typical symptoms of radiculopathy such as pain, numbness, tingling, and weakness or paraplegia as a consequence of spinal lesion.[34] Lung metastases, usually asymptomatic, have been described as a rare cause of dyspnea, cough, or hemoptysis.[35] Metastatic lesions in the peritoneum may result in ascitis, which can also be a sign of portal vein invasion with worsening portal hypertension.

During the course of the disease, up to 20% of patients with HCC manifest a variety of paraneoplastic syndromes; and in approximately 50% of cases, these may be identified at the time of diagnosis. Paraneoplastic phenomena may occur as a result of metabolic dysfunction or

the production of hormone-like proteins. One example of a paraneoplastic phenomenon is the development of hypoglycemia, which may be classified into one of two forms according to etiology.[36] Type A hypoglycemia is a mild form of hypoglycemia that occurs as a preterminal event in patients with poorly differentiated, fast-growing tumors, and is metabolic in origin. Type B hypoglycemia, on the other hand, occurs as a result of tumor production of insulin growth factor II with insulin-like activity,[37] and increased utilization of glucose by the tumor together with decreased gluconeogenesis and glycogenolysis within the diseased liver.[21] Type B hypoglycemia is associated with a severe and sometimes life-threatening hypoglycemia, is difficult to control, and may occur early in the course of the disease in approximately 5% of patients with HCC.[36] Patients with hypoglycemia may present with one or more neurological features including confusion, drowsiness, epilepsy, acute neuropsychiatric disturbance, stupor, or coma.

Drowsiness and confusion may also be related to hypercalcemia. Whilst the majority of patients with hypercalcemia have bone metastases, a pseudohyperparathyroidism can be recognized in 4.5% of individuals due to an overproduction of a parathyroid-related protein which interacts with parathyroid hormone receptors.[38]

Erythrocytosis is present in 2%–10% of patients,[39,40] although it may be difficult to recognize as the expanded plasma volume characteristic of cirrhotic patients falsely lowers the plasma hemoglobin concentration and the hematocrit. The ectopic production of erythropoietin or its substrate by tumor cells and the reduced inactivation of erythropoietin by the hepatic parenchyma have been implicated in the development of polycythemia.[41]

Thrombocytosis (platelet count $>400\,000/mm^3$) associated with increased levels of human thrombopoietin has been described in 2.7% of cases of HCC.[42] Systemic arterial hypertension has recently been reported in a few patients with HCC,[43] as has electrolyte abnormalities as a consequence of watery diarrhea from increased production of secretory peptides.[44] Male patients with HCC can, on rare occasions, present with features of feminization, including sexual precocity in boys, gynecomastia (although this may be related to coexisting cirrhosis), or florid feminization. Other paraneoplastic syndromes include

hypercholesterolemia (serum cholesterol >250 mg/dL) associated with HCC in 13% of cases, cryofibrinogenemia, dysfibrinogenemia, and carcinoid syndrome.

Various cutaneous manifestations, though not specific, have been described in patients with HCC.[45–47] Examples include pityriasis rotunda, dermatomyositis, porphyria cutanea tarda, pemphigus foliaceus, and the Leser–Trélat sign (abrupt eruption of multiple seborrheic keratoses).

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7

Tumor Markers

John Y. H. Chan and Zhi Wang

Introduction

Chronic hepatitis leading to liver cirrhosis is a major risk factor for the development of hepatocellular carcinoma (HCC). Patients with severe chronic hepatitis and cirrhosis should undergo routine surveillance for HCC. The commonly available tests for HCC surveillance are assay for serum α-fetoprotein (AFP) and hepatic ultrasonography (for a review, please see Refs. 1–5). Although widely used, AFP level has limited sensitivity and specificity for HCC, while ultrasonography is dependent on the operator and limited in its ability to distinguish HCC from non-neoplastic lesions.[5] Newer methods such as biomarkers or radiological assays for the early detection of HCC are urgently needed.

Biomarkers are indicators of cellular, biochemical, molecular, or genetic alterations that distinguish normal and abnormal biological processes.[6,7] The ideal marker for HCC would be specific for HCC and not detected in premalignant liver diseases. The test should be sensitive,

enabling detection of HCC at an early stage, when curative treatment is possible.[8] In addition, the biomarker should be easily measurable and reproducible, minimally invasive, and acceptable to patients and medical personnel.[9,10] The various markers for HCC that are being investigated are shown in Table 1.

Table 1. HCC tumor markers that are potentially useful for HCC.

Markers	**Biological material**	**Sensitivity (%)**	**Specificity (%)**
AFP (30 ng/mL)	Serum	65	89
AFP-L3 (15%)	Serum	75–97	90–92
Monosialylated AFP	Serum		
Glypican-3 (GPC3)	Tissue	72	100
Glypican-3 (GPC3)	Serum	53	
GGT-II	Tissue	85	97
GGT-II	Serum	74	
AFU (870 nmol/mL/h)	Serum	82	71
DCP (40 mAU/mL)	Serum	52	87
p16 methylation	Serum	81	
Human hepatocyte growth factor	Serum	100	64
Cytokeratin 19	Serum	47	
90K/Mac-2 BP glycoprotein	Serum	46	61
Transforming growth factor-β1	Serum	69	66
Lipoprotein(a)	Serum	44	
Erythrocyte-binding polyamine	Serum	43	92
Tissue polypeptide–specific antigen	Serum	73	71
C-reactive protein	Serum	48	58
p53 antibodies	Serum	41	
CD24 gene	Tissue	66	
Telomerase activity	Tissue	100	50
Prothymosin alpha	Tissue	82	
Microsatellite DNA analysis	Tissue	100	80
Hepatocellular carcinoma–associated gene 1	Tissue	89	
Pseudouridine excretion	Urine	70	
Epidermal growth factor receptor	Urine	62	
Golgi protein 73	Serum	76	69

Oncofetal Antigens and Glycoprotein Antigens

Alpha-fetoprotein, alpha-fetoprotein–L3, and monosialylated alpha-fetoprotein

The currently, widely used diagnostic biomarker of HCC, alpha-fetoprotein (AFP), is a fetal-specific glycoprotein produced primarily in the fetal liver (Fig. 1).[1,11] Its serum concentration falls rapidly after birth, and its synthesis in adult life is turned off. However, more than 70% of HCC patients have a high serum concentration of AFP because of its secretion from the dedifferentiated tumor.

Serum AFP remains the most useful tumor marker in screening HCC patients since its discovery 40 years ago. The serum concentration of 20–30 ng/mL is usually used as a cut-off value to differentiate HCC patients from healthy adults; however, there are reports indicating that the cut-off value is fluctuant in different racial groups. One possible reason for this difference is the diverse living circumstances, which have a

Fig. 1. Rapid assay kit for alpha-fetal protein. A diagnostic kit has been recently developed to rapidly detect AFP as a biomarker for HCC and liver diseases using the immunological lateral-flow method with colloidal gold labeling (Princeton BioMeditech Corp., USA).

great influence on epidemiology. Besides the purpose of screening HCC, serum and tissue AFP could also be used as prognostic indicators.[12] HCC patients with a high AFP concentration (≥400 ng/mL) tend to have greater tumor size, bilobar involvement, massive or diffuse types, portal vein thrombosis, and a lower median survival rate.[13] This is partially caused by the expression of ephrin-A1 (an angiogenic factor) and the ability of AFP to elicit the escape of carcinoma cells from the host's lymphocyte immune surveillance.[14,15]

Though the measurement of AFP serves as an important tool in screening HCC patients, some reports have indicated that it has limited utility in differentiating HCC from benign hepatic disorders for its high false-positive and false-negative rates, and patients with acute exacerbation of viral hepatitis but no HCC may also have markedly increased AFP levels. Using the cut-off value of 20 ng/mL to differentiate HCC from HCV-infected patients, sensitivities merely range from 41% to 65% with corresponding specificities of 80% to 94%.[1] Moreover, the positive predictive value (PPV) of AFP is significantly lower in detecting HCC patients with viral etiology than in detecting HCC patients with nonviral etiology (70% vs. 94%), and it will not reach 100% in HCC patients with viral etiology unless their serum concentration of AFP is greater than 400 ng/mL. Therefore, AFP is more useful in detecting HCC patients with nonviral etiology.

Total AFP can be divided into three different glycoforms, namely AFP-L1, AFP-L2, and AFP-L3, according to their binding capability to the lectin *Lens culinaris* agglutin (LCA).[16,17] AFP-L1, the non–LCA-bound fraction, is the major glycoform of AFP in the serum of nonmalignant hepatopathy patients. On the other hand, AFP-L3, the LCA-bound fraction, is the major glycoform of AFP in the serum of HCC patients, and it can be detected in approximately 35% of patients with small HCC (<3 cm).[18] At the cut-off level of 15%, sensitivities of AFP-L3 in detecting HCC range from 75% to 97% with specificities of 90% to 92%, respectively (Figs. 2 and 3).[18–20]

Some studies have indicated that a high ratio of AFP-L3 to AFP is closely related to poor differentiation and biologically malignant characteristics (especially portal vein invasion) of the tumor. HCC patients with positive AFP-L3 would have worse liver function, poorer

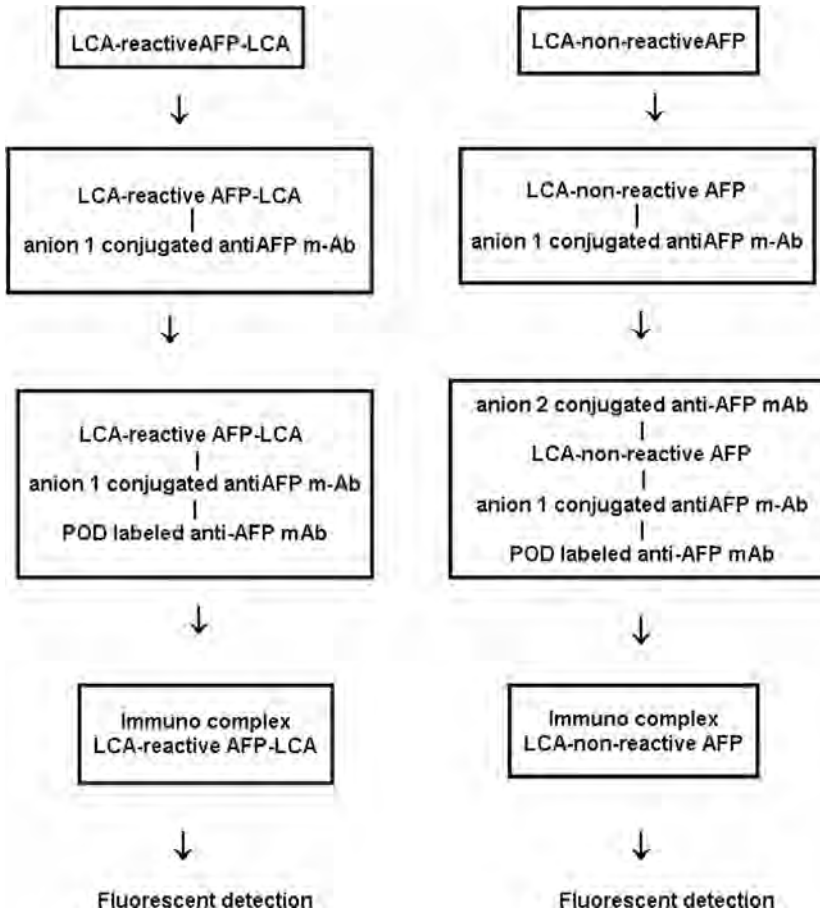

Fig. 2. HCC-specific biomarker AFP-L3 detection in serum of HCC patients. A schematic diagram is shown to detect the various isoforms of AFP with antibodies and binding to *Lens culinaris* agglutinin (LCA) (Wako Chemicals USA, Inc.).

tumor histology, and larger tumor mass. Compared to those with a serum concentration of des-gamma-carboxy prothrombin (DCP) over 100 mAU/mL, HCC patients with a percentage of serum AFP-L3 over 15% also showed a higher incidence of infiltrative-type HCC with an irregular margin and a higher frequency of poorly differentiated HCC.[20] In addition, the monosialylated form of AFP (msAFP) has been documented by a group in Hong Kong (The Chinese University of

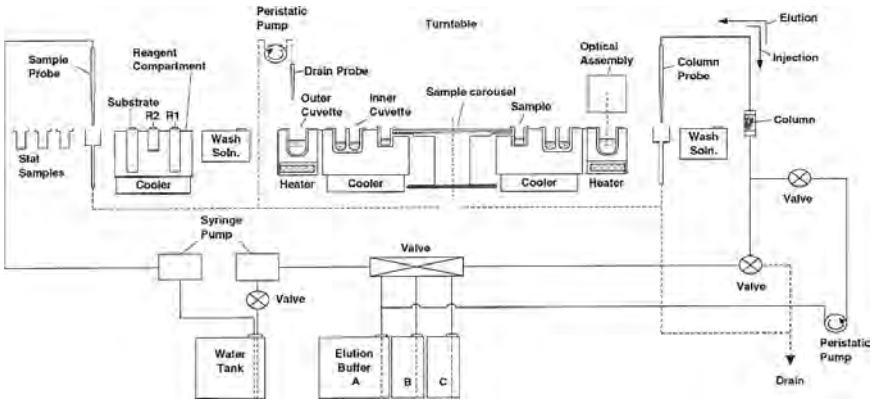

Fig. 3. Schematic diagram of LiBASys clinical auto-analyzer for AFP-L3. An automated analyzer was developed to detect AFP-L3 and total AFP levels with antibody against AFP (Wako Lab, Japan).

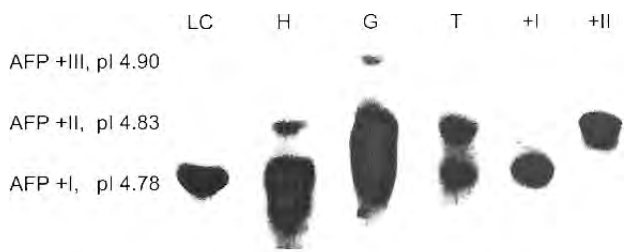

Fig. 4. Analysis of HCC tumor–specific monosialylated AFP glycoform. Samples of serum from HCC patients were analyzed by isoelectric focusing (IEF) gel electrophoresis and immunoblotted with antibody against AFP, showing the tumor-specific glycoform.[21]

Hong Kong, CUHK) to be the HCC-specific glycoform of AFP, and a new test has been developed to rapidly detect it (Fig. 4).[21,22] Therefore, the modified glycoforms of AFP could be used as a valuable indicator of HCC, including patients with poor prognosis.

Glypican-3

Glypican-3 (GPC3) is a heparan sulfate proteoglycan anchored to the plasma membrane. It has been demonstrated that GPC3 interacts

with growth factors and modulates their activities. The GPC3 level (at both mRNA and protein levels) in the serum of HCC patients is significantly higher than that in the serum of healthy adults or patients with nonmalignant hepatopathy,[23,24] and it can be detected in 40%–53% of HCC patients and 33% of HCC patients who are seronegative for both AFP and DCP.[25] The simultaneous determination of GPC3 and AFP has been shown to significantly increase the sensitivity in the diagnosis of HCC. In addition, the soluble GPC3 (sGPC3), the NH_2-terminal portion of GPC3, appears to be better than AFP in the sensitivity of detecting well-differentiated or moderately differentiated HCC.[26]

The simultaneous determination of both biomarkers improves the overall sensitivity from 50% to 72%. Therefore, GPC3 could be a good supplementary tool to AFP in the diagnosis. Moreover, other investigators have reported that GPC3 mRNA is upregulated significantly in tumor tissues of HCC compared to nonneoplastic tissues of HCC, normal liver tissues, and liver tissues of patients with nonmalignant hepatopathy; thus, it could also be a good molecular marker for HCC.[27]

Enzymes and Isoenzymes

Gamma-glutamyl transferase

Serum gamma-glutamyl transferase (GGT) in healthy adults is mainly secreted by Kupffer cells and endothelial cells of the bile ducts in the liver, and its activity increases in the tissues of HCC and fetal liver. GGT can be divided into 13 isoenzymes (I, I′, II, II′, β, δ, ε, φA, VIIB, φC, γA, γB) with polyacrylamide gradient gel electrophoresis. Some of the isoforms (I′, II, II′) can only be detected in the serum of HCC patients. Sensitivities of GGT-II are approximately 74% in detecting HCC and 44% in detecting small HCC.[28] Interestingly, the simultaneous determination of GGT-II, DCP, and AFP can significantly improve the sensitivity over the determination of AFP alone. It is apparently a valuable tumor marker in detecting small HCC and a good supplementary to AFP in the diagnosis of HCC.

Alpha-L-fucosidase

Alpha-L-fucosidase (AFU) is an enzyme that hydrolyzes fucose glycosidic linkages of glycoprotein and glycolipids. Its activity increases significantly in the serum of HCC patients (1418 ± 575 nmol/mL/h) compared with that in the serum of normal adults (504 ± 122 nmol/mL/h), patients with cirrhosis (831 ± 261 nmol/mL/h), and patients with chronic hepatitis (717 ± 206 nmol/mL/h) (Fig. 5).[29] It has been reported that the sensitivity and specificity of AFU at a cut-off value of 870 nmol/mL/h are 82% and 71%, respectively, in contrast with 39% and 99% of AFP at the cut-off value of 400 ng/mL; and that the simultaneous determination of both biomarkers can improve the sensitivity to 83%. This indicates that AFU is a valuable supplement to AFP in the diagnosis (Fig. 6).

HCC will usually develop within a few years in 82% of patients with liver cirrhosis, with serum AFU activity exceeding 700 nmol/mL/h. In addition, the activity of AFU is already elevated in 85% of patients 6 months before the detection of HCC by ultrasonography. Thus, AFU would be a good tumor marker in detecting HCC at an earlier period.[30]

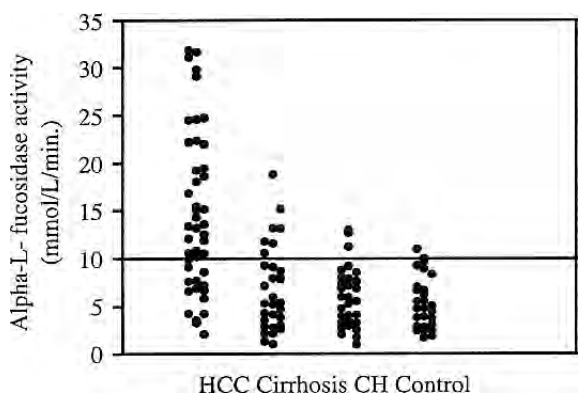

Fig. 5. Diagram of α-L-fucosidase (AFU) enzyme activity in patients with HCC, cirrhosis, and chronic hepatitis. Comparison of the serum AFU activity with various stages of liver diseases showed a positive correlation. The horizontal line represents the cut-off value (10 μmol/L/min).

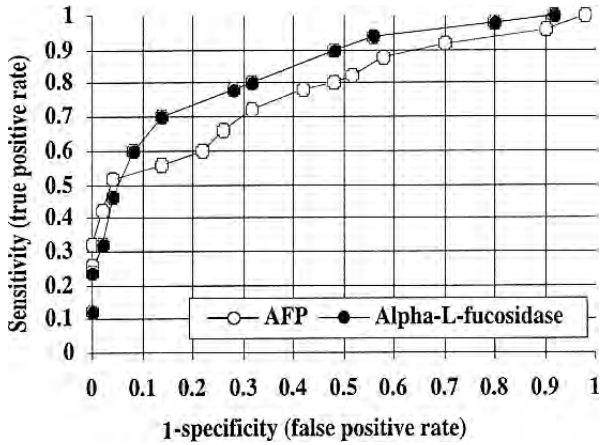

Fig. 6. Comparison of AFP and α-L-fucosidase (AFU) for the diagnosis of HCC in cirrhotics. Receiver operating characteristic (ROC) curves of AFP and AFU were plotted, showing no significant difference in the diagnostic efficacy index (area under the curve).

Des-gamma-carboxy prothrombin

Des-gamma-carboxy prothrombin (DCP) is an enzyme protein induced by vitamin K absence or antagonist II (PIVKA-II), which is an abnormal product from liver carboxylation disturbance during the formation of thrombogen. It also acts as an autologous mitogen for HCC cell lines (Fig. 7).[31] Its serum concentration, which is not correlated to serum levels of AFP, is elevated in HCC patients compared with that in healthy adults and patients with nonmalignant hepatopathy.[32]

Serum and tissue levels of DCP have been proved to be more useful than AFP in differentiating HCC from nonmalignant hepatopathy and in detecting patients with small HCC (Fig. 8).[33,34] The sensitivity and specificity of serum DCP (at the most commonly used cut-off value of 40 mAU/mL) in discriminating HCC from cirrhosis were about 52% and 87%, respectively, which were much better than those of AFP at the cut-off value of 20 ng/mL; and 37% of patients with small HCC had serum DCP values above this level.[35,36] The sensitivity and specificity of serum DCP (at the cut-off value of 125 mAU/mL) in discriminating HCC from nonmalignant hepatopathy were 89%

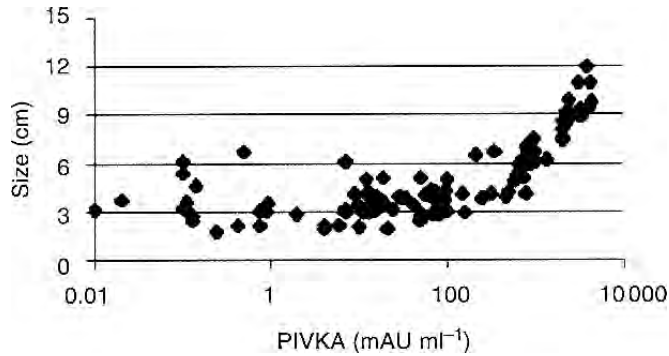

Fig. 7. Correlation between tumor size and protein induced by vitamin K absence or antagonist II (PIVKA-II) level. The HCC tumor size was plotted against the serum levels of PIVKA-II (des-gamma-carboxy prothrombin) in patients with HCC, showing a positive correlation.

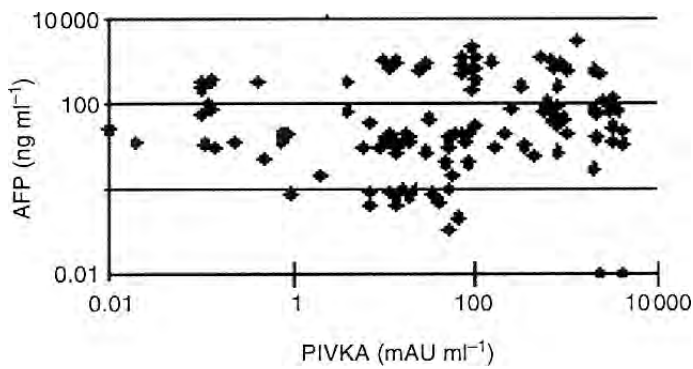

Fig. 8. Relationship between PIVKA-II and AFP levels. The serum levels of PIVKA-II and AFP were compared in a cohort of 120 patients, showing a positive correlation.

and 87%, respectively,[37] which were much better than those of AFP at the cut-off value of 11 ng/mL. Furthermore, the simultaneous determination of DCP and other tumor biomarkers, such as AFP and AFP-L3, may have a greater accuracy than the determination of each of them alone.[24] Newer techniques such as electrochemiluminescence enables the measurement of low concentration of DCP in the serum; and the simultaneous determination of high-sensitive

DCP (at the cut-off value of 40 mAU/mL), AFP (at the cut-off value of 20 ng/mL), and AFP-L3 (at the cut-off value of 10%) gives the highest accuracy (sensitivity of 82%, specificity of 82%, and accuracy of 82%).[38,39]

Serum DCP could also be used as a clinicopathological or prognostic indicator for HCC patients, and may be more useful than AFP in reflecting the invasive characteristics of HCC. It has been reported that patients seropositive for DCP and seronegative for AFP have a higher frequency of HCC with a distinct margin, a large nodule more than 3 cm, a few nodules, and moderate-to-poor differentiation. Moreover, it has been claimed that the simultaneous determination of serum DCP levels and tissue DCP expression is more valuable than either factor alone in predicting the prognosis of HCC patients.[40,41] Immunological kits of DCP have been developed by Sanko Junyaku Co. (Japan), including the Eitest PIVKA-II, Picolumi PIVAK-II, and Lumipulse PIVKA-II kits.

Golgi protein 73 (GP73)

GP73 is a resident Golgi protein that is upregulated in virus-infected hepatocytes.[42] Using Western blot assay, GP73 has been detected in serum, with significantly greater levels in patients with cirrhosis and those with HCC than in healthy subjects and patients with chronic hepatitis. In a pilot study that included 54 patients with cirrhosis and 72 patients with HCC, the mean GP73 levels of 10.3 $\pm$ 9 relative units/mL in patients with cirrhosis and 16.6 $\pm$ 8 relative units/mL in patients with HCC were found.[4] A significant difference in GP73 levels persisted when the comparison was limited to patients with early HCC (T1 and T2). GP73 had an area under the ROC curve of 0.75 (95% confidence interval, 0.67–0.83), sensitivity of 76%, and specificity of 69%; whereas AFP had an area under the ROC curve of 0.69 (95% confidence interval, 0.60–0.77), sensitivity of 52%, and specificity of 84% in differentiating patients with HCC from those with cirrhosis and no HCC. However, the promising results of glypican-3 and GP73 testing need to be confirmed in larger studies.

Growth Factors and Cytokines

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a secreted homodimeric cytokine that enhances neovascularization in tumors (angiogenesis).[43] Recent publications have indicated that angiogenesis is essential in tumor growth and progression, including that of HCCs, which have a high level of vascularization. The expressions of VEGF in typical cancerous tissues of HCC are significantly higher than those in normal liver and in HCC without microscopic venous invasion. HCC patients with overexpression of VEGF have a lower survival rate.[44] Platelets have been reported to act as transporters of tumor-originated VEGF.

Serum VEGF per platelet count, which is an indirect theoretical estimate of VEGF in platelets, is significantly higher in HCC patients than in normal adults and patients with nonmalignant hepatopathy. High serum VEGF per platelet count ($>1.4\ pg/10^6$) is associated with advanced stage of HCC, portal vein thrombosis, poor response to treatment, and shorter overall survival.[45] Therefore, it may be a useful diagnostic or prognostic indicator for HCC.

Interleukin-8

Interleukin-8 (IL-8) is a multifunctional CXC chemokine that affects human neutrophil functions, including chemotaxis, enzyme release, and expression of surface adhesion molecules. It has direct effects on tumor and vascular endothelial cell proliferation, angiogenesis, and tumor migration. Recently, it has been reported that IL-8 regulates tumor cell growth and metastasis in the liver.[46] Additionally, the preoperative serum IL-8 levels in HCC patients are significantly elevated compared with those in normal adults (17.6 pg/mL vs. 1.0 pg/mL); and its high serum levels correlate with a large tumor size (>5 cm), absence of tumor capsule, presence of venous invasion, advanced pathological tumor–node–metastasis (pTNM) stage, and poorer disease-free survival. Therefore, it may be a significant diagnostic or prognostic indicator for HCC.

Transforming growth factor-beta 1

Transforming growth factor-beta 1 (TGF-β1) is a negative growth factor that correlates with cellular immunosuppression during the progression of HCC.[47] However, its serum levels in HCC patients have been shown to be obviously elevated compared with those in normal adults and patients with nonmalignant hepatopathy.[48] The cut-off value of serum TGF-β1 is about 800 pg/mL, which gives a specificity of over 95% in detecting HCC. It is apparently similar to AFP at the cut-off value of 200 ng/mL; but the sensitivity of serum TGF-β1 is 68%, which is better than the AFP sensitivity of 24%. Moreover, the elevated serum TGF-β1 can be detected in 23% of HCC patients with normal serum AFP values. These data indicate that TGF-β1 may be a good complement to AFP in the diagnosis of HCC.

Tumor-specific growth factor

Malignant tumor can release tumor-specific growth factor (TSGF), which results in blood capillary amplification surrounding the tumor, into peripheral blood during its growing period. Therefore, the serum levels of TSGF can reflect the existence of tumor. It has been indicated that TSGF can be used as a diagnostic marker in detecting HCC, and its sensitivity can reach 82% at the cut-off value of 62 U/mL.[49] Furthermore, the simultaneous determination of TSGF and other tumor markers has been shown to give a higher accuracy. It has been reported that the simultaneous determinations of TSGF, AFP, carcinoembryonic antigen (CEA), total sialic acid (TSA), and serum ferritin have a sensitivity of 97%. The simultaneous determinations of TSGF (at the cut-off value of 65 U/mL), AFP (at the cut-off value of 25 ng/mL), and serum ferritin (at the cut-off value of 240 μg/mL) have a sensitivity of 98% and a specificity of 99%. Another growth factor that may be useful as a disease marker is the human hepatocyte growth factor (HGF), but the efficacy of this biomarker remains to be determined.

There are other biomarkers in this category that could be used as diagnostic or prognostic indicators for HCC. Serum insulin-like growth

factor-II (IGF-II) is one of them (at the cut-off value of 4.1 mg/g; prealbumin), and has a sensitivity of 63%, specificity of 90%, and accuracy of 70% in the diagnosis of small HCC.[50] In addition, the simultaneous determination of IGF-II and AFP (at the cut-off value of 50 ng/mL) can improve the sensitivity to 80% and the accuracy to 88%. The other biomarker that can be used is the overexpression of granulin–epithelin precursor (GEP) in HCC, which has been reported to be associated with venous infiltration and early intrahepatic recurrence.[51]

Combined Multiple Tumor Markers

To increase the detection rate of HCC and diagnose it earlier, the concept of combining several HCC-specific tumor markers has been proposed. In one study, AFP was combined with γ-glutamyl transpeptidase (γ-GT), alpha-fucosidase (AFU), tumor necrosis factor-alpha (TNF-α), and DR-70.[52] The positive detection rate of HCC-negative AFP with the combined four markers was 9%; whereas the total positive detection rate of HCC with combined five tumor markers reached 98%, which was significantly higher than that with AFP alone. The positive detection rate of HCC can be increased by combining five tumor markers. It is helpful in diagnosing HCC early and can differentiate HCC from liver cirrhosis. Thus, the combined detection of multiple tumor markers is becoming a comprehensive and accepted approach to accurately diagnose HCC and other cancers.

Genes

Alpha-fetoprotein (AFP) mRNA

Tumor cells or tumor cell fragments can spread into the blood circulation and can be detected. These cells also become the source of recurrence after treatment, which may be the primary reason for the unsatisfactory long-term survival after surgery. The presence of circulating HCC cells may also be indicative of metastasis. Tests were developed for the rapid detection of RNA or DNA of tumor cells and markers in the serum using polymerase chain reaction (PCR) methods.[53,54] Numerous reports have

indicated that serum AFP mRNA detected by the reverse transcription–PCR (RT-PCR) method may be a valuable indicator of tumor and poor prognosis for HCC patients.[55,56] Its expression also correlates with portal thrombosis, nodules of tumor, tumor diameter, and TNM stage.[57] The recurrence-free interval of HCC patients with postoperative serum AFP mRNA positivity has been reported to be significantly shorter than that of HCC patients with postoperative negativity (53% vs. 88% at 1 year, 37% vs. 60% at 2 years),[58] and the recurrence-free survival rates of HCC patients with postoperative serum AFP mRNA positivity have been reported to be significantly lower than those of HCC patients with preoperative positivity (53% vs. 82% at 1 year, 16% vs. 55% at 2 years, 0% vs. 29% at 3 years).[59] The expression of AFP mRNA 1 week after surgery also correlated with the recurrence of HCC, and the simultaneous determination of AFP mRNA and melanoma antigen gene (*MAGE-1*) mRNA may have a higher sensitivity and specificity.[60]

Gamma-glutamyl transferase (GGT) mRNA

GGT mRNA can be detected in the serum and liver tissues of healthy adults or patients with HCC, nonmalignant hepatopathy, hepatic benign tumor, and secondary carcinoma of the liver.[61] GGT can be divided into three types: fetal liver (type A), HepG2 cells (type B), and placenta (type C). Type A is predominant in normal liver tissues or liver tissues with nonmalignant hepatopathy, benign tumor, and secondary carcinoma; on the contrary, type B is predominant in cancerous tissues of HCC.[44] During the development of HCC, the expression of GGT mRNA in liver tissues may shift from type A to type B.[62]

It has been indicated that HCC patients with positive type B would have a worse outcome, earlier recurrence, and more postrecurrence death.[63] Therefore, the expression of type B tissues may be a valuable indicator of poor prognosis for HCC patients. As in liver tissues, the serum levels of type B have also been reported to be significantly higher in HCC patients than in healthy adults. Therefore, type B serum may be an available supplement to AFP in the diagnosis of HCC.

Oncogenes, tumor suppressors, and telomerase reverse transcriptase

The expression of tumor-related genes has been examined in HCC.[64] In particular, the methylation of the tumor suppressor gene *p16* as a molecular diagnostic marker for HCC has been documented earlier using serum or plasma samples of patients in Hong Kong.[65] The results were quite similar to the data obtained from tumor samples (Fig. 9). Moreover, the human telomerase reverse transcriptase gene (*hTERT*) is known to be reactivated in various types of cancer because of the immortalization or increased proliferation of the tumor cells. It has been reported to be detectable in the serum of patients with breast cancer and with HCC. The expression of hTERT mRNA in the serum of HCC patients is significantly higher than in the serum of normal adults or patients with nonmalignant hepatopathy.[66] The use of the newly developed real-time quantitative RT-PCR may improve the efficacy of the diagnosis. The sensitivity and specificity of hTERT mRNA in detecting HCC were reported at about 88% and 70.0%, respectively, which excel those of conventional tumor markers such as AFP mRNA, AFP, and

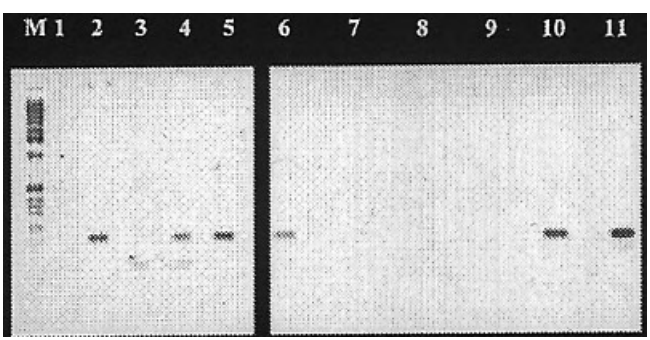

Fig. 9. Aberrantly methylated *p16* sequences as molecular biomarkers in the plasma and serum of HCC patients. The method of methylation-specific PCR was based on the fact that treated DNA with bisulfite would result in the conversion of unmethylated cytosine residues into uracil; methylated cytosine residues would remain unchanged. The bisulfite-modified DNA was amplified using primers for the methylated sequence, which was a 150-bp PCR product in an agarose gel electrophoresis run as shown. Lane M, molecular weight marker; lane 1, water blank; lanes 2–5, plasma samples from HCC patients; and lanes 6 and 8–11, serum samples from HCC patients.[65]

DCP. Moreover, the expression of serum hTERT mRNA — which is associated with the serum concentration of AFP, tumor size, and tumor differentiation degree — may be a valuable indicator of poor prognosis for HCC patients.

Other biomarkers in this category, which could be used as diagnostic or prognostic indicators for HCC, are the simultaneous determination of the tumor suppressor p53 antigen and anti-p53 antibodies, having a sensitivity of about 40%.[67] The overexpression of p53 in the serum or liver tissues of HCC patients is an indicator of poorer prognosis and shorter survival time. HCC patients with positive MAGE-1 or MAGE-3 mRNA die earlier because of metastasis or recurrence.[68] In addition, one report indicated that the human cervical cancer oncogene (*HCCR*) can be used to detect HCC at the cut-off value of 15 μg/mL in detecting HCC with a sensitivity and specificity of 78% and 96%, respectively.[69] Its sensitivities could achieve 77% in detecting HCC patients who were seronegative for AFP and 69% in detecting HCC patients with a tumor size less than 2 cm.

Conclusions

Serum AFP is the most widely studied screening test for detecting HCC. The normal range for serum AFP levels is 10–20 ng/mL, and a level greater than 400 ng/mL is usually regarded as positive. High serum concentration of AFP also correlates with poor prognosis of HCC patients. However, a substantial proportion (60%) of patients with small nodules (less than 4 cm) have serum AFP levels less than 200 ng/mL, and up to one fifth of HCC patients are AFP-negative.[1] AFP has limited utility in differentiating HCC from benign hepatic disorders because of the high false-positive and false-negative rates. Serum AFP-L3 and DCP are starting to be widely used as additional tumor markers for HCC, and have been indicated to be more valuable than AFP alone in differentiating HCC from nonmalignant hepatopathy, in detecting small HCC, and in predicting prognosis. Since there is a large population of patients with cirrhosis and chronic hepatitis in the world, AFP-L3 and DCP may be more useful than AFP in the diagnosis of HCC.

hTERT mRNA and HCCR have been shown to have a higher accuracy than AFP in detecting HCC, but there are not enough researches to show their superiority. Therefore, they may not be the first choice in the detection of HCC. IGF-II has been reported to be more valuable than AFP in the diagnosis of small HCC; more studies are needed to demonstrate its superiority. There are some serum markers, such as GPC3, GGT-II, AFU, TGF-β1, and TSGF, that have been indicated to be available supplements to AFP and DCP in the detection of HCC; and some of them can even detect HCC in patients who are seronegative for both AFP and DCP. The simultaneous determination of these markers may improve the accuracy. Serum AFP mRNA, which has been shown to correlate with metastasis and recurrence of HCC, may be the most useful marker to prefigure the prognosis of HCC patients.

Other biomarkers, such as p53, MAGE-1, MAGE-3, GGT mRNA, VEGF, GEP, and IL-8, are also able to serve as prognostic indicators of HCC patients. The simultaneous determination of AFP and these markers may discover the recurrence of HCC at an earlier period. In addition, cytokeratin 19,[70] activin-A,[71] and proliferating cell nuclear antigen[72,73] — which do not belong to the categories above — can also be used as prognostic or screening indicators for HCC patients, especially when combined with AFP.

In summary, AFP, AFP-L3, and DCP are the most useful serum tumor markers for the detection of HCC; and the simultaneous determination of these markers could improve the accuracy, especially in differentiating HCC from nonmalignant hepatopathy. Other tumor markers cited in this chapter could be used as supplements to AFP and DCP in the diagnosis of HCC, but each of them apparently has no satisfactory accuracy in detecting HCC or prognosis when used alone in the current situation. The new trend in tumor diagnosis is the utilization of multiple tumor markers to increase sensitivity and specificity. For progress to be made in biomarker validation, collaborative research networks should be established such that promising biomarkers identified in preliminary studies can be evaluated further. Additional studies should validate the utility of these biomarkers in the detection of early HCC and develop assays that are reproducible and amenable to a high throughput. The survival benefits and the cost-effectiveness of

screening HCC has to be considered.[74] With increasing application of gene microarrays, proteomics, and tumor immunology, it is anticipated that many new markers unique to (or overexpressed or underexpressed in) patients with HCC will be identified, and assays for detecting these markers or antibodies to these markers in serum will be developed in the next decade.

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8

Imaging

Simon S. M. Ho and Simon C. H. Yu

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, and is responsible for over a million deaths per year worldwide. Most HCCs are related to cirrhosis. Patients' survival of HCC and the possibility for curative treatment are directly related to the residual liver reserve as well as the size and number of lesions at diagnosis. Despite recent advances in imaging, the distinction between HCC and other liver nodules (particularly in cirrhosis) remains a major diagnostic challenge. The radiologist therefore needs to be fully aware of the full range of imaging features and diagnostic limitations of each imaging modality in order to achieve early and accurate diagnosis.

Incidence and Etiology

The most important risk factor for the development of HCC is cirrhosis from all causes, persistent hepatitis B virus (HBV) or hepatitis

C virus (HCV) infection, and alcoholic liver disease. Marked geographical variation in the prevalence of HCC is observed. A significantly higher prevalence of HCC is seen in areas with persistent HBV infection, such as Japan, Southeast Asia, and parts of Africa (up to 50 per 100 000 population); while prevalence observed in North America and Europe is much lower (<5 per 100 000 population).[1]

Pathology and Imaging Features of HCC

In order to facilitate the interpretation of the imaging features of HCC, a comprehensive understanding of the gross pathomorphological characteristics of the disease is a necessary prerequisite.[2]

Cirrhosis, characterized by fibrosis and nodular regeneration, commonly accompanies HCC. It is present in 67%–96% of patients with HCC in Asia versus 38%–50% in the West.[3] HCC arises more commonly from macronodular cirrhosis (nodules >3 mm) than from micronodular cirrhosis (nodules < 3 mm). HCC in cirrhosis develops from a stepwise process of degeneration, from benign regenerative nodules via dysplastic nodules (which may be low grade or high grade) to frank HCC.[4] There is a considerable overlap in the imaging findings between these nodules, and it is vital for the radiologist to be able to identify HCC from the other nodular lesions in the liver.

Regenerative nodules are histologically composed of local proliferation of hepatocytes surrounded by fibrous septa, and develop following liver cell damage. Their blood supply is similar to that of the normal liver, i.e. it is derived mainly from the portal vein with a small contribution from the hepatic artery. Hemosiderin deposition is common, and this produces characteristic imaging features on magnetic resonance imaging (MRI).

Dysplastic nodules histologically contain atypical cells without definite features of malignancy, and are present in 15%–25% of cirrhotic livers at the time of transplantation.[5,6] Depending on the degree of atypia, these can be further categorized into low grade or high grade. Dysplastic nodules have more unpaired arteries (i.e. isolated arteries not accompanied by bile ducts that are indicative of neoplastic angiogenesis)

than regenerative nodules, and the number of unpaired arteries increases as the nodules progress from low grade to high grade to HCC. Thus, it is not surprising that dysplastic nodules are usually hypovascular lesions with predominantly portal vein supply, with increased arterial enhancement seen in a small minority.[7]

HCC can be histopathologically classified into three categories:

1. Solitary massive expansive tumor with or without satellite nodules
2. Multifocal or nodular tumor
3. Diffuse infiltrative or multiple small tumors

Small HCCs less than 3 cm tend to be well differentiated (Fig. 1), while larger tumors are usually less well differentiated and are frequently associated with vascular invasion and metastases. The diffuse infiltrative variety is usually poorly differentiated tumors, and carries a grim prognosis due to rapid portal vein and hepatic vein invasion (Fig. 2).

A few characteristics are useful for distinguishing HCCs from other lesions:

1. Fibrous capsule

External fibrous capsule (pseudocapsule) and internal septae are present in 50% of HCCs of 1.5–2 cm in diameter.[8] They are more common in larger tumors (Fig. 3); the overall occurrence is 80% for all sizes of tumors.[9] Capsular invasion by a tumor occurs in up to 38% of HCCs.[10] When the tumor is not encapsulated, usually in noncirrhotic livers, the tumor boundary is poorly demarcated and irregular.

2. Fat and calcification

Fat may be seen in some well-differentiated HCCs due to the defective release of lipids produced by the functioning hepatocytes, thus suggesting the transformation from dysplastic nodule to HCC. Calcification may be present in 2%–12% of HCCs.

3. Hepatic arterial supply

The massive expansive and nodular types of HCC are typically hypervascular, with blood supply predominantly derived from the hepatic artery. Retention of some portal venous supply is seen in a minority.

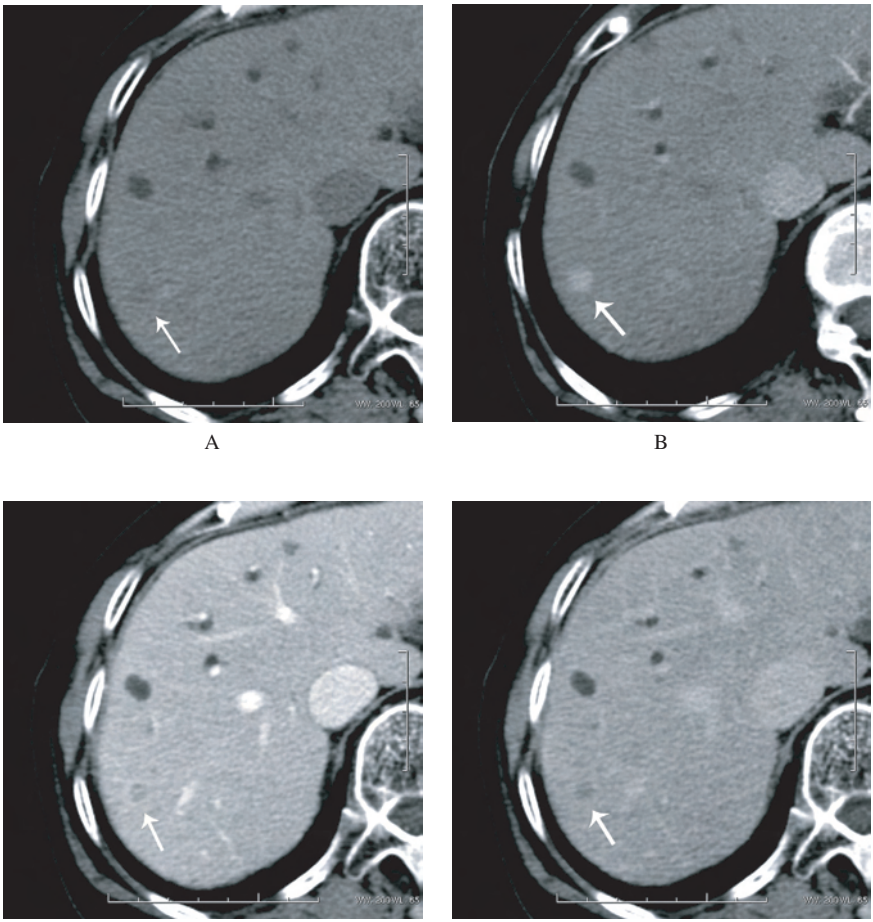
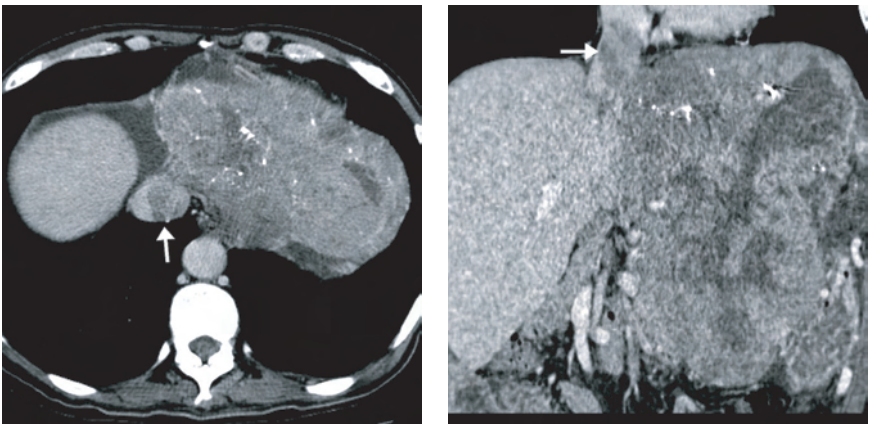


Fig. 1. Triple-phase contrast-enhanced computed tomography (CT) scans showing typical small HCCs. (A) A hypodense HCC (arrow) on the unenhanced scan. (B) Arterial enhancement. (C, D) Contrast washout in the portal phase and the 5-minute delayed phase, respectively.

4. Propensity to invade veins

There is a great tendency for HCC to invade veins, leading to arteriovenous shunting within the tumor. Invasion of the portal vein (Fig. 4), occurring in up to 62% of autopsy cases,[9] provides a channel for spreading to the rest of the liver and occasionally in a retrograde fashion into



A B

Fig. 2. Portal phase CT scans showing a large HCC replacing the left hemiliver with invasion into the interior vena cava (IVC) (arrow). (A) The axial section at the level of the IVC. (B) The coronal reformatted image. Note the scattered foci of calcification within the tumor.

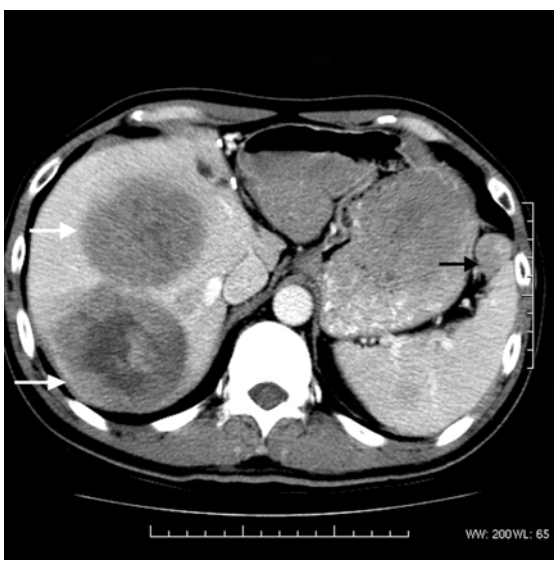
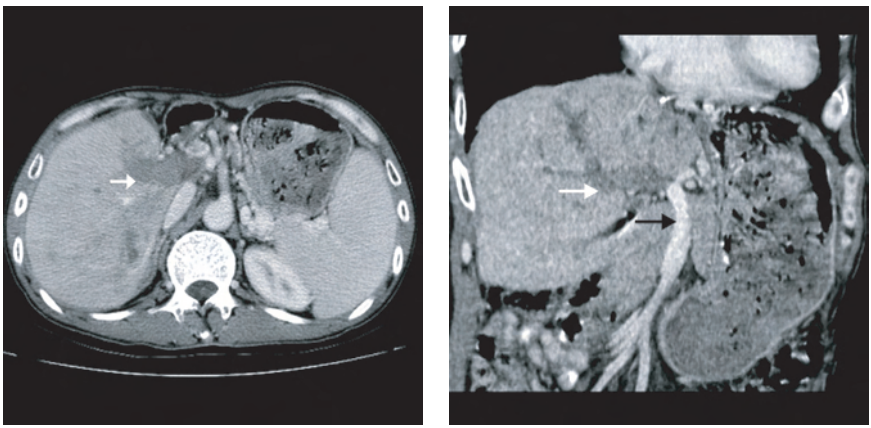


Fig. 3. Axial portal phase CT scan showing two large HCC deposits (white arrows) in the right hemiliver with mildly enhancing pseudocapsule and central necrosis. Note the small peritoneal deposit (black arrow) anterior to the lateral margin of the spleen.



A B

Fig. 4. Portal phase CT scans showing portal vein thrombosis. (A) Lack of enhancement of the portal vein (white arrow) on axial section. (B) Patency of the superior mesenteric vein (black arrow) and thrombosis of the portal vein (white arrow) on multiplanar reconstruction.

the superior mesenteric vein. The presence of portal vein tumor is an important clue to the diagnosis of HCC, as less than 8% of portal vein tumors are due to other malignancies. Tumor invasion of the hepatic vein is also frequent, occurring in up to 26% of autopsy cases and opening up a pathway for systemic spread. Extension into the right atrium via the hepatic vein and inferior vena cava (IVC) (Figs. 2 and 5) may be complicated by pulmonary embolism. In rare cases, there may even be metastases to the pulmonary veins (Fig. 6).

5. Heterogeneous or mosaic pattern

The typical mosaic pattern occurs in 63% of massive and nodular tumors.[10] This occurs when multiple tumor nodules are separated by fibrous or necrotic areas. Both necrosis and hemorrhage, which are common in advanced tumor, also contribute to the mosaic pattern and progress as the tumor increases in size.

6. Local invasion, complications, and metastaticb spread

The massive expansive tumor may proliferate in an extrahepatic direction to produce a pedunculated mass. Spontaneous rupture of the

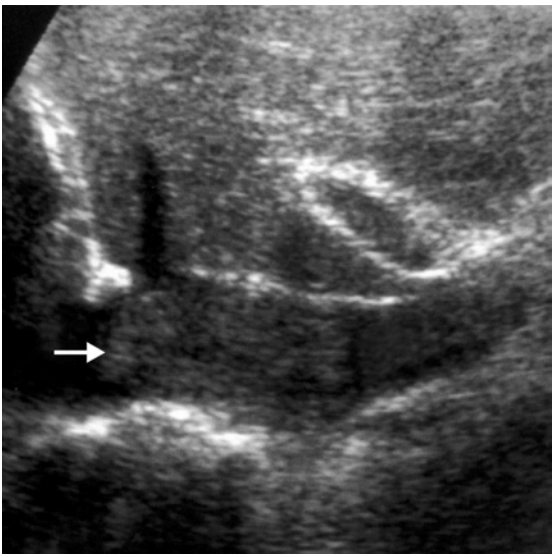
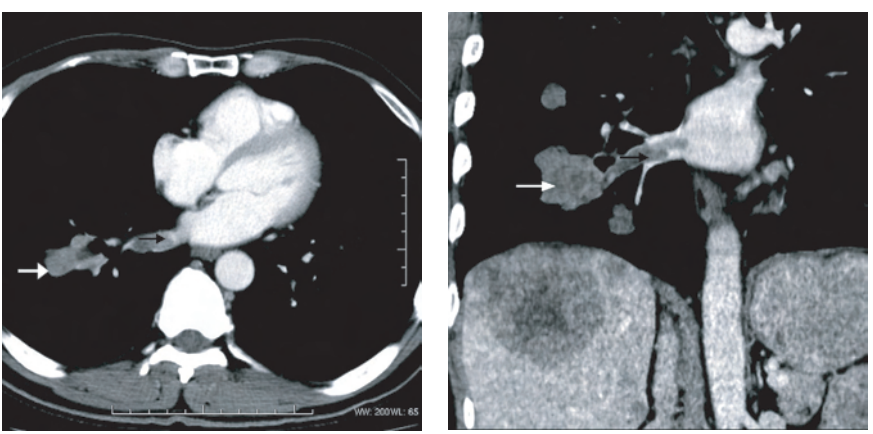


Fig. 5. Ultrasound scan showing echogenic thrombus (arrow) in the IVC. Reprinted from *Clin Radiol*, **59**, Yu SCH, Yeung DT, So NM, Imaging features of hepatocellular carcinoma, pp. 145–56, copyright 2004, with permission from The Royal College of Radiologists.



A B

Fig. 6. Contrast-enhanced CT scans showing lung metastasis invading the right pulmonary vein. (A) Axial section of lung metastasis (white arrow) invading a right pulmonary vein (black arrow). (B) The coronal multiplanar reconstruction. Note also that there is a large deposit of HCC in the liver.

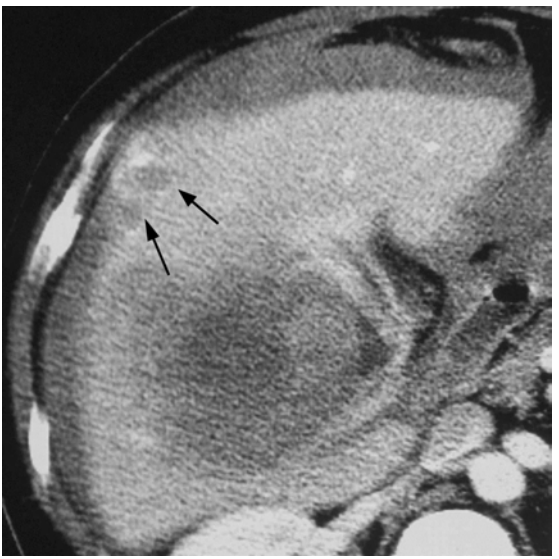


Fig. 7. The ruptured HCC has a protruding contour and presents as a nonenhancing low-attenuation lesion with peripheral rim enhancement. Because of the similar appearance to an enucleated orbital globe with remaining sclera, this was termed the "enucleation sign" (arrows). Note the low-attenuation perihepatic hematoma. Reprinted from *Clin Radiol*, **59**, Yu SCH, Yeung DT, So NM, Imaging features of hepatocellular carcinoma, pp. 145–56, copyright 2004, with permission from The Royal College of Radiologists.

tumor through the liver capsule with intraperitoneal hemorrhage (Fig. 7) occurs in 2.9%–14.5% of cases.

Bile duct obstruction may occur as a result of compression by massive intrahepatic tumors or enlarged nodes at the porta hepatis. It may also be due to direct tumor invasion with or without complicating hemobilia. Intrabiliary tumor fragmentation may also obstruct the common bile duct with tumor emboli, sometimes in the absence of an obvious intrahepatic tumor. Direct invasion of the diaphragm, abdominal wall, pancreas, peritoneum, mesentery, and omentum may occur. Retroperitoneal extension through the bare area of the liver into the superior aspect of the perirenal space in the form of a pedunculated mass may mimick an adrenal tumor (Fig. 8).

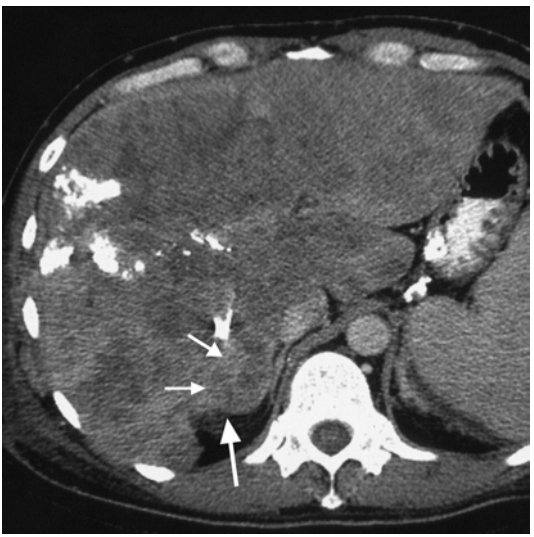
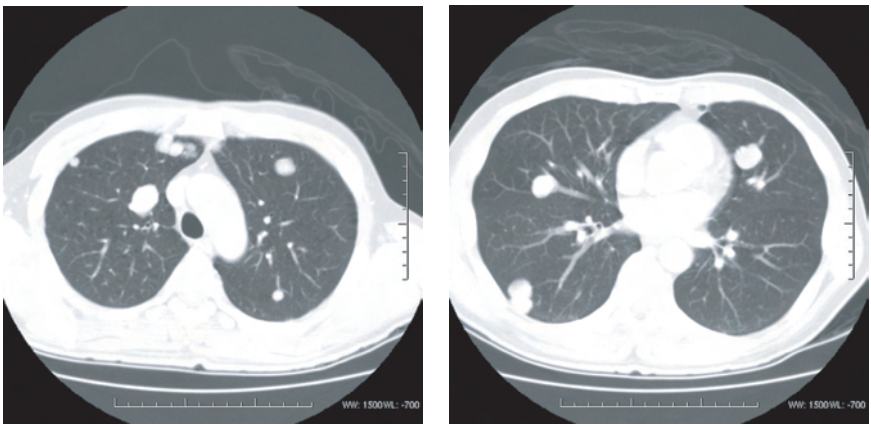


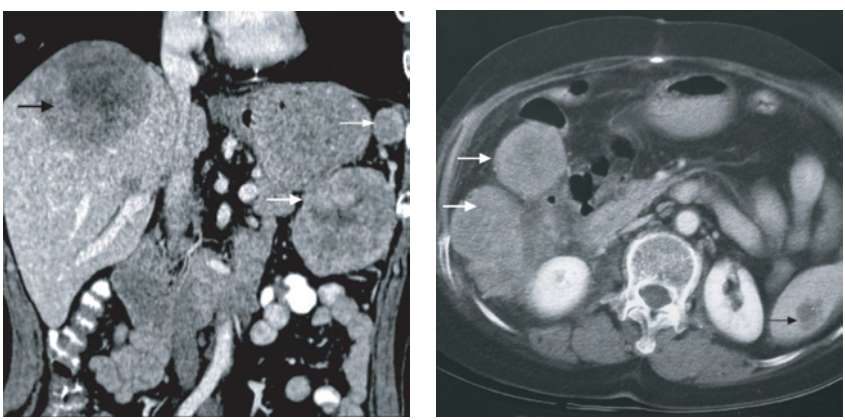
Fig. 8. Portal phase CT scan showing retroperitoneal extension of the diffuse HCC in the right hemiliver extending through the bare area of the liver into the superior aspect of the perirenal space in the form of a pedunculated mass mimicking a right adrenal tumor (arrows).

The lung is the most common site of distant metastasis (Fig. 9). Lymph node metastasis is the second most common one, usually occurring at the porta hepatis, coeliac axis, or around the pancreatic head. Other sites of metastasis include the spleen and other intraperitoneal organs, peritoneum, adrenal gland, bone, skin, breast, and rarely brain. Peritoneal spread of HCCs is quite different from the usual carcinomatosis peritonei; they occur as single or multiple discrete hypervascular masses in the omentum or peritoneum (Fig. 10). Intracranial metastases may be due to either brain metastases or skull metastases without brain involvement. The majority of cases of brain metastasis have simultaneous lung metastasis, but without skull or other bone metastasis. Brain deposits are hypervascular. They may very rarely present as intracranial hemorrhage; the likelihood increases with the size of the tumor. Skull metastasis is rare, and may be multiple and quite large, with brain invasion or extradural extension causing compression on the brain. Skull metastasis is often associated with extracranial bone metastasis without lung metastasis.



A B

Fig. 9. CT lung window images showing multiple lung metastases. (A) Axial section taken at the level of the aortic arch. (B) Axial section taken at the level of the left atrium.



A B

Fig. 10. Portal phase CT scans showing multiple peritoneal metastases. (A) Coronal multiplanar reconstruction image with two rounded peritoneal deposits (white arrows) in the left upper quadrant and a focus of HCC deposit in the liver (black arrow). (B) Axial section demonstrating two rounded peritoneal deposits in the right flank (white arrows) and low-attenuation metastasis in the spleen (black arrow).

The Imaging of HCC

Ultrasonography

The ultrasound appearances of HCCs are related to their size. Small (<3 cm), well-differentiated HCCs are usually homogeneous and hypoechoic (Fig. 11); while large tumors tend to have variable echogenicity due to central necrosis, fatty change, hemorrhage, fibrosis, or calcification. Ebara and coworkers[11] correlated the ultrasound pattern of nodules with their size, and demonstrated a tendency for them to develop from generally hypoechoic to a pattern with a hypoechoic peripheral zone (which represents the tumor capsule) with a more echogenic center, and finally to large lesions with high echoes in advanced diseases (Fig. 12). The homogeneous and hypoechoic echotexture of the majority of small HCCs may not be distinguishable from the echopattern of regeneration nodules in cirrhosis (Fig. 13), and ultrasound-guided biopsy (Fig. 14) may be necessary for a definite diagnosis of these small lesions. In a study of 294 new nodular lesions of <2 cm in cirrhotic patients with nondiagnostic alpha-fetoprotein

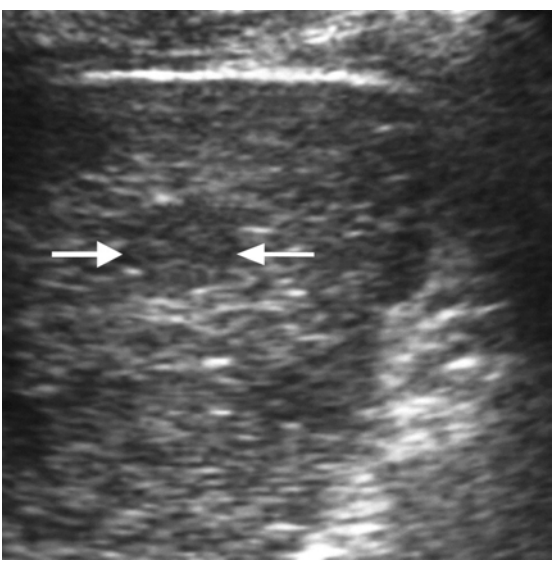


Fig. 11. Ultrasound scan showing a small hypoechoic HCC (arrows).

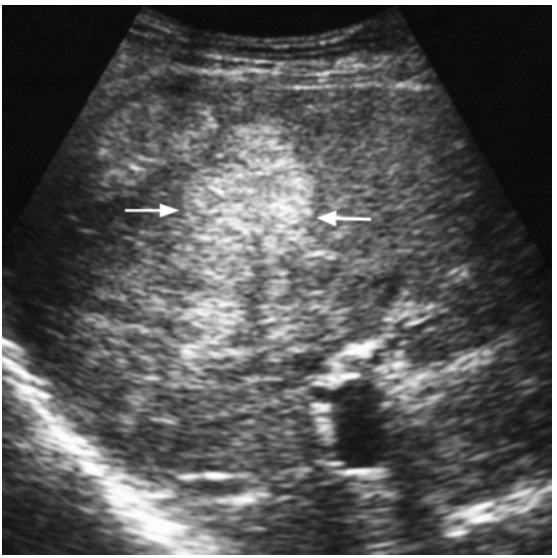


Fig. 12. Ultrasound scan showing an echogenic HCC (arrows).

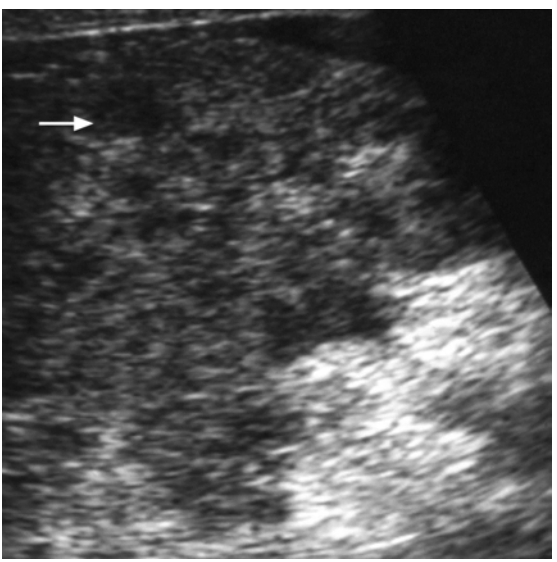


Fig. 13. Ultrasound scan showing a small HCC of homogeneous and hypoechoic echotexture (arrow), which may not be distinguishable from the echopattern of regeneration nodules in cirrhosis.

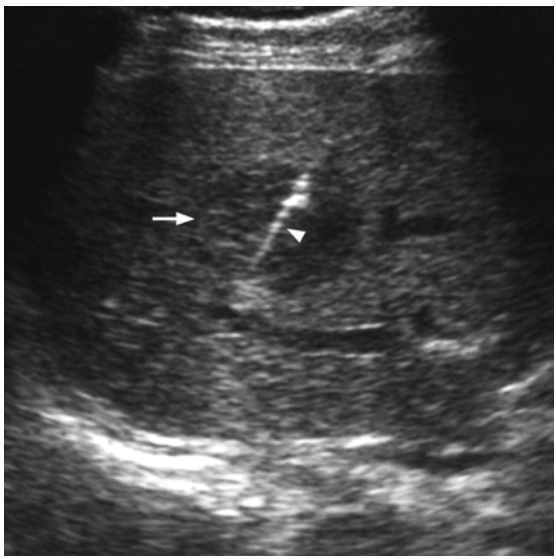


Fig. 14. Ultrasound-guided biopsy of a hypoechoic liver lesion (white arrow), with an echogenic biopsy needle (white arrowhead) seen traversing the target lesion.

levels by Caturelli and coworkers,[12] ultrasound-guided fine needle (20G–21G needles) biopsy demonstrated that 87.6% (258/294) of nodules turned out to be HCCs. In particular, in lesions $\leq$1 cm, 68.7% (33/48) turned out to be HCCs.

The characteristic mosaic pattern and fibrous septae of HCC are well demonstrated with ultrasound, as is the star-shaped central hypoechoic area. The less common type of nodular HCC that appears ultrasonographically to be homogeneous and diffusely hyperechoic is probably due to fatty change or dilated sinusoids. It is usually surrounded by a thin peripheral hypoechoic halo and does not change in appearance when the tumor grows.

In the absence of a definite ultrasonographic finding of a liver mass, indirect evidence such as compression, interruption, or irregularity of the wall of a blood vessel; localized bulging of the hepatic surface; or a dilated intrahepatic bile duct due to extrinsic compression by a tumor mass or intraductal tumor infiltration should raise the suspicion of a liver tumor. In the diffuse type of HCC, ultrasound may show diffuse

distortion of the normal internal architecture of liver parenchyma in which multiple areas of increased echogenicity may be recognized. An isoechoic diffuse HCC may be completely missed. In a background of cirrhosis with regeneration nodules, the detection of small HCCs by ultrasound is much more difficult than the detection of metastases in a normal liver.[13]

In a recent systematic review pooling data from 14 studies, the sensitivity and specificity of ultrasound were estimated to be 60% and 97%, respectively.[14] The use of contrast-enhanced sonography has been advocated by many investigators as a means to increase the sensitivity of ultrasound for detecting HCC (to 83%–98%) and improve the categorization of suspicious liver lesions.[15–18] A HCC would typically be seen as a hypervascular focal liver lesion in the arterial phase in the heterogeneous liver parenchyma, becoming isoechoic or hypoechoic in the portal and late phases (showing washout) (Fig. 15).[17] Portal phase enhancement has been shown to be most useful in identifying benign lesions from malignancies. Positive or sustained portal phase enhancement is present in 95% of benign lesions, while negative portal phase enhancement or washout is present in 93% of malignancies.[18]

Computed tomography (CT)

With the introduction of helical CT, multislice, and now multidetector technology, imaging of the entire liver with thin slices and multiplanar reconstruction in multiple phases has become a widely available reality and has been considered the imaging modality of choice for the determination and staging of HCC.[14,19–21]

At our institution, for imaging of HCC, we routinely perform an unenhanced scan followed by imaging in the arterial phase (30 seconds after injection), portal venous phase (70 s after injection), and delayed phase (300 s after injection). Images are taken with a 16-slice multidetector CT scanner (GE LightSpeed 16). Typically, 100 mL of Omnipaque 240 (iohexol) is administered intravenously at a rate of 2.5–3.0 mL/s. The scanning parameters are as follows: collimation, 20 mm; reconstruction interval, 1.25 mm; table speed, 18.75 mm per rotation; pitch, 0.938:1; 120 kV; and 280–330 mA.

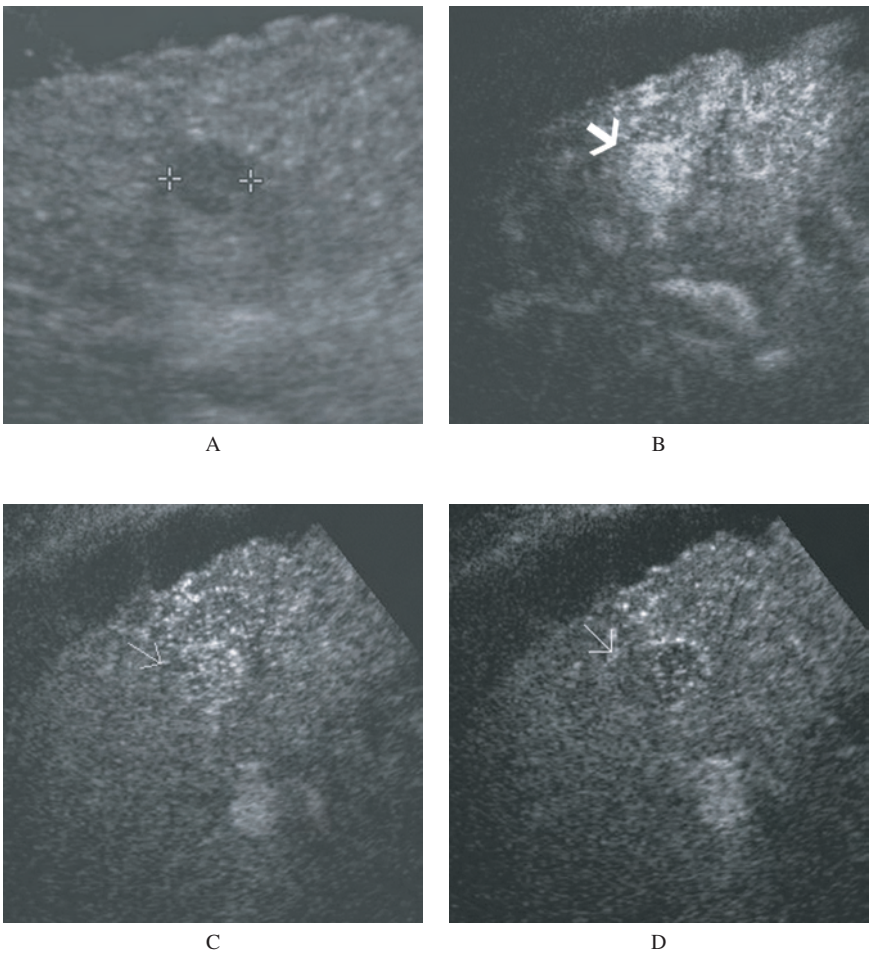


Fig. 15. Ultrasound contrast imaging of HCC (courtesy of Dr Adrian Lim, Charing Cross Hospital, London, UK). (A) A hypoechoic HCC. (B) Avid arterial phase enhancement (arrow). (C) Slight washout of contrast in the portal phase. (D) Further washout of contrast in the delayed phase.

HCC may present as a solitary encapsulated lesion, a lesion with indistinct border, or multifocal lesions. The appearances of HCCs on images obtained using multidetector CT (MDCT) are similar to those described for images obtained using single-detector helical scanners, although a higher prevalence of hypervascular HCC has been detected

by MDCT when compared with single-detector helical scanners.[21] The addition of the unenhanced scan has been shown to be useful in the detection of lesions which have similar enhancement characteristics as the normal liver and are therefore not visible after contrast.[22] HCC derives its blood supply predominantly from the hepatic artery, and the inclusion of arterial phase scanning has been shown to improve the detection of small malignant hepatic neoplasms when performed in addition to portal venous phase scanning.[23]

The imaging characteristics of HCCs are related to the size of the lesions. Most small HCCs show homogeneous enhancement on the arterial phase images, though they may also be isoattenuating on the arterial phase, and appear hypoattenuating (showing washout) on portal venous phase and delayed phase images (Figs. 1 and 16). For larger lesions, mixed attenuation may be seen due to the complex nature of the lesion, and they show a mosaic pattern on both the arterial and portal venous phase images. HCCs also have very variable appearances on portal venous phase images: small tumors may show as lesions of different attenuations, while large lesions always show central necrosis.

The fibrous tumor capsule does not enhance on the arterial phase, may appear hypoattenuating to hyperattenuating on the portal venous phase, but almost always enhances on the delayed phase images. In addition, heterogeneous washout may also be present in the delayed phase images, and the addition of delayed phase imaging has therefore been shown to be helpful in the characterization of HCCs in approximately one seventh of patients.[24] Hyperattenuating lesions seen on the arterial phase represent an active process of tumoral vascular enhancement and enable a relatively specific diagnosis of a hypervascular tumor, while hypoattenuating masses seen on the portal venous phase only correlate with a larger spectrum of neoplastic and nonneoplastic lesions.

Intratumoral vascularity can sometimes be seen. Intratumoral arteries may course randomly, and may be nontapering and irregular. As HCC has a propensity for portal and hepaticovenous invasion, intraluminal low attenuation with enlargement of the occluded venous segment would be suggestive of tumor thrombus. A malignant thrombus can be differentiated from a bland thrombus by the presence of expansion of the main portal vein diameter ($\geq$23 mm) and the presence of intrathrombus

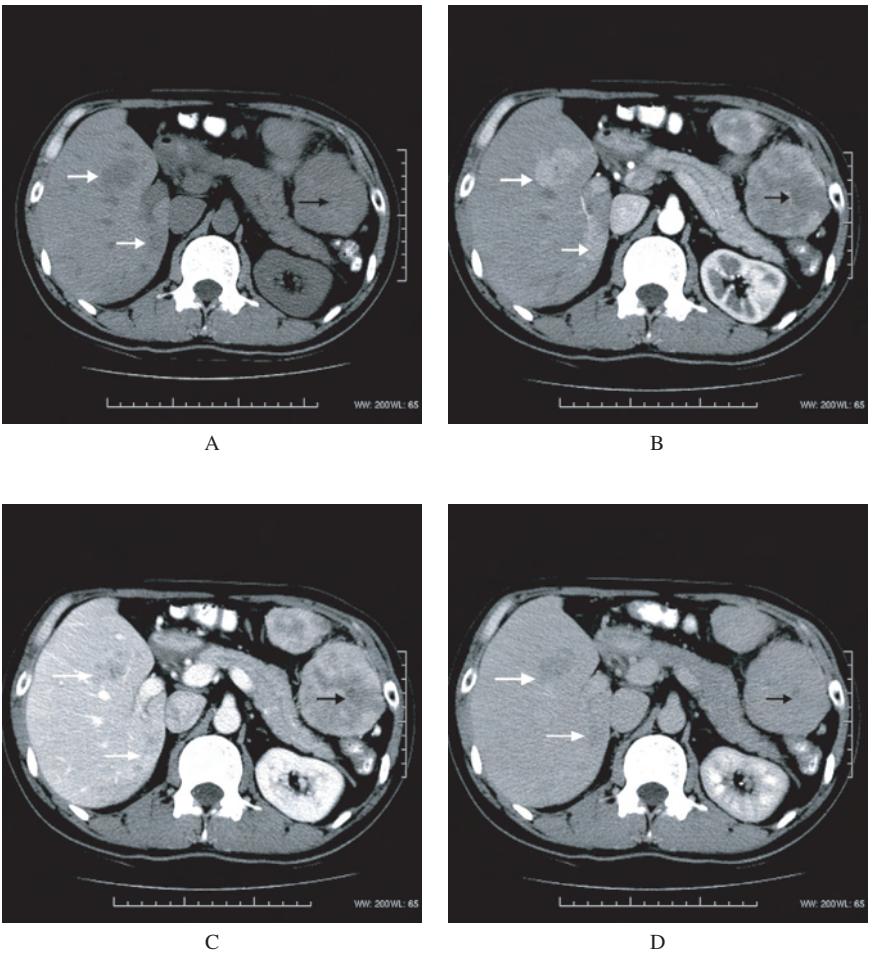
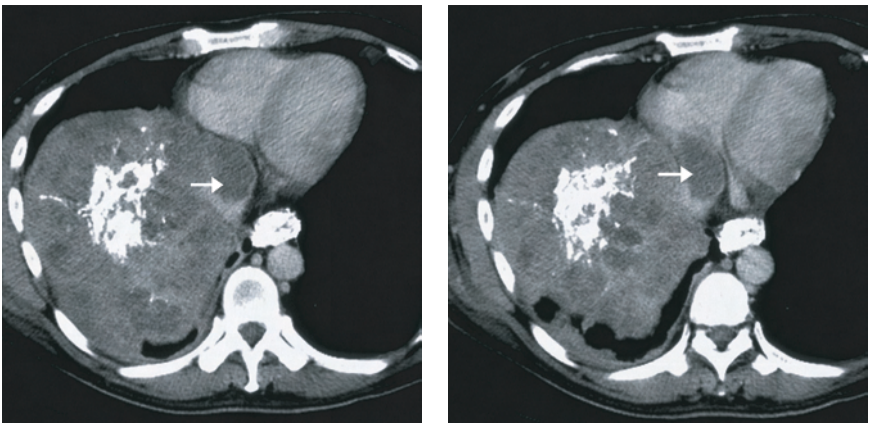


Fig. 16. Triple-phase contrast-enhanced CT scans showing two foci of HCC in the right hemiliver. (A) Two hypodense HCCs (white arrows) on the unenhanced scan and a large peritoneal metastasis (black arrow). (B) Arterial enhancement in both foci. (C, D) Contrast washout in the portal phase and 5-minute delayed phase, respectively.

neovascularity on arterial phase imaging. Direct extension of the HCC into the contiguous portal vein with generalized enhancement of thrombus is highly suggestive of malignancy. Hepatic venous tumor thrombus may extend into the inferior vena cava (IVC) and to the right atrium (Figs. 2 and 17). Infrequently, HCC can also cause biliary obstruction



A B

Fig. 17. CT scans showing lipiodol-retaining transarterial chemoembolization (TACE)-treated diffuse HCC involving the right hemiliver. (A) Tumor thrombus (arrow) extending into and expanding the IVC. (B) Tumor thrombus extending into the right atrium (arrow).

with dilatation of intrahepatic ducts. It is thus crucial to distinguish these tumors from intrahepatic cholangiocarcinomas.[13]

Around 11% of the HCC will spontaneously rupture.[25] The ruptured tumors tend to be located at the periphery of the liver and have a protruding contour.[26] During the arterial phase, the ruptured tumor may show as a nonenhancing low-attenuating lesion with focal discontinuity and peripheral rim enhancement. Because of the similar appearance to an enucleated orbital globe with remaining sclera, this was termed the "enucleation sign". Discontinuity of the hepatic surface can be seen. Hematoma with high attenuation can be present around the ruptured mass. Active extravasation can rarely be detected from the tumor during scanning (Fig. 18).

Magnetic resonance imaging (MRI)

Most HCCs are hypointense on unenhanced T1 images, although isointensity and hyperintensity are not uncommon — this is caused by areas

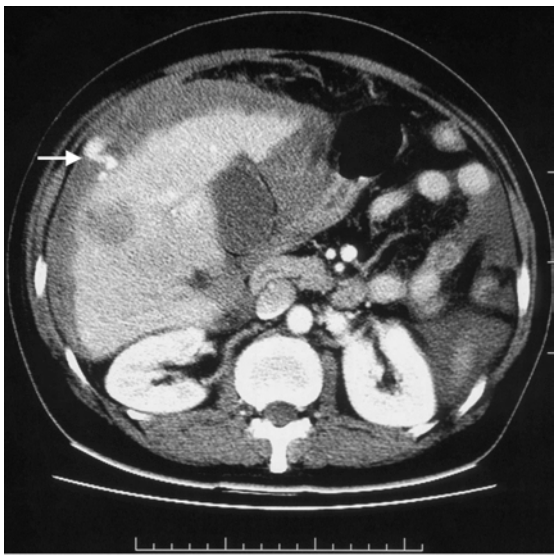


Fig. 18. Contrast-enhanced CT scan showing active extravasation (arrow) from a ruptured HCC. Reprinted from *Clin Radiol*, **59**, Yu SCH, Yeung DT, So NM, Imaging features of hepatocellular carcinoma, pp. 145–56, copyright 2004, with permission from The Royal College of Radiologists.

of hemorrhage and high lipid or protein content. On T2-weighted fast spin-echo sequences, HCCs are typically hyperintense (Fig. 19); and this allows distinction of HCCs from dysplastic nodules, which are typically hypointense on T2 (Fig. 20). Well-differentiated HCCs, however, can be isointense or occasionally hypointense, although dysplastic nodules are rarely (if ever) hyperintense on T2.[1] Importantly, a T2 high-signal focus within a hypointense or isointense nodule is highly suggestive of HCC developing within a dysplastic nodule.

Gadolinium-enhanced T1-weighted imaging improves the detection of HCCs, particularly with small hypervascular lesions which may only be detectable on contrast-enhanced sequences. Indeed, some authors advocate the use of gadolinium 3D T1-weighted MRI as a stand-alone sequence for the diagnosis of HCC.[27] At our institution, the standard MRI sequences for HCCs include (1) axial T2 turbo spin-echo (TSE) sequence with fat saturation; (2) T1 fast low-angle shot (FLASH) 3D fat

saturation sequences performed precontrast and postcontrast (typically, three phases acquired in the arterial phase, portal phase, and 5-minute delayed venous phase are included); and (3) a postcontrast T1 FLASH 2D water excitational breathhold examination.

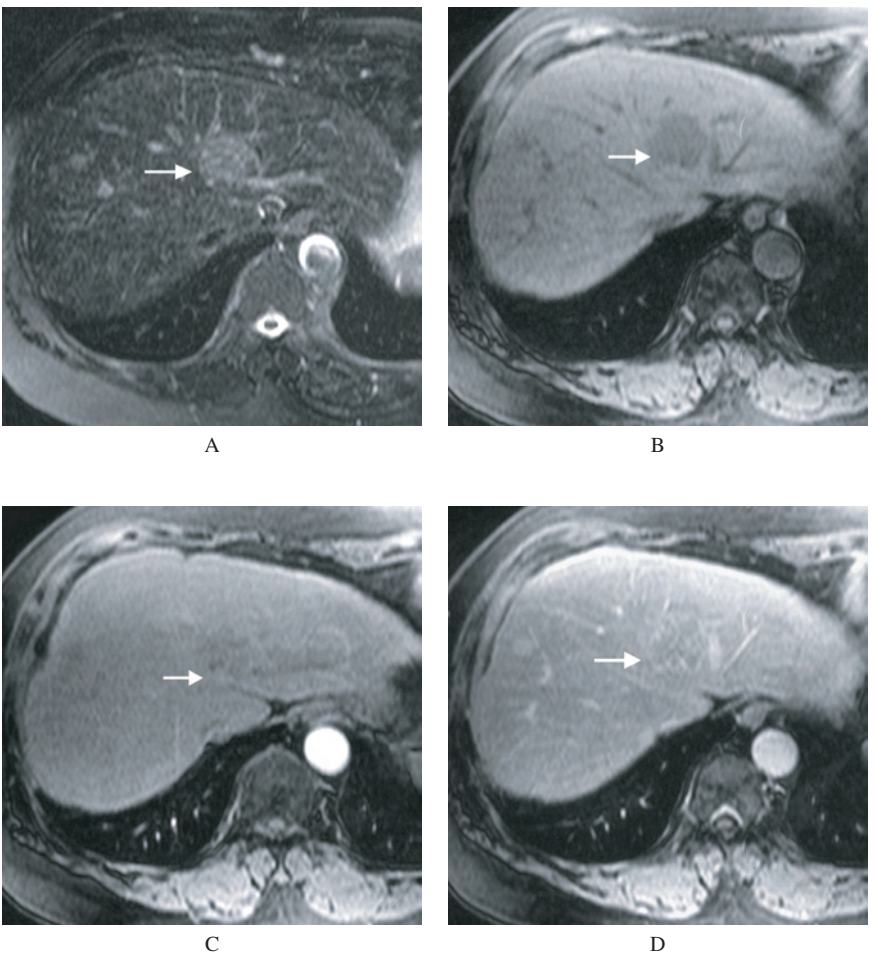
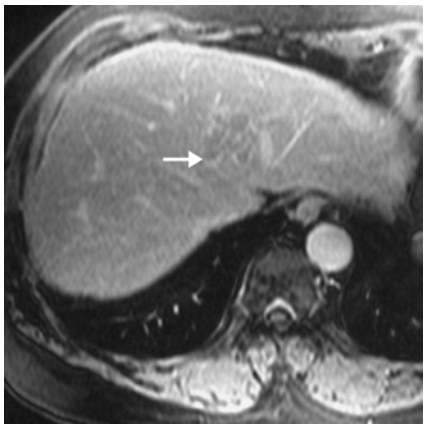


Fig. 19. Typical MRI appearance of HCC. (A) A rounded hyperintense HCC (arrow) on spectral presaturation with inversion recovery (SPIR) TSE T2-weighted image (T2WI). (B) The same lesion, which is hypointense on T1 FLASH 3D sequence. (C) Arterial enhancement of the HCC. (D) Mild portal phase enhancement persisting in the HCC. (E) Five-minute delayed phase contrast washout from the same HCC.



E

Fig. 19. (*Continued*)

Three-dimensional sequences are preferred by the authors and others[1,27,28] because of a higher signal-to noise ratio and a thinner effective slice thickness compared to 2D techniques. Fat saturation is used because the conspicuity of contrast enhancement is improved and signal cancellation artefact at fat–water interfaces is eliminated. During dynamic gadolinium-enhanced imaging, the lesion enhances in the arterial phase because of abundant neovascularity. In the portal phase, HCCs are usually isointense; in the delayed phase, HCCs are hypointense because of contrast washout of the tumor (Fig. 19). However, some HCCs show progressive or minimal/slight enhancement in the dynamic imaging. Subtracting the precontrast images from the postcontrast images can augment the presence of slight enhancement, which can sometimes be difficult to appreciate on source image.

Tissue-specific MR contrast agents that produce T1 enhancement in hepatocytes — including mangafodipir (MnDPDP), gadobenate (Gd-BOPTA), and gadoxetic acid (Gd-EOB-DTPA) — have been shown to have a limited role in the discrimination of HCC from other benign lesions, as all of these agents are taken up by both well-differentiated HCC and benign hepatic nodules.

Superparamagnetic iron oxide (SPIO) particles, on the other hand, appear more promising, as they are taken up by cells of the

reticuloendothelial system (Kupffer cells); and Kupffer cells are rarely present in HCCs. They enhance T2 and T2* relaxation by increasing local field inhomogeneities, causing a marked decrease in signal intensity of liver tissue and benign hepatocellular nodules on T2-weighted

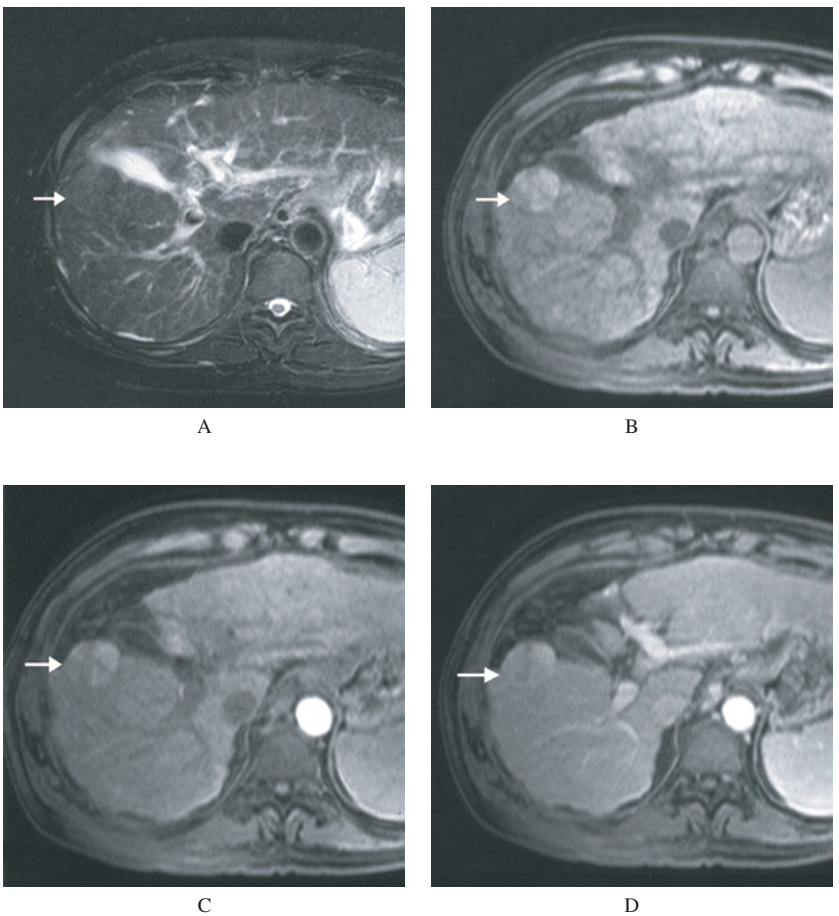
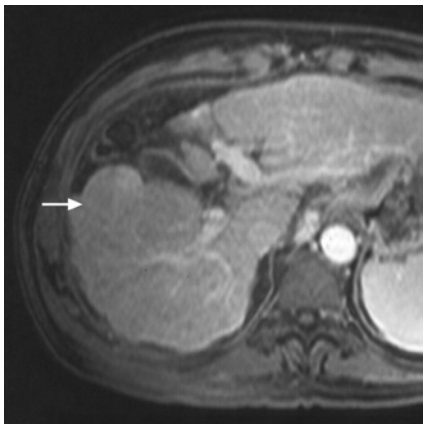


Fig. 20. Typical MRI appearance of a dysplastic nodule. (A) A dysplastic nodule (arrow) with homogeneous hypointensity on SPIR TSE T2WI. (B) Homogeneous mild hyperintensity on T1 FLASH 3D sequence. (C–E) The dysplastic nodule enhances to a similar extent as the adjacent liver parenchyma in the arterial phase, portal phase, and 5-minute delayed phase scans, respectively.



E

Fig. 20. (*Continued*)

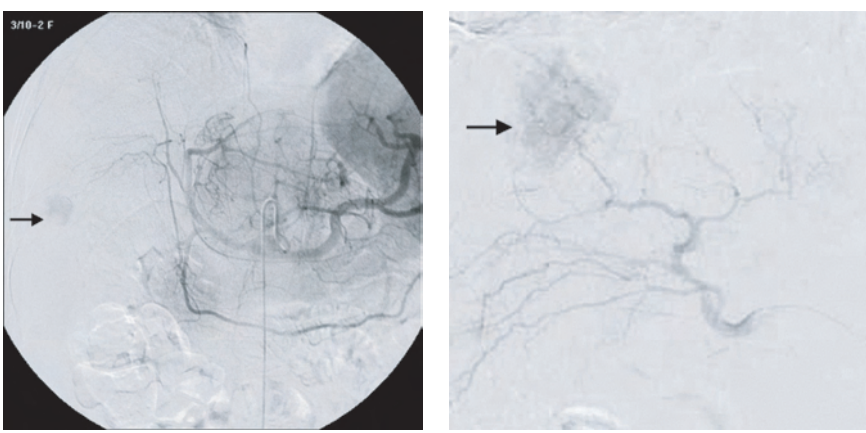
images. A recent study has shown SPIO-enhanced MRI and MDCT to have a similar diagnostic accuracy, sensitivity, and positive predictive value for the detection of HCC in patients with relatively mild hepatitis B–induced cirrhosis, with a trend ($p > 0.05$) towards increased sensitivity on both a per-lesion and a per-patient basis for SPIO-enhanced MRI (mean, 84.7% and 94.7%, respectively) compared with MDCT (mean, 76.9% and 88.6%, respectively).[28] Other authors favor the use of dual-contrast-agent MRI administering both SPIO and gadolinium, demonstrating that both dysplastic nodules and HCCs can be characterized with greater confidence on the basis of their combined enhancement characteristics.[29]

Apparent diffusion coefficient (ADC) and choline levels measured at hydrogen-1 magnetic resonance spectroscopy have been shown to be potentially useful in the monitoring of treatment responses of transcatheter arterial chemoembolization (TACE). In a study of 20 patients with HCC, choline levels significantly decreased in 90% of patients after TACE, while a significant increase in ADC was observed in all patients after TACE ($p < 0.01$ in the observed changes in both parameters).[30]

Angiography

Most HCCs are hypervascular (Fig. 21).[31] The arterial feeders to the tumor are often dilated, tortuous, distorted, and displaced. Neovasculatures show a chaotic and disorganized pattern. There is often an intense tumor stain. Vascular lakes or venous pools are common. On the other end of the spectrum, some tumors are only mildly hypervascular with mild tumor staining, which can only be demonstrated in a good-quality superselective arteriogram. Central necrosis is not uncommon in large hypervascular tumors, and it is represented angiographically by a hypovascular area.

Invasion of the portal trunk and its major branches is not uncommon in HCC. The "thread-and-streaks" appearance seen in hepatic arteriograms is due to tumor invasion of the vasa vasorum of the portal vein.[32] Arterioportal shunting[33] is also common with premature opacification of the portal venous system during the arterial phase. Because the normal portal vein is a low-pressure system, arterioportal shunting often causes retrograde filling of the superior mesenteric vein and splenic vein.



A B

Fig. 21. Hypervascular HCC in the right hemiliver as shown on digital subtraction angiography (DSA). (A) Coeliac axis angiogram demonstrating a hypervascular tumor (arrow) in the right hemiliver. (B) Selective right hepatic artery angiogram of the same lesion.

The hepatic veins are usually not opacified during hepatic arteriography, unless there is a change in hemodynamics. Tumor invasion of the major hepatic veins causes such a change. It has similar angiographic appearances to portal vein invasion, apart from their difference in location.[34] The "thread-and-streaks" sign of tumor invasion is seen in the region of the major hepatic veins. Often, tumor casts can be seen within the hepatic veins, causing complete or partial obstruction; they can even extend into the IVC or the right atrium.

Lipiodol CT has been used by many authors for the detection of HCC. Although sensitivity decreases with both modalities as tumors become small and well differentiated, helical CT shows a higher sensitivity than lipiodol CT in detecting well-differentiated HCC nodules smaller than 2 cm.[35] In a more recent study of 28 patients comparing MDCT with hepatic arterial phase and portal venous phase acquisitions, digital subtraction angiography (DSA), and lipiodol CT in the detection of HCC, Zheng and colleagues[36] found the same sensitivity for all three modalities for the detection of nodules >2 cm and no significant difference in sensitivity among the three modalities for nodules 1–2 cm in diameter. The sensitivity of MDCT was greater than that of lipiodol CT, which in turn was greater than DSA for the detection of nodules <1 cm in size. However, some nodules could only be detected by lipiodol CT (Fig. 22). The authors share the conclusion that MDCT and lipiodol CT are complementary modalities, and that currently MDCT does not obviate the need for DSA and subsequent lipiodol CT.

Positron emission tomography (PET)

The most commonly used tracer for PET imaging is the radiotracer 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) because of its relatively long half-life (110 minutes), which means that the isotope can be commercially synthesized and supplied to PET scanners remotely from the cyclotron manufacturing sites.[37] FDG is taken by cancer cells through a facilitative glucose transporter. Once taken into cells, glucose or FDG is phosphorylated to glucose-6-phosphate or FDG-6-phosphate, respectively. While glucose-6-phosphate can travel down the glycolytic and oxidative pathways and be metabolized, FDG-6-phosphate cannot

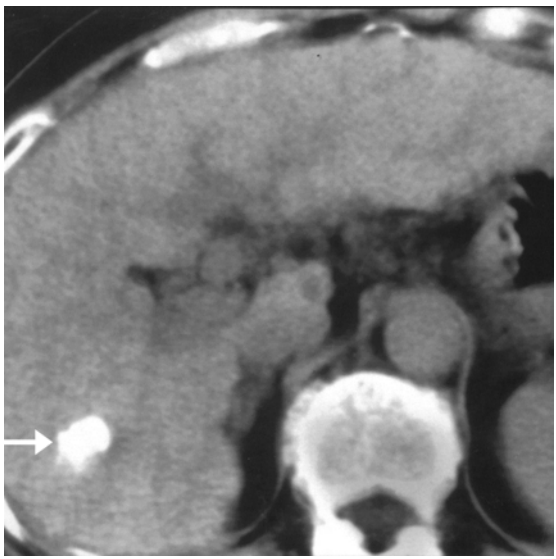


Fig. 22. Lipiodol CT scan showing a lipiodol-retaining HCC (arrow) in the right hemiliver that was not detectable by other imaging modalities.

and becomes trapped. FDG-6-phosphate can be dephosphorylated and cleared by glucose-6-phosphatase in normal cells — glucose-6-phosphatase, in particular, is expressed in high concentrations in normal liver cells. In contrast, many cancer cells show decreased expression of glucose-6-phosphatase and thus retain FDG within them.

The sensitivity of FDG-PET for the detection of HCC is about 50%.[38,39] There appears to be an association between histologic differentiation and FDG uptake. The enzymology of a well-differentiated HCC is similar to that of a normal liver and it is likely that the HCC has a higher concentration of glucose-6-phosphatase, thereby explaining the nonvisualization of these tumors on PET. In less-differentiated HCCs, the expression of glucose-6-phosphatase is lower and therefore they show intense FDG uptake. The additional use of the short-lived PET tracer [1-^{11}C] acetate in conjunction with FDG has been shown to increase the sensitivity of HCC detection to 100%.[40] Most of the well-differentiated HCCs in the study by Ho and coworkers[40] showed intense ^{11}C-acetate uptake, whereas the poorly differentiated tumors showed poor ^{11}C-acetate uptake.

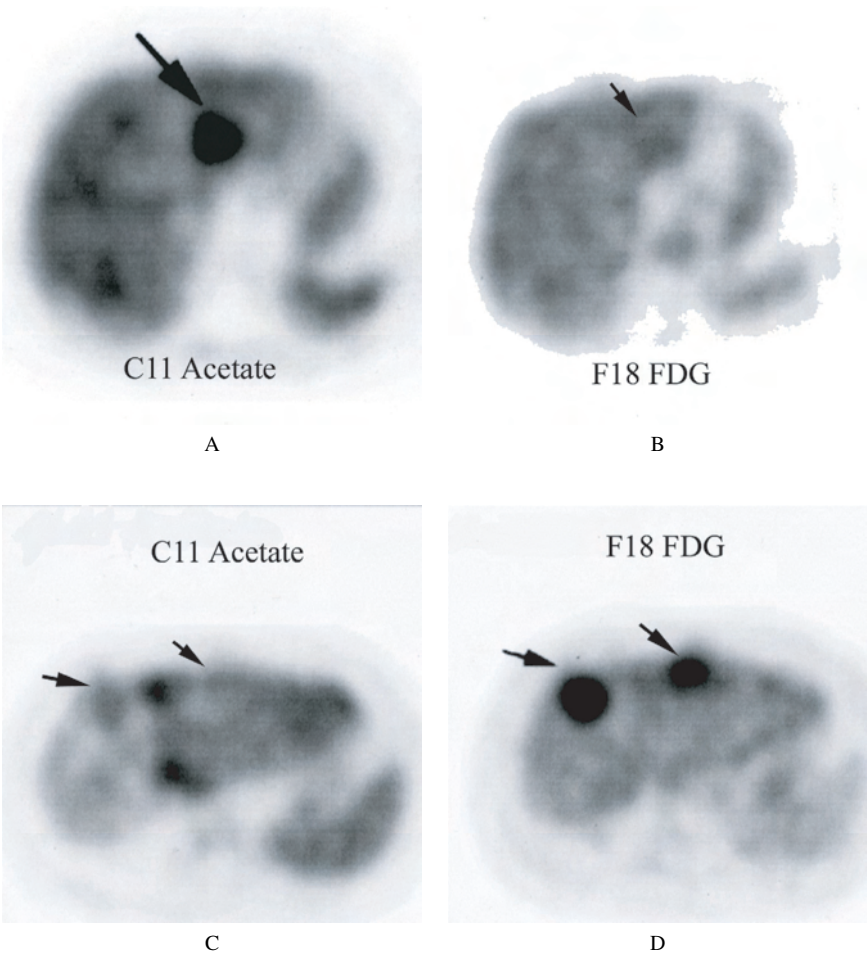


Fig. 23. PET imaging of HCC with ^{11}C-acetate and ^{18}F-FDG. (A) A liver lesion in the right hemiliver (arrow) with avid uptake of ^{11}C-acetate, thus likely to be a well-differentiated HCC. (B) The same lesion with no significant ^{18}F-FDG uptake. (C) Another patient with two liver lesions (arrows) in the liver with no significant ^{11}C-acetate uptake. (D) The same two liver lesions with avid ^{18}F-FDG uptake. These lesions may represent poorly differentiated HCC or non-HCC malignancies.

With an apparently high specificity of ^{11}C-acetate for HCC, the authors concluded that when a liver lesion is positive for either ^{11}C-acetate on its own or for both ^{11}C-acetate and FDG, the likelihood of HCC is high (Fig. 23). If a liver lesion is positive for FDG alone, then it may represent either a poorly differentiated HCC with non-HCC malignancies being possible or differential diagnoses. When a lesion is negative for both tracers, then benign pathology is most likely. As promising as this may seem, with the short half-life of ^{11}C isotopes, this technique can only be used in centers where an on-site cyclotron is available.

Conclusions

Despite the recent advances in imaging, there is currently still no single imaging modality that can provide the perfect imaging test for the detection of HCC and for the differentiation of HCC from other nodules. Ultrasound may continue to be used as a screening tool (together with serum alpha-fetoprotein) and a guide for percutaneous biopsy because of its wide availability and lack of radiation, with MDCT and MRI (depending on local availability) being the likely next step in imaging for further detection and characterization of suspicious liver nodules. Subsequent lipiodol CT, in conjunction with hepatic angiography, has a complementary role to MDCT in the detection and characterization of small foci of suspected HCC. The use of ultrasound contrast agents and newer MRI contrast agents is likely to improve the sensitivity for HCC detection for these two imaging modalities. Although the combined use of ^{11}C acetate and ^{18}F FDG has shown promise in increasing the sensitivity of HCC detection to close to 100%, the availability of the short half-life ^{11}C isotopes only to centers with on-site cyclotrons is likely to limit its widespread use.

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9

Pathology

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Introduction

Hepatocellular carcinoma (HCC) is a malignant tumor derived from hepatocytes. It is the most frequent primary tumor of the liver; in a series of 6391 cases of primary liver cancer, 4317 (67.5%) were found to be HCCs.[1] The most common etiological factors related to HCC are hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, dietary aflatoxin ingestion, and chronic alcohol abuse.[2]

Gross Appearance

The gross appearance of HCC can be simply grouped into diffuse, nodular, and massive types. More detailed classifications have been employed,[3,4] and the Liver Cancer Study Group of Japan[5] proposed a subclassification for nodular HCCs to accommodate small tumors and the presence or absence of accompanying liver cirrhosis. None of

the classifications has shown significant correlation with etiology, biology, or prognosis. We have found it convenient to describe the varied gross appearances of HCC as follows: (1) massive, in which a solitary mass replaces most of one or both lobes with small satellite nodules in the surrounding liver (Fig. 1); (2) multinodular, comprising sharply demarcated, somewhat rounded nodules scattered throughout the liver; (3) diffuse, in which numerous small tumor nodules are present throughout the liver and are difficult to distinguish from the background of cirrhotic nodules (Fig. 2); (4) pedunculated, which is a subcapsular tumor often in the undersurface of the right lobe near the anterior edge (Fig. 3); and (5) fibrolamellar, which is a well-circumscribed tumor of brown coloration and with a central scar.

For each type, consideration is given to the presence of encapsulation and cirrhosis in the surrounding liver. The presence of macroscopic invasion of intrahepatic vessels and bile ducts is also noted.

The nodular or massive type is the most common type, and the uncommon pedunculated HCC may be the only macroscopic variant of prognostic relevance. The latter are more common in females, and tend to be more readily resected because of their peculiar exophytic nature

Fig. 1. A distinct circumscribed hepatocellular carcinoma arises in the right lobe of the liver in a background of cirrhosis.

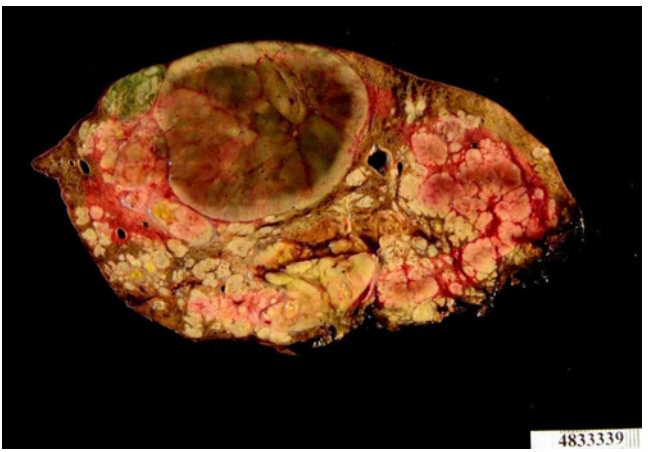

Fig. 2. A distinct dominant tumor mass is present in a background of multiple smaller tumor masses of different sizes that are difficult to separate from cirrhotic nodules in the rest of the liver.

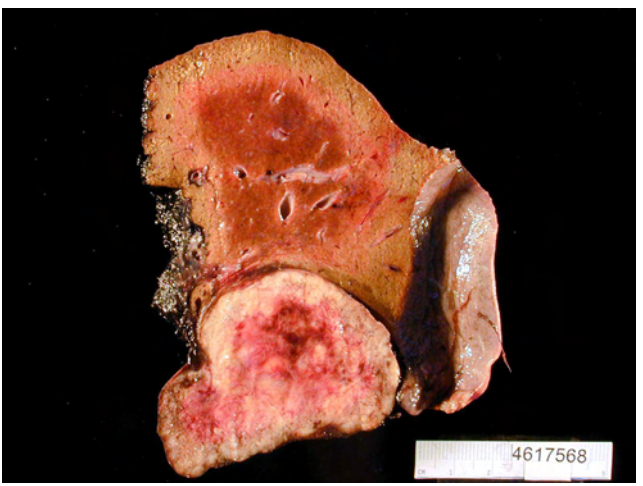

Fig. 3. A pedunculated subcapsular tumor at the anterior edge in the location of the quadrate lobe. The liver is not cirrhotic.

and subcapsular location. Furthermore, they show little invasion into the liver and are not usually associated with cirrhosis. Their location suggests an origin in the accessory lobes of the liver. Encapsulation of solitary nodules also imparts a better prognosis, as such lesions are often associated with a lower incidence of liver invasion, vascular permeation, or formation of daughter or microsatellite tumor nodules.

Microscopic Appearances

The identification of HCC is based on the resemblance of the tumor cells to normal hepatocytes in terms of both cytologic appearance and the plate-like pattern of growth. These features can usually be found in some part of the tumor. However, architecture and cytology are generally highly variable between different tumors and within the same tumor, especially in larger tumor nodules. While often conforming to a monotonous pattern, the appearances may be so variable as to be difficult to distinguish from cholangiocarcinoma and metastatic carcinoma.

Architectural variants

Conventionally, several architectural patterns have been described. These include the trabecular plate-like (sinusoidal), pseudoglandular (acinar or adenoid), compact solid, and scirrhous types, and fibrolamellar carcinoma.[6]

The trabecular or plate-like type is composed of well-formed trabeculae of five-to-eight cell layers thick (microtrabecular) (Fig. 4), and is sheathed by flattened endothelial cells of intervening sinusoidal blood spaces. While often described as cord-like in appearance, they actually represent plates of cells of several layers thick. Occasionally, less differentiated trabeculae are more than eight cell layers thick (macrotrabecular). Sometimes, cavernous blood-filled spaces may be present in this type of HCC (Fig. 5).

The pseudoglandular or acinar type is formed of trabeculae with intervening acinar-like spaces. These spaces are not true glands, but represent dilated canaliculi that may contain bile or a dense eosinophilic material representing the breakdown products of inflammatory debris

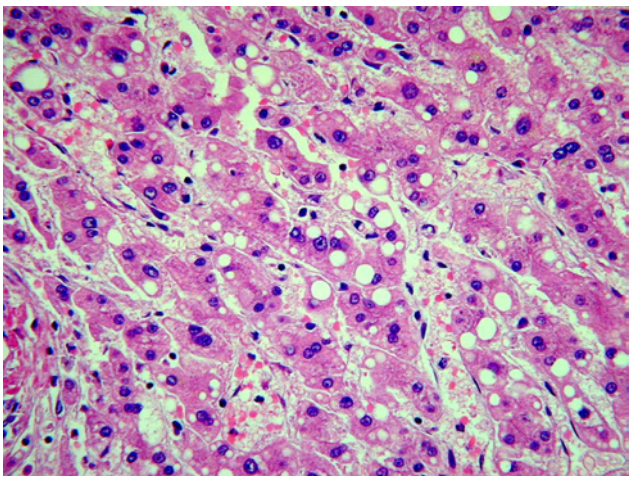

Fig. 4. A well-differentiated hepatocellular carcinoma showing a microtrabecular pattern comprising plates of well-differentiated liver cells of two-to-three cell layers thick. There is fatty change in the neoplastic hepatocytes, and binucleated cells are also evident.

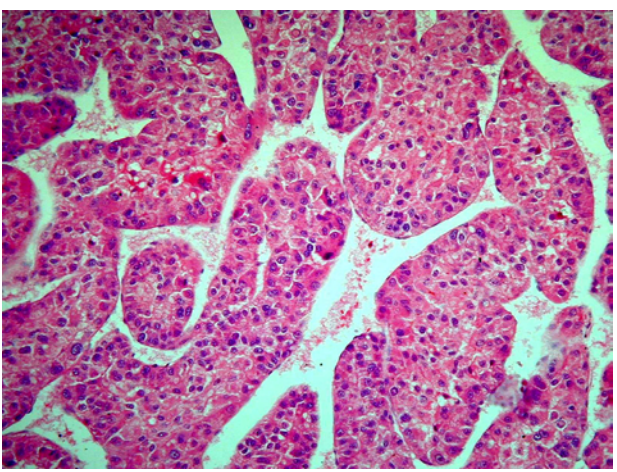

Fig. 5. Macrotrabecular variant formed by plates that are up to eight cell layers thick with intervening dilated sinusoidal spaces (in the present example, emptied of blood).

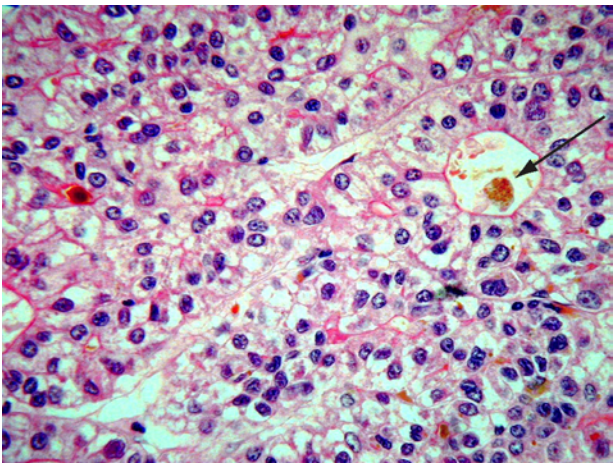

Fig. 6. This pseudoglandular or acinar variant is composed of sheets of tumor cells that form scattered gland-like spaces (arrow) representing markedly dilated bile canaliculi and containing bile and/or breakdown products of inflammatory debris.

and exudate (Fig. 6). Although occasionally staining with periodic acid-Schiff (PAS)–diastase, the colloid-like material is not mucin but fibrin. The trabecular and pseudoglandular types are the most common histologic patterns seen in moderately differentiated to well-differentiated HCCs.

The compact pattern is more often seen in moderately to poorly differentiated HCCs. In this variant, trabeculae are still present, but they are poorly formed and often in disarray. The tumor appears to be composed of mostly solid sheets of cells, with the blood spaces rendered inconspicuous by compression (Fig. 7).

Scirrhous HCC is uncommon and shows prominent desmoplasia, with fibrous septa dissecting nests or groups of malignant cells. Although this variant is more often reported following irradiation or chemotherapy and infarction, it may occur in the absence of these factors.

The fibrolamellar variant of HCC is distinctive because it is found in a younger age group, has better prognosis, and usually occurs in the left lobe of a noncirrhotic liver. The tumor often has a characteristic gross appearance, being a rich brown color, well circumscribed, and displaying central fibrosis. Unidirectional or lamellar fibrous strands flank narrow

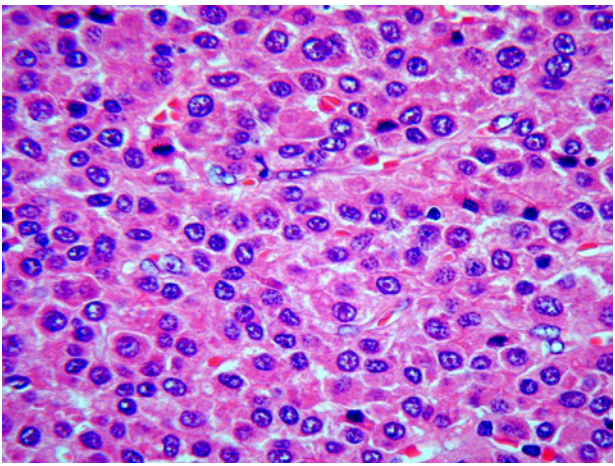

Fig. 7. The compact variant occurs in moderately or poorly differentiated HCCs, and is composed of solid sheets of tumor cells with inconspicuous blood spaces.

plates of tumor cells that also form solid sheets. The malignant cells have abundant mitochondria, which account for their distinctive cytoplasmic eosinophilia and granularity, and prominent pale cytoplasmic bodies (Fig. 8) and dense PAS-positive inclusions may be present.

Cytological variants

HCC shows a number of cytological variants. The hepatic or liver-like cell variant comprises polygonal cells with vesicular nuclei and prominent nucleoli. The nuclear/cytoplasmic ratio as well as the degree of nuclear pleomorphism and hyperchromasia vary with the level of differentiation of the tumor. The cytoplasm is generally granular as in normal hepatocytes, but shows a greater degree of basophilia. Often, it is this cytoplasmic basophilia that distinguishes the cells of HCC from nonneoplastic hepatocytes.

The pleomorphic variant comprises cells that are often large and contain multiple bizarre nuclei. These cells rarely form sheets or compact masses, and usually comprise only a small portion of the tumor.

The clear cell variant has cells with abundant, pale, finely granular, or vacuolated cytoplasm as a result of abundant glycogen, fat, or water

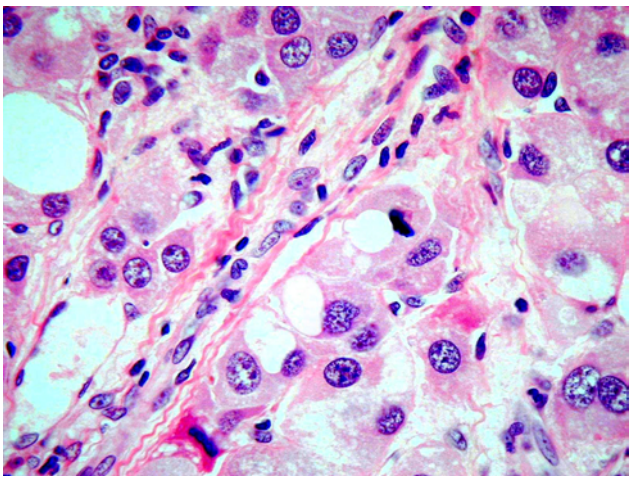

Fig. 8. Fibrolamellar carcinoma composed of large tumor cells with granular eosinophilic cytoplasm and distinctive pale cytoplasmic inclusions. These inclusions stain for fibrinogen, and should not be mistaken for the ground-glass hepatocytes induced by the hepatitis B virus.

(Fig. 9); and show centrally located nuclei. The clear cells can predominate in the tumor and often retain a trabecular growth pattern. Rarely, they grow in solid sheets, and require distinction from metastatic renal cell carcinoma and other metastatic clear cell tumors. Although better prognosis has been suggested with this variant,[7] this has yet to be substantiated.[8]

Less common cytologic variants are the oncocyte-like, spindle cell, giant cell, and rhabdoid types. Oncocyte-like cells seen in fibrolamellar HCC are moderately to well differentiated, and are fairly regular in size and shape with eosinophilic cytoplasm and small hyperchromatic nuclei. The spindle cell variant is reported to be more common in patients with a history of anticancer therapy, which can result in phenotypic change in tumor cells. Spindle cells usually show a transition from more conventional HCC, either of the trabecular or compact architectural type, and immunostaining reveals the coexpression of cytokeratin and vimentin. Such tumors should be considered spindle cell carcinomas, and not carcinosarcomas or mixed tumors.

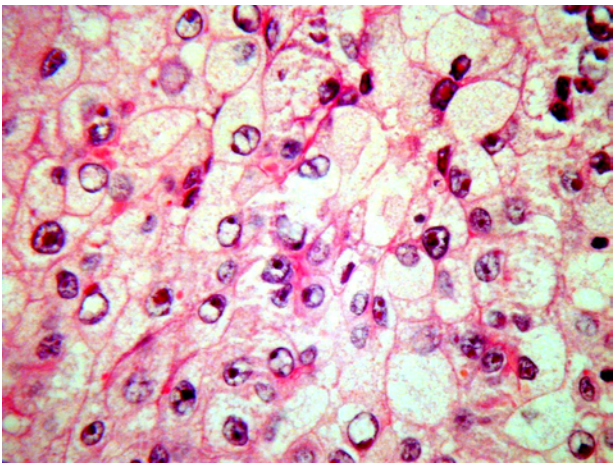

Fig. 9. The clear cell variant of HCC is composed of cells with water-clear, PAS-positive cytoplasm rich in glycogen, fat, or water.

Cytoplasmic inclusions

Several types of cytoplasmic inclusions may be seen in the tumor cells of HCC. These include Mallory bodies, which have been demonstrated to be masses of clumped intermediate filaments using electron microscopy.[9] The pale cytoplasmic inclusions or bodies frequently seen in fibrolamellar HCC stain positive with antifibrinogen antibodies and represent fibrillary structures within cystically dilated endoplasmic reticulum.[9] Granular hyaline bodies of varying sizes may be seen in as many as 15% of HCCs, and may be intracellular or extracellular in location (Fig. 10). These granules are often weakly acidophilic and stain with the PAS stain. They stain orange to red with trichrome stains; and can be immunohistochemically shown to be one of the liver products such as albumin, alpha-fetoprotein, alpha-1 antitrypsin, bile, or ferritin. The presence of Mallory's hyaline and alpha-1 antitrypsin globules is not related to alcohol intake or deficiency of alpha-1 antitrypsin, respectively. Although the hepatitis B surface antigen (HBsAg) producing the characteristic ground-glass cytoplasm may be seen in the surrounding hepatocytes, it is a very rare occurrence within tumor cells. The pale cytoplasmic bodies in the tumor cells of fibrolamellar HCC may

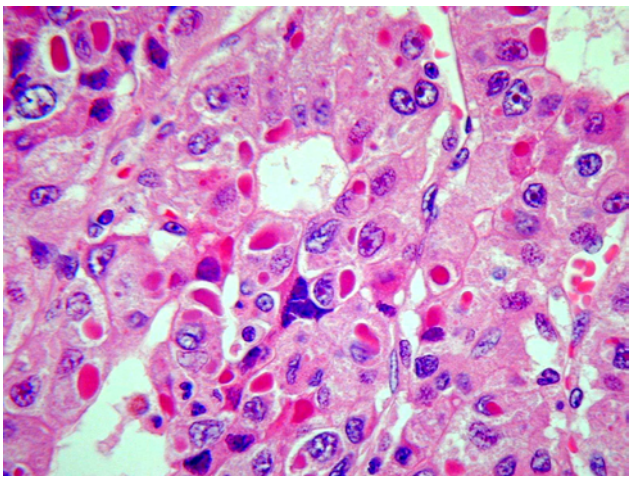

Fig. 10. Hyaline bodies may occur in as many as 15% of hepatocellular carcinomas, and may be intracellular or extracellular in location as seen in this case. These hyaline bodies stain positive with PAS stain.

be mistaken for ground-glass hepatocytes, but they do not stain for HBsAg.

Grading

The Edmondson and Steiner system[10] grades HCC into four grades. Grade I HCC is most commonly seen in lesions of less than 3 cm in diameter and can be difficult to differentiate from hepatocellular adenoma, whereas grade IV HCC may be difficult to distinguish from metastatic carcinoma. The two extremes of the spectrum in this four-tiered system can be difficult to recognize, and the great variability of pleomorphism within the same tumor makes accurate grading a problem. The recent WHO grading system employs a somewhat similar four-tiered system of well-differentiated, moderately differentiated, poorly differentiated, and undifferentiated types.[11]

Despite several classifications of HCC according to gross or microscopic appearances and attempts at grading, few pathologic parameters have proven to be really useful in predicting the recurrence or behavior

of HCC. Besides prognostication, the purpose of tumor grading is to provide a correlation with biological data such as laboratory parameters and tumor markers. Grading of HCC has had a very small impact on prognosis and is probably not of great significance. The pathologic parameters also do not appear to relate to the common etiologic agents. Despite identifiable differences in the clinical presentation of HBV- and HCV-associated HCC, studies from Japan have failed to demonstrate clear differences in the pathology of the tumors between these two groups.[12,13]

Natural History and Spread

At the Prince of Wales Hospital, Hong Kong, from 1993 to 1996, over 82% of resected livers with HCC had associated macronodular cirrhosis, 5% had mixed cirrhosis, 2% had micronodular cirrhosis, and 4% had moderate to severe portal fibrosis.[14] Only 7% had no evidence of fibrosis or cirrhosis. When the tumor was not resectable, the majority of patients (if symptomatic) died within 3 to 6 months.

Within the liver, most HCCs show a sinusoidal or replacing growth pattern that is most evident at the periphery of the tumor. The tumor cells grow in the sinusoids in an infiltrative fashion and compress the surrounding liver cell cords. HCCs may also show a replacing growth pattern in which the tumor cells replace hepatocytes within the liver cell cords. This method of infiltration is considered to be the basic growth pattern in HCC, and is frequently observed in small or early HCCs. A direct infiltrative method of extension into adjacent liver tissue is less common.

The pattern of metastasis of HCC is monotonously similar and occurs at a relatively late stage of the disease. More than 70% show extrahepatic metastases, a feature more common in noncirrhotic than cirrhotic livers. Nearly twice as many patients dying with HCC which occurred in a cirrhotic liver were free of metastases compared to those with carcinomas in noncirrhotic livers[3]; this was probably because patients with HCC and cirrhosis developed hepatic failure and died sooner before metastases developed. An incidence of metastasis of

74.2% and 58.4% was reported for noncirrhotic and cirrhotic Japanese patients, respectively.[15]

Hematogenous and lymph node metastases are the most common routes for dissemination of the tumor cells (Fig. 11). Kojiro[15] reported hematogenous metastases in 50.8% of HCCs, while lymph node metastases occurred in 25.5%. The most common site of spread is the lung, occurring in over 40% of tumors in one series.[16] Nearly equal in frequency is the involvement of the portal vein with retrograde extension into the extrahepatic portion of that vessel. The next most common metastatic site are the periportal lymph nodes, which accounted for 43% in noncirrhotic livers and 16.5% in cirrhotic livers.[3] Other sites of metastases are adrenal gland, gastrointestinal tract, bone, spleen, serosal surfaces, gallbladder, heart, and kidney. Lymph node metastasis was reported in 25.5% of 660 consecutive autopsy cases,[17] with the hepatic hilar, peripancreatic, perigastric, and periaortic nodes being favored.

HCC has a tendency to extend into adjacent branches of the portal vein and cause multiple intrahepatic secondaries, rarely spreading to involve gastric and esophageal veins to produce varices that sometimes account for variceal hemorrhage in the absence of cirrhosis. HCC also

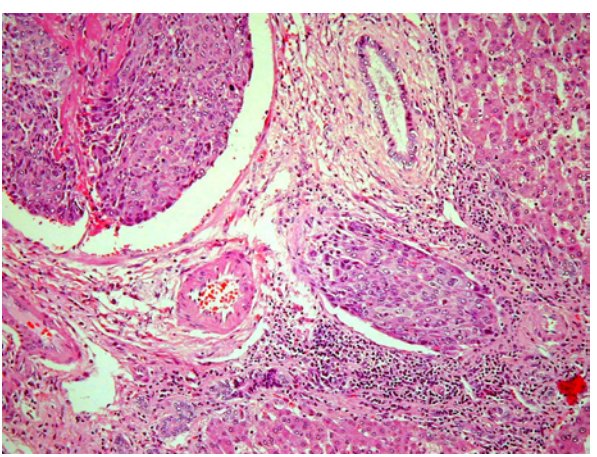

Fig. 11. Hematogenous and lymph node metastases are the most common routes of dissemination of HCC. Lymphovascular invasion by two masses of malignant hepatocytes is present in the portal tract.

extends into the hepatic venous system to involve the hepatic vein radicals with access to the right heart and lungs via the inferior vena cava (IVC). The propensity for local intravascular invasion and spread is a major factor in the development of spontaneous tumor rupture, which results from widespread thrombotic occlusion, infarction, or hemorrhage, seen in about 10% of our cases. HCC also infiltrates the intrahepatic bile ducts with extension into the common bile duct, both of which may be observed macroscopically. Obstruction and hemorrhage can produce obstructive jaundice. Other sites of metastases include the bones and lymph nodes of the porta hepatis. Decompensation of liver function is often the cause of death, even before metastatic disease is extensive.

Prognostic Features

A thorough analysis of 20 pathologic features in 278 resected tumors from Hong Kong found that capsule formation and heavy intratumoral chronic inflammatory cell infiltrate were independent favorable factors related to tumor recurrence.[18] Negative resection margins and heavy intratumoral chronic inflammatory infiltrates were independent favorable factors correlating with postoperative survival. The previous claims that recurrence and survival were related to tumor size were not substantiated. Tumors larger than 5 cm were associated with a higher tumor recurrence rate by univariate analysis, but this was not an independent prognostic factor by multivariate analysis. Furthermore, there was no difference in survival rates between patients with large and small tumors — a finding that contradicted Japanese reports.[19]

Precursor Lesions

Small HCC

This is a recent concept that has arisen because advancements in imaging techniques have allowed the detection of increased numbers of small HCCs. When first introduced, the term referred to tumors of 5 cm or less in diameter, but it is now defined as tumors of 2 cm or less in

diameter. Small HCCs are reported to have better 5-year survival rates than other types of HCCs. Small HCCs can be further divided into two groups, namely, those with distinct and indistinct nodules.[20,21] The distinct nodule type usually shows clear demarcation and circumscription by a thin fibrous capsule. The indistinct nodule is usually difficult to discern grossly in a macronodular cirrhotic liver because the tumor nodule blends in with the nodular background. The tumor nodule is usually paler or light yellow in color, while the nontumor nodules are usually tan or bile-stained (bile staining is enhanced by oxidation and fixation in formaldehyde).

The most striking characteristic of small HCCs is that they are often composed of well-differentiated tumor cells resembling normal hepatocytes.[21] Cellularity is increased and the compact tumor cells are arranged in a vaguely trabecular pattern, frequently with pseudoglandular or acinar structures. The cytoplasm displays increased staining affinity and can be either eosinophilic or basophilic, with the nuclei being round and mildly hyperchromatic — hence, an increased nuclear/cytoplasmic ratio. Fatty change is frequent. Many portal tracts are present within the tumor nodule, and tumor cell invasion into the portal tracts may be seen. Often, there is a less well-differentiated component that is invariably surrounded by the well-differentiated component, the areas of the well-differentiated tumor diminishing in size as the tumor enlarges. There is no true capsule formation and the neoplastic cells blend in with the surrounding hepatocytes, the neoplastic cells proliferating as though they are replacing normal hepatocytes, thus making microscopic delineation of the tumor nodule difficult. These small HCCs are said to correspond to carcinoma *in situ*.[10] They tend to preserve normal liver architecture (including portal tracts), receive portal blood supply, and do not show tumor blushing in angiographic examinations. The latter properties are in contrast to those of HCC which, even when small, show tumor blushing without portal blood flow.[22]

Dysplasia

The term "liver cell dysplasia" introduced by Anthony[23] refers to the presence of large, abnormal cells with bizarre, hyperchromatic, and

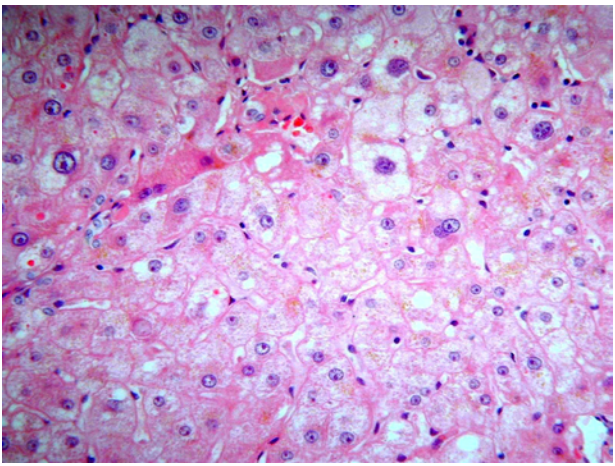

Fig. 12. Large cell dysplasia is a common feature in cirrhotic nodules. Hepatocytes with large nuclei are evident in the upper half of the field. The nuclei are up to three times the size of normal hepatocytes in the lower half of the field.

occasionally multiple nuclei; these cells were seen to occur in clusters and sometimes occupy entire cirrhotic nodules. This form of dysplasia has come to be known as "large cell dysplasia" (Fig. 12). While its occurrence is not disputed, the earlier suggestion that it represents an independent risk factor for the development of HCC has not been irrefutably proven.

"Small cell dysplasia" is a more recent term coined by Watanabe *et al.*[24] Cells with such changes were observed in HCCs and occurred in clusters with prominent nuclear crowding. Their small nuclei and relatively less than normal, often basophilic, cytoplasm resulted in an increased nuclear/cytoplasmic ratio. In addition, there were cytologic abnormalities in the form of nuclear pleomorphism and sometimes multinucleation. Watanabe *et al.*[24] concluded that these cells were premalignant. While small cell dysplasia appears to be readily identified in HCCs in Japan and in the Asian population, it seems less common in the West; and there is expressed uncertainty as to the distinction of small cell dysplasia from regenerative changes.[25]

It should be noted that dysplastic nodules or adenomatous hyperplasia need not be composed of hepatocytes displaying either large or small cell dysplastic changes.

Dysplastic nodules

The terms "dysplastic nodule, low grade" (DNLG) (adenomatous hyperplasia) and "dysplastic nodule, high grade" (DNHG) (atypical adenomatous hyperplasia) represent an area of some confusion, particularly as there is currently no objective phenotypic or genotypic criteria for distinction and morphologic criteria are still under discussion.[10,26] Dysplastic nodules are generally regarded as preneoplastic and may account for the multicentric occurrence of HCC.[27] The regenerative nodules of macronodular cirrhosis can sometimes grow to a large size and present as a mass, mimicking a small HCC or a metastatic tumor. These macroregenerative nodules have also been referred to as "adenomatous hyperplasia" or "dysplastic nodule".[28] While most frequently described in the Japanese population, macroregenerative nodules appear to have a comparable frequency in the West.[29] Macroscopically, such nodules may be distinguished from their surrounding tissue in terms of size, texture, and color, being yellowish to greenish or bile-stained, sometimes of a lighter tan color than the surrounding cirrhotic liver — not different from well-differentiated HCCs on the one hand and from large regenerative nodules on the other hand. Microscopically, they display a moderate increase in cell density with a mildly irregular trabecular pattern and retain normal architecture with many portal tracts. The nuclear/cytoplasmic ratio may be slightly increased because of a reduction in the amount of cytoplasm and there is often heterogeneity in nuclear size, but they are generally clearly distinguishable from well-differentiated HCCs.[30]

DNHG or atypical adenomatous hyperplasia is equivalent to a borderline lesion of HCC, and may be difficult to separate from well-differentiated HCC. The nodules, which range from 10–15 mm, are slightly larger than those of DNLG and are grossly indistinguishable from well-differentiated HCCs, which have indistinct margins. There is a marked increase in cell density focally within the nodule and fatty change is frequently present. Furthermore, there are varying degrees of sinusoidal capillarization in DNHG, making distinction from HCC even more difficult[31] such that diagnostic reproducibility is low even among experts.[30] Infiltration of the stroma and portal tracts has been

employed to distinguish DNHG from well-differentiated HCC, but the separation of the two entities clearly requires further clarification and the diagnostic criteria require refinement.[32]

Hepatocellular adenoma

This benign tumor of hepatocytes is well recognized for its association with the use of oral contraceptive steroids and androgenic/anabolic steroids. True malignancy resulting from the intake of such steroids is very rare. Progestogens do not appear to carry any risk, and the risk with modern low-dose oral contraceptives is very much reduced.[33,34] The most commonly incriminated androgens are methyltestosterone, oxymetholone, and norethandrolone. With the exception of peliosis hepatis, the other side effects of synthetic gonadal steroids — including cholestatic jaundice, Budd–Chiari syndrome, and sinusoidal dilatation — are seldom seen in combination with adenoma. While other etiologic agents such as danazol, norethisterone, clomiphene, diabetes mellitus, glycogen storage disease types Ia and II, and Klinefelter's syndrome have been implicated, many do not seem to have an identifiable etiology.

Patients with hepatocellular adenoma may be asymptomatic and present mostly with intratumoral hemorrhage or, less frequently, with rupture into the peritoneum. Malignant transformation is rare. Hepatocellular adenomas are usually solitary. Multiple adenomas are uncommon, although rare instances of multiple adenomatosis have been reported.[35]

Macroscopically, the tumor mass may be as large as 30 cm in diameter and 3000 g in weight. Dilated vessels commonly traverse its bulging surface, and it is clearly demarcated but not encapsulated. It has a soft friable consistency with areas of hemorrhage or necrosis. Focal scarring marks sites of previous hemorrhage and infarction. Microscopically, the tumor lacks a lobular architecture; bile ducts are completely absent; and the liver plates are no more than two-to-three cells thick and separated by narrow, inconspicuous sinusoids lined by endothelium. Kupffer cells may be present in variable numbers. The hepatocytes do not display pleomorphism, although they are generally larger than normal, and

their cytoplasm is pale or clear due to excess of glycogen. Large tortuous arteries and dilated veins may be present, and foci of hematopoiesis may be seen in adenomas occurring in children. Besides peliosis hepatis, which may occur when associated with anabolic steroid intake, alpha-1 antitrypsin globules as well as appearances simulating alcoholic hepatitis with fatty change, neutrophils, and giant cell granulomas may be present.

While not difficult to diagnose in the gross state, in needle biopsies it can be difficult to separate hepatocellular adenoma from well-differentiated HCC. The latter is diagnosed by the presence of thick liver plates of more than three cell layers, pseudoacinar formation, cytologic atypia, cytoplasmic basophilia, loss of the reticulin pattern, absence of Kupffer cells, stainable alpha-fetoprotein, and vascular invasion. An appropriate clinical history is useful for the diagnosis of hepatocellular adenoma.

Benign Lesions

Focal nodular hyperplasia (FNH)

Focal nodular hyperplasia (FNH) occurs most frequently in young women, but is also seen in males and at all ages.[36] Its alleged association with oral contraceptive use is controversial, and FNH is thought to be a vascular malformation with arteriovenous anastomoses and local overgrowth of liver elements.[37] FNH is usually asymptomatic and discovered incidentally as a solitary lobulated mass of less than 5 cm in diameter with a prominent central stellate scar. The cut surface bulges, it is circumscribed but not encapsulated, and it is paler than the surrounding liver tissue (Fig. 13). Multifocal nodular hyperplasia is associated with systemic abnormality of angiogenesis, including hepatic hemangioma, intracranial vascular malformation and tumors, and dysplasia of large muscular arteries.[38] Microscopically, it is composed of nodules of liver parenchyma separated by fibrous septae. A discernable hierarchical structure defined by the arterial distribution is evident, with branching arteries terminating in the center of one of the small nodules that make up the entire mass. Larger arteries may show degenerative

Fig. 13. Focal nodular hyperplasia. The well-circumscribed lobulated tumor is distinctive in appearance in that it bulges, is circumscribed but is not encapsulated, and is of a paler color than the surrounding liver. It contains a characteristic central stellate scar of fibrovascular tissue.

changes in the media and eccentric intimal fibrosis. The arteries run in the fibrous stroma without portal veins, and are generally associated with proliferating bile ductules with cholestasis and neutrophils as well as lymphocytes.

The distinction of FNH from hepatocellular adenoma in a needle biopsy specimen is often difficult and sometimes not possible. Accurate diagnosis is dependent on tissue sampling. However, diagnosis is aided by the presence of prominent proliferating bile ductules in the fibrous septae and the clinical findings of a solitary lesion with a central vascular scar.[25,39] The remaining liver is usually normal.

Nodular regenerative hyperplasia

Nodular regenerative hyperplasia (NRH) is also known as noncirrhotic nodulation, nodular transformation, partial nodular transformation, and a variety of other names. It is characterized by small regenerative

nodules in the liver associated with a variety of diseases that seem to share the common feature of some form of vascular or circulatory abnormality. These diseases include rheumatoid arthritis, Felty's syndrome, lupus erythematosus, scleroderma, polyarteritis nodosa, diabetes mellitus, and hematolymphoid proliferative disorders. NRH has also been reported following bone marrow and kidney transplantation. It has been suggested that NRH occurs as a result of tissue adaptation to the uneven distribution of hepatic blood due to a variety of causes.[40] NRH is most often asymptomatic, although it may be a cause of noncirrhotic portal hypertension and rarely has caused intraperitoneal hemorrhage.

Macroscopically, the liver shows a fine granularity from multiple diffuse nodules of 1–10 mm in size. It is not associated with cirrhosis or fibrosis, and the severity of nodulation may be variable with accentuation near the porta hepatis. Microscopically, the nodules are composed of normal-appearing hepatocytes that are arranged in plates of two-to-three cell layers thick. Lobular architecture is maintained with evenly distributed portal structures and no evidence of fibrosis. The expansive nature of these nodules is best demonstrated with reticulin stains. Obliterative vascular changes may be seen in all types of intrahepatic vessels. Diagnosis by needle biopsy is obviously difficult, and the differential diagnoses are FNH and hepatocellular adenoma.

Combined HCC and Cholangiocarcinoma

Combined HCC and cholangiocarcinoma (CC) is rare, and is defined as a tumor composed of both elements of HCC and CC.[41,42] The components of the combined tumor may occur separately (double cancers), be adjacent to each other or mixed as one tumor mass (combined), or be intimately mixed (mixed). Another study separated combined tumors into collision tumors, transitional tumors, and cases of fibrolamellar HCCs with a mucus-secreting component. The explanation for such combined tumors is based on the theory that hepatocytes and biliary epithelial cells originate from the same pleuripotent progenitor cell.[43] While clinically combined HCC-CC is similar to HCC, the presence of bile duct differentiation or a sarcomatous component appears to impart a poorer prognosis.[44]

Liver Carcinoma in Children

HCC accounts for about 20% of all primary hepatic tumors in childhood, and is the third most common one following hepatoblastoma and vascular tumors. The most common disorders related to childhood HCC are biliary atresia, chronic hepatitis B infection, glycogen storage disease type I, hereditary tyrosinemia, and familial cholestasis.

Childhood HCC

Landing[45] argued that the data of many previous studies failed to distinguish epithelial hepatoblastoma from true HCC. He suggested that helpful criteria to distinguish the two tumors included the presence of a typical broad cord-like trabecular pattern in HCC and the presence of both a larger HCC and smaller embryonic cell epithelial component in epithelial hepatoblastoma. In our experience, hepatoblastoma is the most common primary liver tumor in childhood. Of six cases of HCCs in patients of less than 21 years, five were related to chronic viral B infection and the other was a small HCC (< 2 cm) in a 3-year-old boy with biliary atresia. All of the six patients had liver cirrhosis. The microscopic appearances of childhood HCC are not significantly different to those seen in adult patients, with the exception that they are generally well-differentiated tumors.

Hepatoblastoma

Hepatoblastoma is the most common liver tumor in childhood; rare adult cases have been reported. Hepatoblastoma is a malignant tumor that arises in embryonic fetal hepatocytes. It presents usually as a single large mass and its macroscopic appearance is determined by the presence or absence of mesenchymal components, often showing necrosis, cystic change, and hemorrhage. Vascularity is prominent and a thin capsule may be present. Liver cirrhosis is not commonly associated.

The tumor can be epithelial or mixed with both epithelial and mesenchymal components. Rarely, they may be of the anaplastic small cell, macrotrabecular, teratoid, or mucoid variant.[46] The epithelial variant

shows two kinds of cells, namely, fetal and embryonal. The former resemble fetal hepatocytes, and are arranged in irregular two-cell–thick plates with bile canaliculi and sinusoids. The polygonal cells have round to oval nuclei and single nucleoli. Hematopoiesis is frequently seen in the fetal type of hepatoblastoma. The embryonic-type cells are small, elongated, or spindle-shaped, with basophilic cytoplasm and a high nuclear/cytoplasmic ratio. They grow in a compact or trabecular pattern, and often form rosettes, cords, or ribbons. Extramedullary hematopoiesis is not found in this type of tumor. Transition between the two types of tissue is often present. A separate anaplastic type of hepatoblastoma with a poorer prognosis has been recognized[47]; these tumors are composed of small anaplastic cells that are poorly cohesive and difficult to distinguish from neuroblastomas and other small round cell tumors of childhood.

The mixed type of hepatoblastoma is composed of both epithelial and mesenchymal elements. The latter include connective tissues such as osteoid, chondroid, and undifferentiated spindle cells.

Immunohistology

HepPar 1 antigen is localized to the cytoplasm of benign and neoplastic hepatocytes, and is not found in bile ducts or other nonparenchymal tissues.[48] It has high specificity for HCC; but staining is variable, so caution should be employed when tumor tissue for assessment is scanty. Alpha-fetoprotein (AFP) is a marker of high specificity, but with a sensitivity of less than 50%. Both HepPar1 and AFP are expressed by hepatoid tumors from other sites. CK19, CK20, and CDX2 allow the separation of HCC from CC and metastatic carcinoma, CC labeling for CK19 while metastasis from the gastrointestinal tract staining for the latter two antigens.[48] Polyclonal carcinoembryonic antigen stains canaliculi to produce a "chicken wire fence" pattern in the normal liver, and the presence of bile canaliculi allows the identification of hepatocytes and their neoplasms. CD10 (common acute lymphoblastic leukemia [ALL] antigen) similarly stains canaliculi; an abnormal pattern of staining will help identify HCC, and focal abnormalities are seen in liver cell adenoma and FNH.

The other area of utility of immunohistochemistry lies in the distinction of well-differentiated HCC from precursor lesions and liver cell adenomas, and is based on the demonstration of capillarization of sinusoids that occurs with malignant change. Normal liver, livers with chronic hepatitis, cirrhotic nodules, and macroregenerative nodules display few or no arterial elements in the parenchyma and perisinusoidal cells are increased compared to HCC, allowing a method of distinction. The sinusoids of HCC acquire type IV collagen and laminin, reflecting the capillarization associated with the increased arterial blood flow that occurs with malignant transformation. Immunostaining for these basal lamina components can thus help identify malignant change in adenomatous hyperplasia.[49] More recently, CD34 — which labels endothelial cells — highlights sinusoids that have undergone capillarization seen in HCC (Fig. 14) and small well-differentiated HCC, but

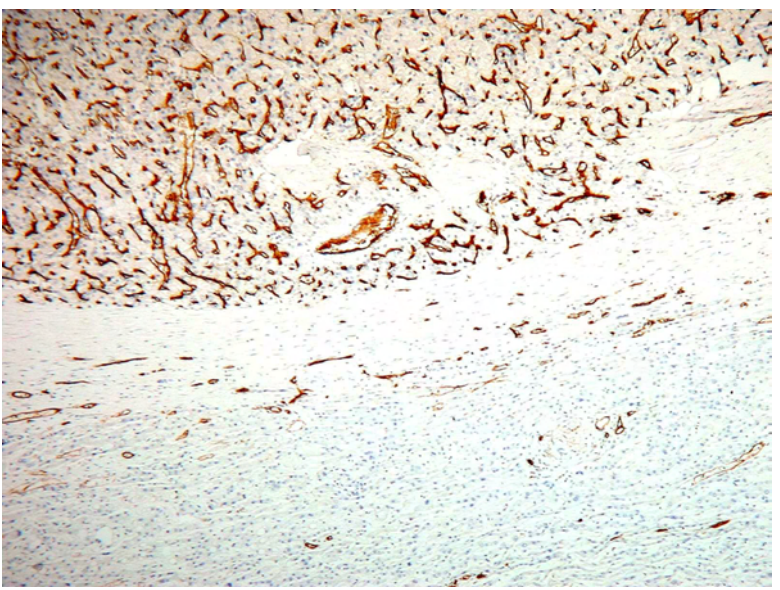

Fig. 14. The well-differentiated HCC in the upper half of the field is clearly demarcated from the nonneoplastic liver tissue by the striking capillarization of sinusoids, as shown with staining for CD34. The same pattern may be demonstrated with stains for the basal lamina elements collagen type IV or laminin.

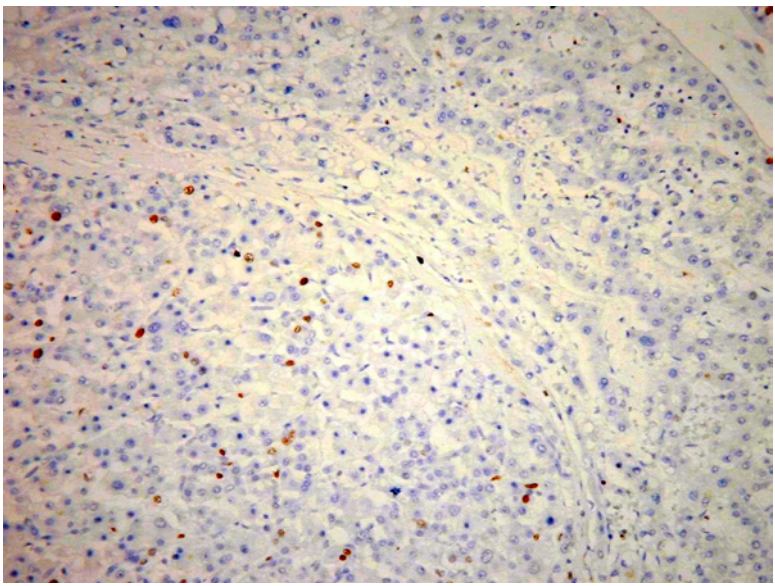

Fig. 15. The nodule of well-differentiated HCC in the lower left field is clearly separated from the adjacent liver tissue by the increased proliferative activity, as shown here with staining for Ki-67.

similar reactivity may be seen in liver cell adenoma and focal nodular hyperplasia.[50] Cell proliferation markers (Fig. 15) may have potential in distinguishing DNHG and small well-differentiated HCC from regenerative nodules,[51] but it is anticipated that the separation will not be clear-cut.

Conclusions

While HCC can usually be readily distinguished from nonneoplastic proliferations of hepatocytes in resected specimens, this task may occasionally be difficult in needle core specimens. The advent of modern imaging techniques combined with isotopes has enabled the detection of small HCCs and malignant transformation in regenerative nodules. Despite the accumulating information on such lesions, the refinement of diagnostic criteria, and the contributions of ancillary techniques

such as immunohistochemistry, diagnosis on the basis of morphological grounds alone can be difficult, particularly in needle core biopsies. Accurate diagnosis requires both clinical and radiological correlation as well as information of clinical data such as serum alpha-fetoprotein level and existence of associated etiologic factors.

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10

Molecular Aspects

John Y. H. Chan, Kenneth K. H. Lee, Yiu-Loon Chui and Macus T. Kuo

Introduction

The etiology of hepatocellular carcinoma (HCC), like many other kinds of cancer, has been shown to be multifactorial and multistage in nature (for a review, please see Refs. 1–9). The risk factors for HCC are divided into environmental factors, including biological and chemical agents, and genetic factors (Fig. 1). The major biological agents are the hepatitis viruses including the hepatitis B virus (HBV) and hepatitis C virus (HCV), and parasites such as the liver fluke which contributes to parasitic hepatitis. Chemical agents that contribute to HCC are aflatoxin, nitrosamines, vinyl chloride, peroxisome proliferators, and alcohol. Most of these agents either directly or indirectly induce mutations or alterations in DNA and the genome, or act as promoters which facilitate the proliferation of hepatocytes and the fixation of DNA lesions. In addition, genetic factors such as metabolic disorders, DNA repair defects, and altered susceptibility genes may also contribute to the development of HCC. Differential susceptibility to the development of liver

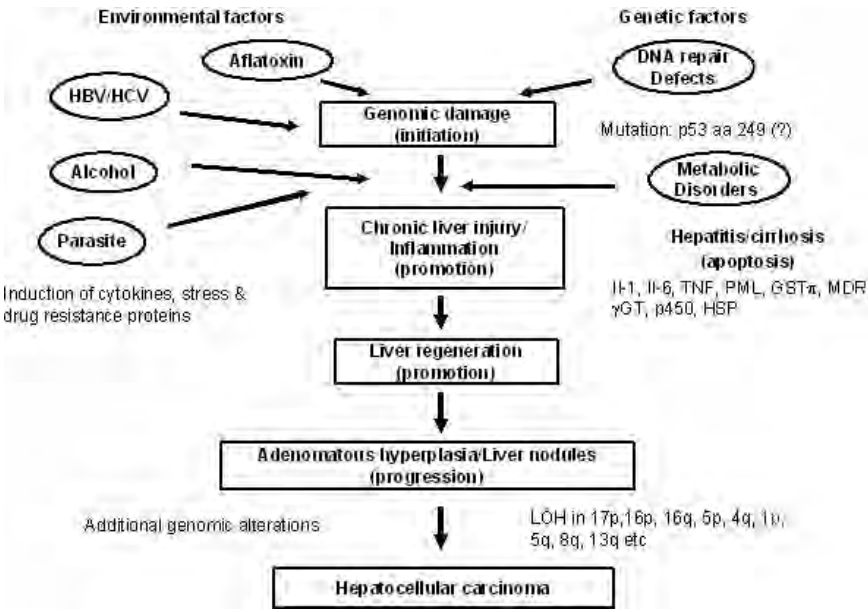

Fig. 1. Proposed sequences of carcinogenesis of human hepatocellular carcinoma. The environmental risk factors — including HBV/HCV, chemical carcinogens such as aflatoxin B_1 and alcohol, and parasites — are listed. Genetic factors such as intrinsic levels of metabolizing enzymes, DNA repair defects, and other alterations are also shown.

cancer varies considerably among different rodent species and strains; while in humans, familial clustering of HCC has been described in Chinese and Alaskan natives.

The development of HCC may be divided into several stages: genomic/DNA damage (initiation); chronic liver injury (promotion), which produces inflammation, cirrhosis, and cell death; liver regeneration (promotion); adenomatous hyperplasia/dysplasia (progression); and HCC. Specific genetic and epigenetic changes, including the differential expression of genes, have been identified for some of these stages. It is hoped that these molecular studies will be informative in dissecting the multifactorial etiology of HCC, and in setting priorities for the implementation of prevention and treatment.

Molecular Analysis of Hepadnavirus Infection and HCC

The life cycle of HBV and the genomes of HBV and HCV

The life cycle of HBV can be summarized as shown in Fig. 2, and the image of HBV is shown in Fig. 3. The virus enters the hepatocyte via attachment of the cell membrane, and the uncoated DNA either enters the nucleus to form covalently closed circular DNA (cccDNA) as episomes or integrates into the cellular genome. Several RNA transcripts are synthesized, including short hepatitis B surface (SHBs), middle HBs (MHBs), long HBs (LHBs), and HB core (HBc)/polymerase (Pol). Viral proteins are then synthesized in the ribosomes, and the viral particle is reassembled in the endoplasmic reticulum (ER) and ejected by exocytosis.

Hepadnaviruses (including HBV and HCV) are known to be associated with the development of liver neoplasia, accounting for more than 80% of human HCCs worldwide; however, the molecular mechanism

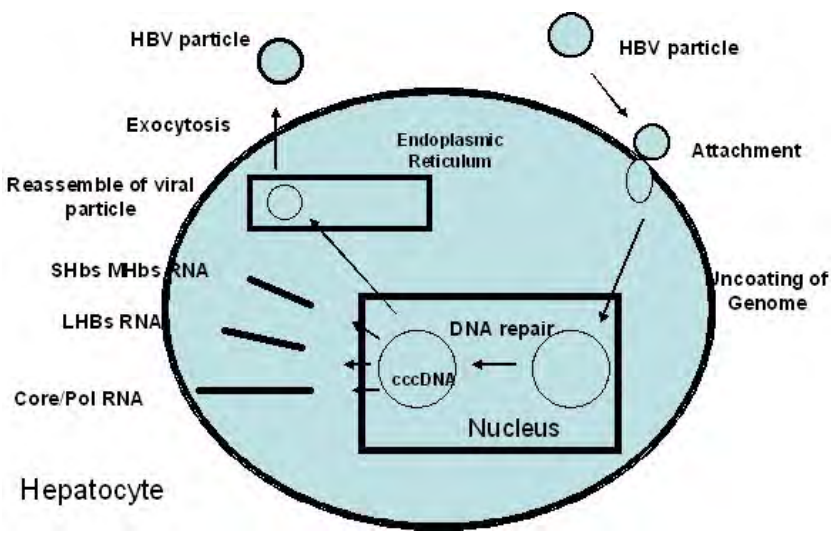

Fig. 2. Life cycle of hepatitis B virus in hepatocytes. The schematic diagram of the life cycle of HBV is presented, showing the attachment of the virus to the hepatocyte, the formation of cccDNA in the nucleus, the reformation of the viral particle in the endoplasmic reticulum (ER), and the exit of the virus via exocytosis.

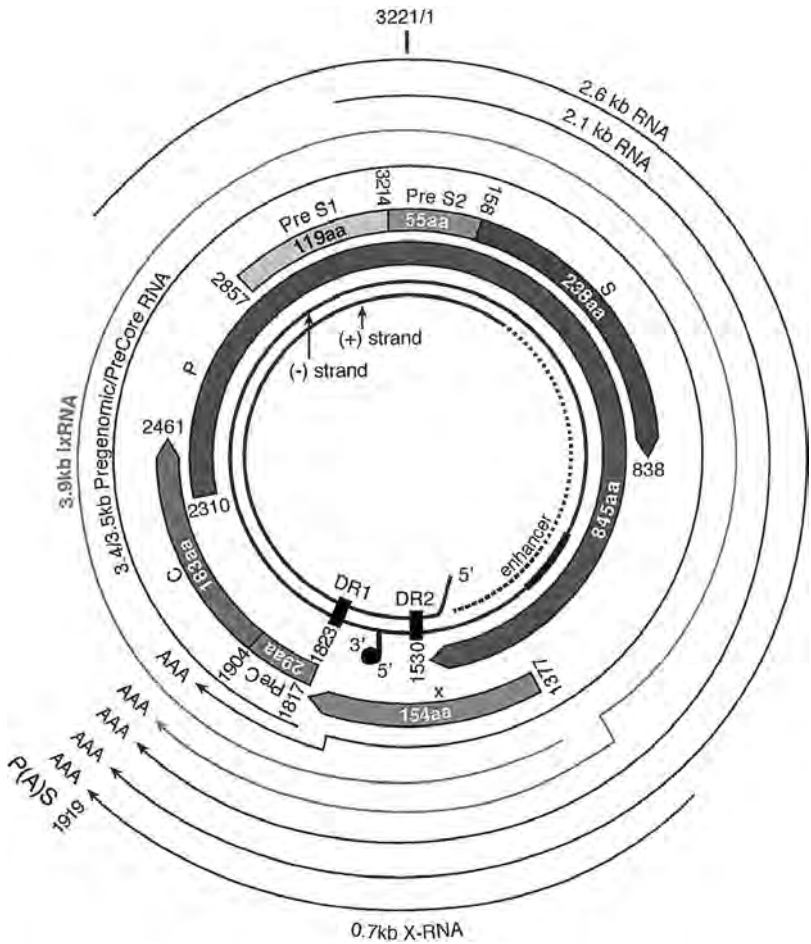

Fig. 3. Genetic map of the HBV DNA. The broad arrows represent the four open reading frames (ORFs) encoding the envelope (preS1, preS2, and S), capsid (preC and C), polymerase (P), and X proteins. The thin arrows indicate mRNA of the HBV. The direct repeats (DR1 and DR2) and the regulatory elements (enhancer I and II) are involved in replication and transcription.

is still quite unclear (for a review, please see Refs. 2, 3, 10, and 11). The HBV genome is relatively small, consisting of a 3.2-kb circular DNA with a single-stranded region of variable length in different molecules (Fig. 3). It contains four open reading frames (ORFs) in the complete

strand of DNA[10]: (1) the envelope protein, which encodes the hepatitis B surface antigen (HBsAg); (2) the core protein, which encodes the nucleocapsid core protein including the hepatitis B core antigen (HBcAg) and the e antigen (HBeAg), a truncated form of the major core protein; (3) the polymerase (P) protein, which encodes the reverse transcriptase, DNA polymerase, and RNAase H activities; and (4) the HBx protein, which is a small polypeptide with the capability to transactivate cellular genes. Two direct repeat sequences of 11 bp in length, namely DR1 and DR2, which are involved in viral DNA replication, are localized at the terminal ends on the DNA strands. In addition, the viral DNA contains four promoter elements for transcription, two enhancer elements designated enhancer 1 and 2, and a polyadenylation signal used by all major transcripts within the preC region.

The genome of HCV was identified in 1989 and shown to comprise a positive-stranded RNA molecule of approximately 9500 nucleotides (Fig. 4).[3] Sequence comparisons indicate that HCV is distantly related to both the animal pestiviruses and the human flaviviruses. The genome of HCV contains a single ORF, which encodes a large polyprotein precursor of just over 3000 amino acids. The proteins encoded by HCV include the structural protein gene RNA-binding nucleocapsid C and the envelope glycoprotein genes *E1* and *E2*, followed by six genes that encode the presumed nonstructural proteins: *NS2*, a Zn metalloproteinase; *NS3*, a serine protease/helicase; *NS4A* and *NS4B*, with

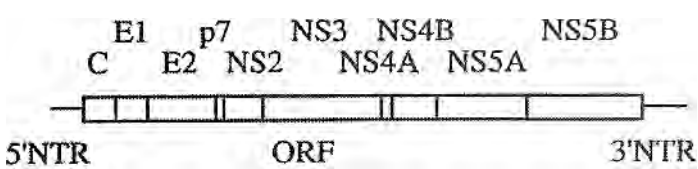

Fig. 4. Genetic map of the HCV genome. The RNA genome of HCV contains a single ORF, which encodes a large polyprotein precursor. The proteins encoded by HCV include the structural protein gene RNA-binding nucleocapsid C and the envelope glycoprotein genes *E1* and *E2*, followed by six genes that encode the presumed nonstructural proteins: *NS2*, a Zn metalloproteinase; *NS3*, a serine protease/helicase; *NS4A* and *NS4B*, with unknown function; *NS5A*, with possibly replicase function; and *NS5B*, which has RNA-dependent RNA polymerase homology.

unknown function; *NS5A*, with possibly replicase function; and *NS5B*, with RNA-dependent RNA polymerase homology. HCV has been found to be associated with non-A, non-B hepatitis; and has been suggested to be the main cause of cryptogenic chronic hepatitis, cirrhosis, and HCC. Although chronic HCV infection is considered a global disease and the number of carriers is estimated to be about 300 million, the number of HCV-associated HCCs is still much less than those associated with HBV.

Insertional mutagenesis and cis-activation of cellular genes by HBV DNA

HBV DNA has been found in approximately 85% of HCCs, and mostly occurs as the integrated form of viral DNA. It is believed that the integrated HBV DNA may play a role in the pathogenesis of HCC; however, the complete viral sequence is usually not found in the integrated DNA and the infected tissues do not contain the replicative form of viral DNA. In the woodchuck model of HCC, HBV DNA is preferentially integrated in the c-*myc* or N-*myc* regulatory or coding sequences; while in humans, specific HBV insertion in cellular genes has been found only in single cases in genes such as *erb-A*, cyclin A, and retinoic acid receptor.[5,9,10] The viral DNA appears to contain preferred sites for integration, since more than 50% of the junctions are at or near the cohesive 5′ ends of the direct repeat (DR) sequences. The sites of integration in the host DNA are random, but a certain degree of preference has been found. The integration appears to occur mostly at repeated sequences such as Alu DNA, satellite III DNA, α-satellite DNA, minisatellite DNA, or variable number tandem repeat (VNTR) DNA. Most of the integrations are of multiple clonal type, each at a different cellular site.

At the site of integration, alterations in the host chromosomal DNA have also been found. These alterations include the following: (1) microdeletion (approximately 10 bp), which is apparently a part of the illegitimate recombination process; (2) large deletion, which occurs in some HCCs and appears to be formed by a mechanism other than illegitimate recombination; (3) translocations, which involve host DNA from two different chromosomes joined to the viral sequence;

(4) inverted repeats of viral and cellular DNA, which are identical or common sequences brought together during the recombination process; (5) amplification of cellular DNA; and (6) other alterations including allelic deletion and point mutation in host DNA. Although these genetic changes in the HCC DNA indicate that the viral genome can act as factors for insertional mutagenesis, there has been no consensus on specific cellular genes being disrupted by the virus insertion.

Trans-activation of cellular genes by HBV DNA

HBV still appears to be a prime candidate for the initiation event in the multifactorial–multistep model of hepatocarcinogenesis. Since HBV does not contain a direct oncogene and the virus apparently integrates randomly into the human genome, a common *cis*-acting effect on activating cellular genes appears to be unlikely. There is therefore great interest in identifying the role of the virus in the development of HCC. Whether the proliferative stimuli created by chronic inflammation of the liver by HBV might be sufficient for HCC induction is still debatable.

Earlier publications indicated that HBV genes may act in *trans*-effect in activating critical cellular genes. The first is the HBx gene, which encodes the HBx protein. The HBx protein has been found to interact with the tumor suppressor p53 and with the repair protein Excision Repair Cross Complementation Group 3 (ERCC3).[11] Interaction between HBx and the cellular protein XAP-1 — the human homolog of the monkey UV-damaged DNA-binding protein (UV-DDB), which is defective in some xeroderma pigmentosum group E patients — was also reported earlier. This suggests that the important DNA repair process may be affected by HBV, and that the resulting genetic instability may contribute to HCC development. In addition, HBx can abrogate p53-induced apoptosis, whereas the wild-type p53 can inhibit the function of the promoter of the HBV core gene (*HBc*). It is likely that the HBx gene may play some role in viral–cell interactions, but the oncogenicity of the *HBx* gene is still unclear. Although one report indicated that *HBx* has an oncogenic potential in transgenic mice, opposite findings have been reported by others. The *HBx* gene had no effect on the malignant

transformation of normal cells, and only partially transformed cells such as NIH-3T3 or affected cells immortalized by SV40 T-antigen. As not all HBV-associated HCCs contain the activated *HBx* gene, the role of *HBx* in hepatocarcinogenesis remains unclear.

The second HBV *trans*-activator is the truncated middle surface (*preS2/S*) gene. The 3′ truncations of the middle HBV surface gene ($MHBs^t$) were found in some HCC DNA and in cotransfection experiments. This truncated gene was demonstrated to have *trans*-activation function. The truncated region is defined as the "*trans*-activator on" (TAO) domain, and the aberrant protein was found to be localized to the endoplasmic reticulum of the cells. The truncated *preS2/S* gene can utilize transcriptional factors such as NF-κB and AP1 for *trans*-activation. The target genes for the *trans*-activation were found to include the proto-oncogenes c-*myc* and c-*fos* as well as the inflammation-associated cytokine *IL-6*. The activation of these proto-oncogenes or critical cellular genes may be the basis of cellular transformation and oncogenesis in HCC.

In a majority of HBV-associated HCCs from Asia and elsewhere, novel mutations at or around the TAO region of the *preS2/S* gene were found by us and others.[12] A large number of HCCs displayed mutations at codons 124–147 of the surface antigen *S* gene, defined as the "A loop", which is known to cause immunoescape for the virus against the host defense mechanism. The frequent occurrence of mutations around the *trans*-activator domain of the *preS2/S* gene in the HCCs of this endemic region indicates that these molecular defects may be causally related to the development of HCC from HBV carriers. A high proportion of HBV from chronic active hepatitis and HCC contained aberrant sequences for the *preS1* and *preC/C* regions of the HBV. Increased frequency of *preC/C* mutations was also found in tissues of acute hepatitis, tissues of chronic hepatitis, and nontumorous-to-tumor tissues of HCC patients.[13] Since both *preS1* and *preC/C* regions of the HBV are associated with the immunodeterminants, these mutations may play important roles in the immunoescape for the virus against the host defense mechanisms. Mutations at the promoter region of *preC/C* and at the C-terminal domain of the HBx protein were also found in the reactivated HBV from patients undergoing cytotoxic chemotherapy.[14]

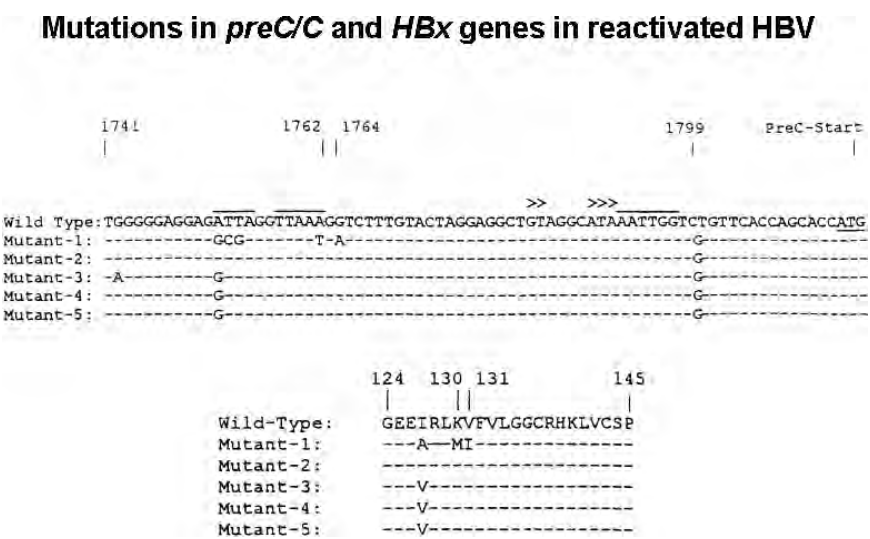

Fig. 5. Mutations in the reactivated HBV DNA. Five patients with solid tumors receiving cytotoxic chemotherapy developed severe liver disease as a result of reactivation of the HBV. DNA sequencing indicated that mutations were developed in the promoter region of the *preC/C* gene and amino acid substitutions in the carboxy-terminal part of the X protein.

These data indicate that these mutations may contribute to the rapid selection and enhanced replicative ability of the viruses, and could serve as biomarkers of viral reactivation (Fig. 5).

Interactions Between Chemical Carcinogens, HBV, and Cellular Genes

Another major risk factor for HCC is the hepatocarcinogen aflatoxin. Aflatoxins are mycotoxins generated by the fungi *Aspergillus flavus* and related strains.[15] The carcinogens are generated because of the improper storage of crops (e.g. peanuts, corn, rice), which occurs most frequently in underdeveloped nations. Under hot and humid conditions, mold grows favorably. To assess the extent of exposure to aflatoxin, antibodies against aflatoxin B_1 (AFB_1), the most potent moiety of the compounds, have been generated. The measurements of minute amounts of DNA

adducts in body fluids and tissues were made possible by innovative techniques such as the ^{32}P-postlabeling technique and the immunodetection of protein and DNA adducts. For individuals at risk for both HBV infection and exposure to aflatoxin, such as those living in the Qidong Province of China and in sub-Saharan Africa, the relative risk was found to be significantly higher.[4,5]

In reviewing the mutation spectrum of the *p53* gene in HCC from endemic regions for the fungus, a high frequency of mutations was found in codon 249 (50% or 8 out of 16, of which 7 were G-to-T and 1 was a G-to-C transversion) that are apparently specific for AFB–DNA interactions. However, the gene was found to be less involved in the non–AFB_1-associated cases (20%–25%). A variety of mutations were found in different sites of the *p53* gene in these non–AFB_1-associated HCCs. It was also reported that the *p53* mutation is rare in HBV-associated HCCs. The HBV-encoded x antigen (HBxAg) has recently been suggested to be bound to the wildtype *p53* and inactivating it. The low frequency of the *p53* mutation in these cases implies that *p53* inactivation may occur predominantly by complex formation with HBxAg.[11]

In HBV transgenic mice, treatment with several chemical carcinogens (including AFB_1) resulted in an earlier appearance and higher incidence of HCC, suggesting an interaction between HBV and chemical hepatocarcinogens. Two isoforms of the cytochrome p450 (2a and 3a), which are involved in the activation of AFB_1, were progressively induced in hepatocytes of HBV transgenic mice. Similarly, p450-2A6 and p450-3A4, both of which are involved in AFB_1 activation in humans, are also induced in cirrhotic liver and HBV hepatitis. This is consistent with the notion that HBV-infected cells are more susceptible to AFB_1 by increasing the enzymes for activating carcinogens.

It is also known that the expressions of genes for drug metabolism, including the phase I and II enzymes, are altered during hepatocarcinogenesis. Enhanced expression of multiple drug resistance (*mdr*) genes was previously reported in human and rodent HCCs. Glutathione-*S*-transferase π (GSTπ), γ-glutamyl transferase (γGT), and ornithine decarboxylase (ODC) are known to be induced during hepatocarcinogenesis and in HCC. Abnormal cytoplasmic localization of the O^6-alkylguanine DNA transferase in HBV-induced cirrhotic liver has been reported. The increased expression of these drug-metabolizing

proteins is apparently a programmed cascade of events during HCC development, but they may also play a role in the natural selection of malignant clones and account for the intrinsic drug resistance of HCC.[5]

"Yin–Yang" (Negative and Positive) Regulation of Hepatocarcinogenesis: Alterations of Proto-oncogenes, Tumor Suppressors, and Other Critical Genes in HCC

The development of HCC, similar to other cancers, can be summarized by the "yin–yang" (negative and positive) regulation of tumorigenesis, as shown in Fig. 6. The "yins" are the negative regulators of

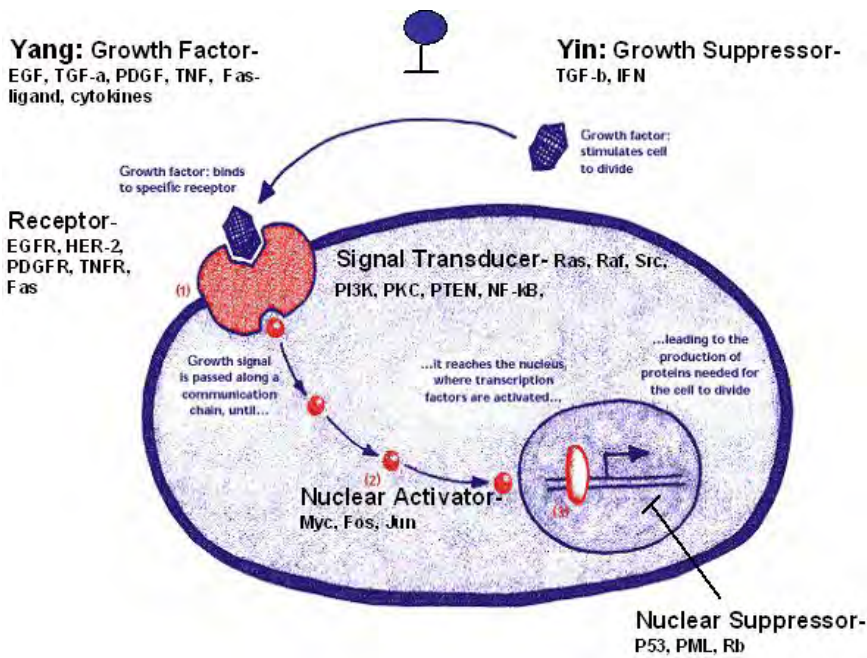

Fig. 6. "Yin–yang" hypothesis of negative and positive regulation of cancer development. The development of cancer can be attributed to imbalances in the negative and positive regulation of cell growth and differentiation. The "yins" are the negative regulators of cellular proliferation and differentiation, including tumor and cell cycle suppressors; while the "yangs" are the positive regulators, such as proto-oncogenes, growth factors, receptors, and signal transducers.

cellular proliferation and differentiation, including tumor and cell cycle suppressors; while the "yangs" are the positive regulators, such as proto-oncogenes, growth factors, receptors, and signal transducers. In this context, the third etiological factor for HCC is cirrhosis and chronic inflammation of the liver.[5,6] There is an associated liver cirrhosis in 70%–90% of Oriental HCC patients. The overall rate of HCC developing in patients with hepatic cirrhosis is about 2%–5% annually. Other risk factors for HCC, such as HBV and HCV infection as well as alcohol consumption, all cause liver cirrhosis; however, the role of cirrhosis is believed to be at the promotion or progression phase of the carcinogenic process. One notion for the involvement of cirrhosis in HCC development is that cell damage and programmed cell death in cirrhotic liver induce signals for liver regeneration.[15,16] The proliferative stimuli can then act as a promoter for carcinogenesis in preinitiated hepatocytes. The subsequent rounds of replication act to fix the DNA lesions as mutations.

Chronic inflammation of the liver may induce the expression of many growth factors, cytokines, stress proteins, and hormones that directly or indirectly promote the clonal expansion of preneoplastic cells.[5] The growth factors for hepatocytes that have been previously documented are (1) direct mitogens, such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor α (TGFα), acidic fibroblast growth factor, (aFGF) and hepatocyte stimulatory substance (HSS); (2) indirect mitogens or comitogens, including insulin, glucagon, norepinephrine, vasopressin, angiotensin II, and vasoactive intestinal peptide (VIP); and (3) inhibitors such as transforming growth factor β (TGFβ), interleukin 1, interleukin 6, and leukemia inhibitory factor (LIF).

Enhanced expression of growth-related proto-oncogenes — including c-*fos*, c-*jun*, c-*myc*, c-H-*ras*, c-*met*, and *MAGE-1* — have been reported. Increased mRNA and proteins for growth factors, receptors, and molecules for the signal transduction pathways such as TGFα, insulin-like growth factor II (IGF-II), and EGF receptor (*erb-B*) have been reported earlier in human and experimental rodent HCCs.[8,9] The increased expressions of many of these growth-related genes are apparently not specific for HCC, since many of these changes have been observed in cirrhotic and regenerating livers. However, studies on

amplification and overexpression of the cyclin D1 gene, which is located at 11q13, demonstrated that such alterations occurred in the HCC in patients at advanced stage (11% to 13%). The authors suggested that these changes may be associated with the aggressive behavior of tumors. It is believed that amplification and overexpression of the cyclin D1 gene result in the deregulation of the cell cycle. Amplification of the c-*myc* gene was also detected in 50% of HCCs by differential polymerase chain reaction (PCR). These findings correlated with overexpression of the c-*myc* gene found in many HCCs.

Transgenic mice harboring the c-*myc* and *TGFα* transgenes were found to develop HCC, indicating that c-*myc* and *TGFα* play a role in HCC development. Similarly, altered or decreased expression of tumor suppressor genes such as *Rb* and *p53* have been documented.[15,16] Whether these alterations reflect the increases in cellular proliferation or the appearance of the transformed or malignant phenotypes of those neoplasias is still unknown. Nevertheless, these alterations are part of the programmed cascades of growth signals leading to the development of HCC, and can be used as biomarkers for HCC. Other alterations include the membrane proteins such as annexin I and adhesion molecules, which may play a role in the loss of contact inhibition and disrupted intercellular communications. It was reported earlier that the PML-RARα protein induces hepatic neoplastic lesions in transgenic mice,[16] indicating that this fusion gene deregulates hepatocyte proliferation and is involved in hepatocarcinogenesis *in vivo*. It is interesting to note that mutation of the *ras* genes are frequently found in many cancer types. The *ras* family genes (Ha-, Ki-, and N-*ras*) are activated by point mutation at codons 12, 13, and 61. Although these mutations have been reported in considerable numbers of HCC from rodents, they are infrequent in human HCC (0% to 20%)[15,16] and their role remains obscure.

Other critical genes with altered expression in HCC and liver diseases as reported by us include *Cox-2*, *PML*, and nucleophosmin (*B23*).[17–19] *Cox-2* catalyzes the conversion of arachidonic acid derived from membrane phospholipids to prostaglandins as part of the signaling of the apoptosis-inflammation-proliferation pathway.[20] It was found that *Cox-2* expression correlates with that of *HBx* in liver and HCC tissues, and that the transfection of the *HBx* gene upregulates *Cox-2* expression

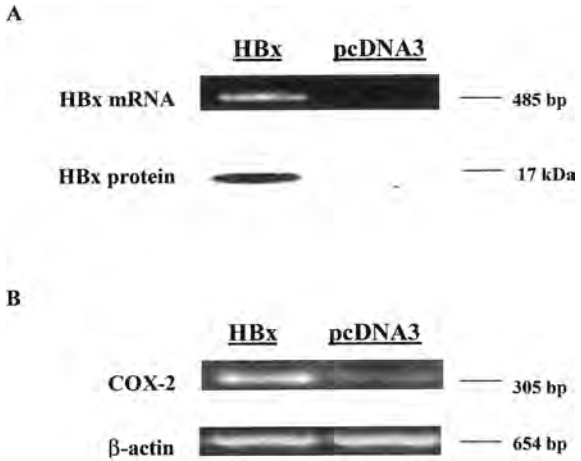

Fig. 7. Activation of the inflammation-and-growth–associated gene *Cox-2* by the HBV *trans*-activator *HBx*. The *HBx* gene was transfected into Hep3B HCC cells. (A) At 48 hours posttransfection, *HBx* mRNA and protein were expressed as shown by using reverse transcription–polymerase chain reaction (RT-PCR) and Western blot analyses, respectively. (B) *Cox-2* mRNA was upregulated in *HBx*-transfected cells when compared with sham-transfected cells. β-actin was also amplified to assess the equality of RNA amount in both samples. With permission from Ref. 17.

in HCC cells (Fig. 7).[17] On the other hand, the tumor suppressor *PML* and nucleophosmin play essential roles in many nuclear processes including signal transduction.

Genomic Instability and Chromosomal Alterations in HCC

Cancer is believed to arise from cells that have undergone genetic alterations and clonal expansion. These genetic alterations include activation of proto-oncogenes, inactivation of tumor suppressor genes, and reactivation of telomerase activity. As the altered hyperplastic foci of hepatocytes progresses to the intermediate stage, namely that of adenomatous dysplasia (dysplastic/hyperplastic nodules), and then into HCC, additional genetic changes expressed as chromosomal aberrations are observed. The identification of specific genetic changes that drive the neoplastic process has led to a better understanding of the process of

cancer progression, and has provided useful markers for early detection and prognosis — these changes will be discussed in the following sections. The accumulation of somatic genetic changes in HCC cells has been investigated using a number of techniques, including cytogenetic, molecular genetic, and, recently, molecular cytogenetic methods.[21]

Allelotyping

A widely used strategy to search for allelic alterations in the genome is through loss of heterozygosity (LOH) analysis at polymorphic markers mapped to specific chromosomal regions. By PCR-based microsatellite polymorphism analysis, specifically deleted regions containing tumor suppressor genes involved in the tumorigenesis of HCC can be identified.

Allelotypes of HCC have been completed by several groups. A comprehensive study by Boige *et al.*[22] examined 275 microsatellite loci across the entire genome in 48 HCCs. The frequently deleted chromosome regions were 8p (60%), 17p (48%), 1p (44%), 4q (42%), 16p (40%), 16q (39%), 6q (35%), 9p (30%), and 13q (29%). Nagai *et al.*[23] studied allelic loss in 120 HCCs and found significantly elevated LOH in loci on 1p, 4q, 6q, 8p, 13q, and 16p. In contrast, allelotype studies by our group in 45 HBV-associated HCCs from Chinese patients in Hong Kong showed a different pattern of deletion[24]: the highest frequency of LOH was found in chromosome 16q (80%); while other regions frequently affected by deletion included 17p (71%), 13q (67%), 8p (60%), 4q (60%), 16p (60%), 9p (56%), and 1p and 1q (50% each).[24] The reason for the difference in the patterns of LOH is not known, but it may be related to the different etiological factors involved in specific populations from different geographic regions.

Comparative genomic hybridization analysis

The classical methods of cytogenetic analysis are generally not applicable in HCC, since most solid tumors including HCC produce very limited numbers of mitotic figures. Only a few karyotypings have been reported

and no consistent abnormalities have been found. However, with the newly developed comparative genomic hybridization (CGH) analysis, which hybridizes differentially labeled DNA from tumor and normal tissues to mitotic figures of normal cells, nonrandom genomic changes have been demonstrated.[25]

In 50 primary HBV-related HCCs, chromosome losses were frequently found in the regions of 4q (70%), 8p (65%), 16q (54%), 17p (51%), and 13q and 6q (37% each). Deletions observed in these regions agree well with the findings of allelotyping and LOH studies described earlier, and indicated that inactivation of the tumor suppressors on these regions may contribute to HCC tumorigenesis. On the other hand, frequent gains were found to occur in the chromosome regions of 8q (60%), 1q (58%), 6p (33%), and 17q (33%). This study has also revealed several amplified regions including 11q12, 12p11, 14q12, and 19q13.1 in some of the cases, suggesting that there could be oncogene(s) residing on these chromosome regions. A recent CGH study in Hong Kong indicated that DNA losses were frequently seen in chromosomes 4, 10q, 11q, 14q, 17p, 18q, and X; while consistent chromosomal gains were found in 1q21–22, 6p, 8q, 17q, and 20.[26]

Chromosome 16q and E-cadherin

In CGH and allelotyping studies, frequent deletions of several chromosomal regions including chromosomes 16q, 17p, 8p, 13q, 4q, and 1p were observed. Despite the large number of potential tumor suppressor gene (TSG) loci that have been identified, only a few specific genes have been conclusively implicated in the development of HCC. Loss of chromosome 16q appears to be one of the most common genetic defects in HCC. A high frequency of 16q deletion has been documented in both LOH and CGH studies. LOH of 16q has been found in up to 80% of HCCs from Hong Kong patients.[24]

A commonly deleted region — 16q22–23 — has been reported, suggesting the presence of a tumor suppressor gene in this region. One of the candidate targets is the E-cadherin gene, which is located on 16q22.1. Although no mutations or gross structural alterations of this gene have been reported in HCC, loss of E-cadherin expression has

been observed. Recently, *de novo* methylation of the 5′ CpG island of the E-cadherin gene has been found in 46% of liver tissues, showing chronic hepatitis or cirrhosis and in 67% of HCCs analyzed.[27] It was also demonstrated that such epigenetic change correlated significantly with reduced E-cadherin expression. The silencing of the E-cadherin gene may lead to the loss of intercellular adhesiveness, which in turn may contribute to unrestrained cell growth. It is suspected that the inactivation of this gene by deletion or hypermethylation of the promoter region may play an important role in the development of HCC.

Chromosome 17p and p53

Deletion at 17p and alterations of the *p53* gene at 17p13 are common genetic changes reported in human cancers. The tumor suppressor gene *p53* encodes a 53-kD nuclear phosphoprotein that acts as a transcription factor. The major functions of the gene are blockage of cell cycle progression in response to DNA damage, and mediation of DNA repair or apoptosis.

In HCC, a high percentage (48%–71%) of LOH at 17p was identified.[22] This finding strongly suggests that the *p53* gene is the target gene involved during the development of HCC. As mentioned previously, it was hypothesized that *p53* mutations were common in the HCCs associated with aflatoxin B_1 exposure (about 50%) and a consistent mutation at codon 249 was observed in these tumors. On the other hand, the reported discrepancy between the consistently high frequencies of LOH at 17p and low frequencies of *p53* deletion in some of the HCCs indicated that there may be other deleted tumor suppressor gene(s) on 17p in HCC.

Chromosome 13q and Rb and BRCA2

Chromosome 13q is often (37%–67%) found to be deleted in HCC by both LOH and CGH analyses.[22,25] Detailed deletion mappings have identified two distinct common deletion regions that appear to contain the tumor suppressor genes *Rb* (13q14) and *BRCA2* (13q12).

These genes have been suggested to be the candidate targets for HCC tumorigenesis. The status of the *Rb* gene in HCC has been previously investigated, and alterations of the gene seem to be rare in this cancer. For *BRCA2*, mutations were found in 3 out of 60 HCCs examined. It is possible that other genes on this region may contribute to the development of this cancer, or that the *Rb* and *BRCA2* genes are inactivated by epigenetic changes such as aberrant methylation.

Chromosome 8p and the platelet-derived growth factor (PDGF) receptor β–like tumor suppressor

From both LOH and CGH analyses,[22,25] chromosome 8p loss is also one the most common abnormalities (60% to 65%). It was also found that LOH at 8p was present in up to 85% of HBV-positive HCCs from China. The loci with the highest frequency of LOH have been observed in 8p21 and 8p23. An 8-cM commonly deleted region at 8p21.3–p22 on deletion mapping of 142 HCCs was documented. This region contains a putative tumor suppressor gene, PDGF receptor β–like tumor suppressor, which has been shown to be mutated in two HCCs. However, the involvement of this gene in HCC needs further examination and no other candidate tumor suppressor genes have been reported in this region.

Chromosome 9p and p16

Although reports of chromosome 9 loss are uncommon in HCC, recent data demonstrated that LOH at 9p21 occurs frequently (54%–63%) in HCC.[28] A homozygous deletion region at 9p21 has also been identified in some of our cases from Hong Kong[29]; this region includes the tumor suppressor genes *p16* and *p15*. Hypermethylation of *p16* was found in many of the HCCs without 9p deletions, indicating that the inactivation of *p16* is a frequent event. Both *p16* and *p*15 genes encode the negative regulator proteins for cell cycle progression. These proteins bind to cyclin-dependent protein kinases, CDK4 and CDK6, and prevent the CDKs from forming an active complex with the cyclin D protein. Inhibition of the catalytic activity of the CDK/cyclin D complex prevents

phosphorylation of the Rb protein, and subsequently inhibits the cell cycle progression from G_1 to S phase.

The alteration of the *p16* gene has been examined by several groups,[28] and it was noted that mutations and homozygous deletion of the *p16* gene were infrequent in HCC. However, it was demonstrated that *de novo* methylation of the 5′ CpG island of the *p16* gene was found in 48% of HCCs examined. These findings indicate that alterations of the *p16* gene may be involved in the genesis of HCC, although it is not directly related to the LOH observed in 9p. On the other hand, the relationship of the *p15* gene in HCC is still not known.

Other chromosomal alterations

Several other losses of chromosomal regions that are not associated with known tumor suppressor genes have been found in HCC. For example, chromosome 4q has been reported to undergo LOH in 50%–77% of HCCs, while this region is less involved in other cancers. The commonly deleted region was localized at 4q12–4q23.[21] Deletion of chromosome 1p was found to occur frequently in early and well-differentiated HCCs[21,22]; and this abnormality is clustered at the distal part of chromosome 1p, with a common deleted region at either 1p35–36 or 1p34–36. Amplification of chromosome 8q has been found in 44% of HCCs examined by Southern blotting of the polymorphic markers on this region, a finding later confirmed by CGH analysis.[25] The earlier study defined the amplification region to be distal to 8q24, where the proto-oncogene c-*myc* resides.

Reactivation of telomerase activity in HCC

Progressive shortening of telomeres with age is known to occur in normal somatic cells in culture and *in vivo*. Thus, the maintenance of telomere length and the expression of enzyme activity are assumed to be obligatory steps in the progression of tumor cells (Fig. 5). Reactivation of telomerase activity and shortening of the length of the terminal restriction fragment (TRF) have been reported in a majority of human and

rodent HCCs.[30,31] One study of Chinese patients from Hong Kong showed that over 80% of HCCs analyzed contained telomerase activity; however, there was no significant correlation between telomerase activity and clinical-pathological features of HCC.[32] Nevertheless, it was suggested that telomerase may be a useful diagnostic marker of HCC, regardless of tumor size.

Reactive Oxygen Species and HCC

Many inducers of HCC — such as hepatitis viral infections, carcinogens, toxins, steroid hormones, and dietary interventions — have different cellular targets and modes of cytotoxic effects. However, one common denominator of these agents is the formation of reactive oxygen species (ROSs) (Fig. 8). Signals related to ROSs play important roles in the development of liver cancer (for a review, see Ref. 33).

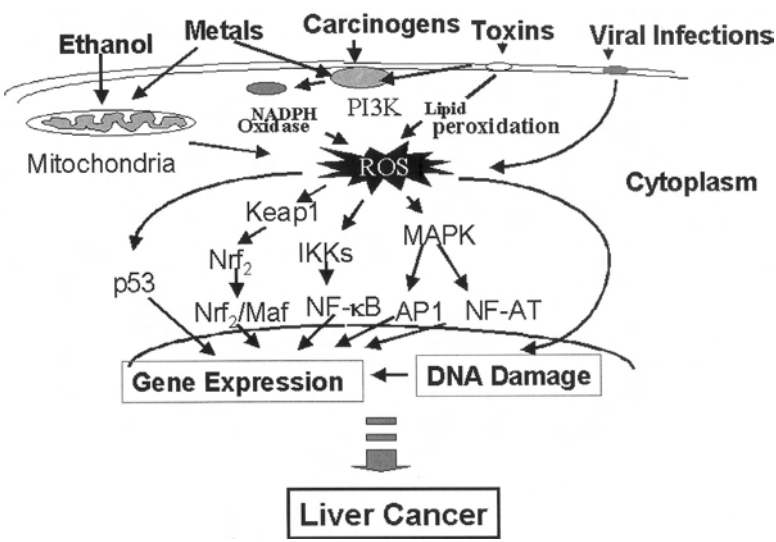

Fig. 8. Induction of HCC by oxidative stress. Reactive oxygen species (ROSs) play a critical role in the induction and signaling of HCC development by both exogenous and endogenous agents.[33]

Chronic viral infections and ROSs

Because chronic HBV and HCV infections are the major risk factors for liver cancers, transgenic mice carrying liver-targeted expression of HBV and HCV genes have been developed. Studies have shown that chronic HBV and HCV infections are associated with an increased production of ROSs because of the action of HBx protein[34] and core protein NS5A[35] encoded by these viruses, respectively. Elevated 8-oxo-2′-deoxyguanosine (oxo-dG) contents were found in the microscopic nodules and HCCs of transgenic animals carrying the HBV surface antigen gene, an indicator of ROS-induced oxidative stress in these lesions. In the HCV transgenic mouse model, expression of the entire core protein resulted in late onset of HCC.[36] The association between oxidative stress attack and hepatocarcinogenesis is evidenced by the elevation of lipid peroxidation in these animals.

Carcinogens and ROSs

AFB_1 is a well-known hepatoxin and hepatocarcinogen that contaminates cereal grains. AFB_1 is activated mainly by CYP450 enzymes to form the reactive intermediate AFB_1-8,9-epoxide. The intermediate then reacts with cellular macromolecules, mainly DNA, and forms N^7–guanyl adducts, which are considered critical in the carcinogenicity of AFB_1. Elevated ROSs were directly detected in cultured hepatocytes exposed to AFB_1, and ROS-induced DNA damage was found in these cells.

Another hepatocarcinogen, 2-acetylaminofluorene (2-AAF), and its metabolites, 2-nitrosofluorene and *N*-hydroxy-2-aminofluorene, are known to induce oxidative stress through mitochrondrial redox cycling. It was also demonstrated that 2-AAF induces ROS production by activating NADPH oxidase through the PI3 kinase (PI3K) pathway.[37] PI3K and its downstream AKT pathway have been implicated in carcinogenesis in association with upregulation or downregulation of many oncogenes and tumor suppressor genes.[38]

Xenobiotics and ROSs

Peroxisomes are cytoplasmic organelles that contain an array of more than 60 proteins, mainly oxidases. Proliferation of peroxisomes can be stimulated by a variety of therapeutic agents, industrial chemicals, and environmental pollutants. Activation of peroxisome proliferator–activated receptors (PPARs) is associated with elevated expression of peroxisomal enzymes, accounting for as much as 20% of oxygen consumption and the formation of substantial amounts of H_2O_2.

A receptor-based activation mechanism mediated by PPARα, PPARβ/δ, and PPARγ is involved in such a diverse group of compounds to PPARs. These receptors play a major role in hepatic response to xenobiotic PPARs and endogenous ligands involved in fatty acid metabolism. Persistent PPAR-mediated peroxisome proliferation induces hepatocarcinogenesis.[39] Knockout mice with deletion of acyl-CoA oxidase (AOX), which is the first enzyme involved in peroxisomal oxidation in the metabolism of very-long-chain fatty acids, develop HCC because of sustained activation of PPARα with increased production of ROSs.[40]

Growth factors, oncogenes, and ROSs

Previous studies have demonstrated that cultured cells treated with epidermal growth factor (EGF) or platelet-derived growth factor (PDGF) have increased intracellular ROS levels, predominantly H_2O_2. The production of H_2O_2 depends on the tyrosine kinase activities of the receptors that activate the NADPH oxidase system through PI3K and the small G protein Rac. ROS production is also associated with the effects of many other growth factors, including angiotensin, insulin, tumor necrosis factor α, transforming growth factor α, and peptide hormone endothelium 1. Activation of oncogene c-*myc* expression is also associated with ROS elevation.

Double-transgenic mice bearing liver-targeted expression of transforming growth factor and c-*myc* developed HCC between 4 and 8 months of age.[41] Elevated levels of ROSs were detected after 2 to 3 months, as indicated by elevated lipid peroxidation, mitochondrial

damage, and reduced levels of antioxidant glutathione (GSH). Dietary supplementation started at weaning age and the free radical scavenger antioxidant vitamin E decreased ROS generation, resulting in 65% decrease in tumor incidence and prevention of malignant conversion. In this system, vitamin E downregulated NADPH oxidase–generated ROSs.[42]

Enzymes for metabolizing ROSs

Superoxide dismutase (SOD) knockout *Sod1*$^{-/-}$ mice had a reduced lifespan and increased incidence of neoplastic changes in the liver.[43] Metal overload Wilson ATPase (ATP7B) knockout mice also developed late-onset HCC.[44] Knockout rodents with an oxidative stress-responsive gene, *Nrf1*, developed spontaneous hepatic cancer with steatosis, necrosis, and inflammation.[45] Similarly, mice with deletion of IKKb — a kinase in activating the transcriptional factor NF-κB — exhibited increased susceptibility to hepatocarcinogenesis, with increased oxidative stress and elevated ROS production.[46] On the other hand, chronic alcohol consumption results in reduced ATP production and redox shift, and enhances the activity of ROS-producing enzymes and ROS production. It also enhances the hepatocarcinogenic process induced by viral, chemical, and hormonal agents.

Human HCC and ROSs

Increased levels of ROSs were found in the liver of patients with chronic hepatitis and HCC.[47] Reduced levels of SOD were found with the progression of HCC, while ROS-induced DNA damage was found in many adjacent liver lesions of HCC.[48] ROSs are highly reactive and induce direct damage to many important cellular constituents including DNA, lipids, and proteins. ROS-induced lipid peroxidations were found in many HCCs.[49] Low concentrations of ROSs regulate many genes whose expression affects cell cycle regulation, cell proliferation, and apoptosis. It is this persistent oxidative stress that ultimately leads to neoplasm formation and uncontrollable growth. Inactivation of NF-κB prevents the development of liver cancer in *mdr2* knockout

mice, while NF-κB activities were increased in 87% of the peritumoral and tumoral parts of HCC.[50] Other redox-regulating transcription factors for cell growth and angiogenesis, such as AP1, FOS, JUN, STAT, SPI, AP2, ATF4, PI3K, β-catenin/Wnt, and PTEN, are signal cascades that are activated by oxidative stress relevant to human cancers including HCC.[51]

Gene Profiling, Microarray, and Proteomics in HCC

Regarding gene profiling, recent studies of cDNA microarrays indicate that heterogeneous carcinogenetic pathways exist in HCC, similar to other cancers (Figs. 9 and 10) (for a review, please see Refs. 52–56).

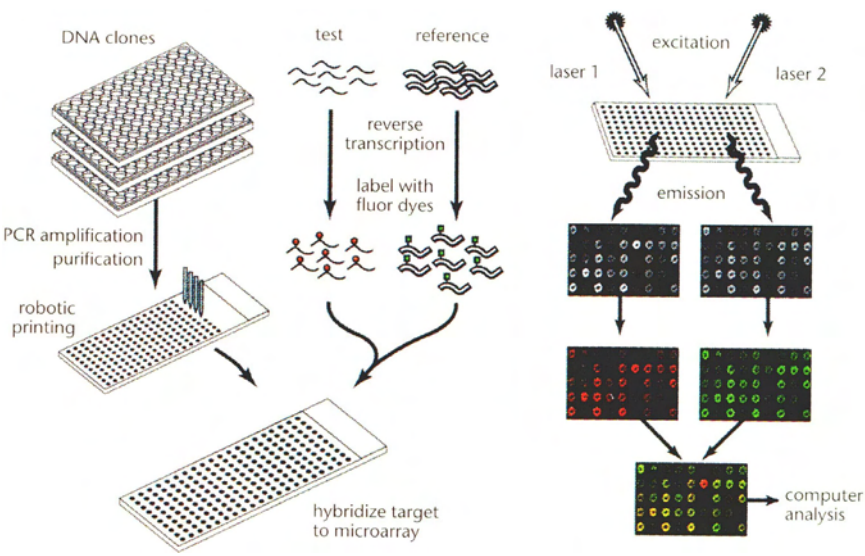

Fig. 9. Principles of microarray in profiling the gene expression of HCC. Microarray analysis is one of the best approaches currently available to determine the global gene expression of tumors. Messenger RNAs are isolated from HCC and from control normal liver, and cDNAs are separately synthesized using cy3- and cy5-labeled dUTP. The fluorescent-labeled probes from the two different samples are then mixed and hybridized to a glass slide arrayed with thousands of cDNAs of various genes. The intensity of the label is an indication of the abundance of the specific mRNA in the sample.

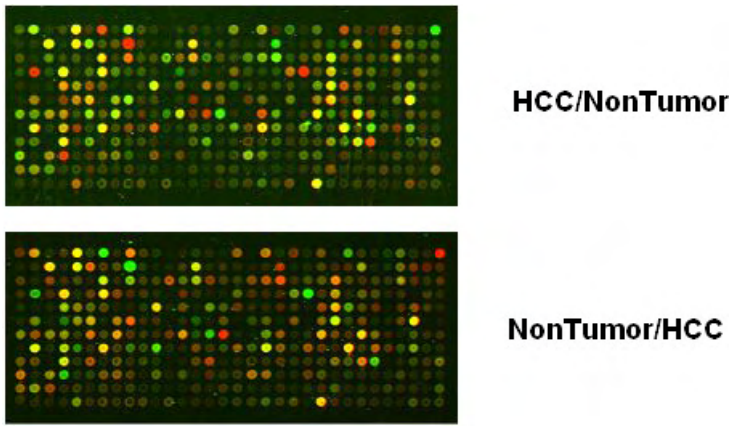

Fig. 10. Microarray analysis of HCC mRNA. Microarray analysis of a sample of HCC vs. normal liver tissues, together with the reciprocal array with reverse labelings of the samples.

These pathways are related to cell proliferation, cell cycle, apoptosis, and angiogenesis, and are dysregulated during the carcinogenic process. For example, the cell cycle negative regulators p53, p27, and p10 are less expressed; while many cyclins and cyclin-dependent kinases are overexpressed in HCC. These combinations may drive the hepatocytes into proliferation.[54–56]

Expression of Wnt and mutation in β-catenin also contribute to HCC development. Aberrant expression of mitogen-activated protein kinase (MAPK) and associated proteins as well as the downregulation of insulin-like growth factor–binding protein 3 (IGFBP3) are apparently involved in altered signal transduction in HCC. Other changes associated with HCC include, but are not limited to, a variety of cellular processes like cell signaling, transcriptional regulation, RNA splicing, protein degradation, and cell adhesion. Cellular matrix and cytoskeleton proteins such as fibronectin, tubulin alpha 1, matrix metalloproteinase 14, osteonectin (SPARC), and RhoA are upregulated; they play major roles in cell motility and invasion. In a microarray analysis of metastases of HCC, it was found that osteopontin is a lead gene in the metastatic HCC signature.[54] Detections of new genes associated with HCC were also reported. Using the innovative technique of differential display of

Table 1. Genes set to predict early intrahepatic recurrence.[52]

Description	Function
Platelet-derived growth factor receptor α (*PDGFRα*)	Signal transduction
Tumor necrosis factor α inducible protein 3 (*TNFAIP3*)	Immune response
Lysosomal-associated multitransmembrane protein (*LAPTM5*)	Protein interacting with ubiquitin
HLA-DRα heavy chain (*HLADRα*)	Immune response/MHC class II antigen
Rel proto-oncogene (*REL*)	Transcription/Proto-oncogene
Staf50 (*TRIM22*)	Transcription/Interferon-inducible
Putative serine/threonine protein kinase (*SGK*)	Sodium transport/Stress response
MADS/MEF2-family transcription factor (*MEF2C*)	Transcription
HUMLUCA19 human cosmid clone LUCA19 from 3p21·3 (*SEMA3F*)	Embryonic development/Cell motility
DEAD-box protein p72 (*DDX17*)	RNA helicase/RNA processing
Vimentin (*VIM*)	Cytoskeleton/Liver metastasis
KIAK0002 gene (*CCND2*)	Control of cell cycle

mRNA in HCC and normal tissues, a mitochondria proteolipid–like gene (*MPL*) was repressed in HCC. Microarray analysis was able to identify a 12-gene set that may be able to predict early intrahepatic recurrence of HCC (Table 1),[52] while gene profiling and single nucleotide polymorphism of HCC was documented in tumor diagnosis.[57,58]

On the other hand, proteomics of HCC were usually performed by analyzing cellular proteins with two-dimensional SDS-PAGE electrophoresis (2DE), and the results were compared to those of paired adjacent nontumorous liver tissues. For mass spectrometry (MS) fingerprinting, protein spots with differential intensity between HCC and nontumorous liver were directly cut out of gels and processed for matrix-assisted laser desorption/ionization–mass spectrometry (MALDI-MS) and nano-liquid chromatography–electrospray ionization–tandem mass spectrometry (nano-LC-ESI-MS/MS) analysis, followed by database searching to identify the proteins of interest (Fig. 11).[59] Another

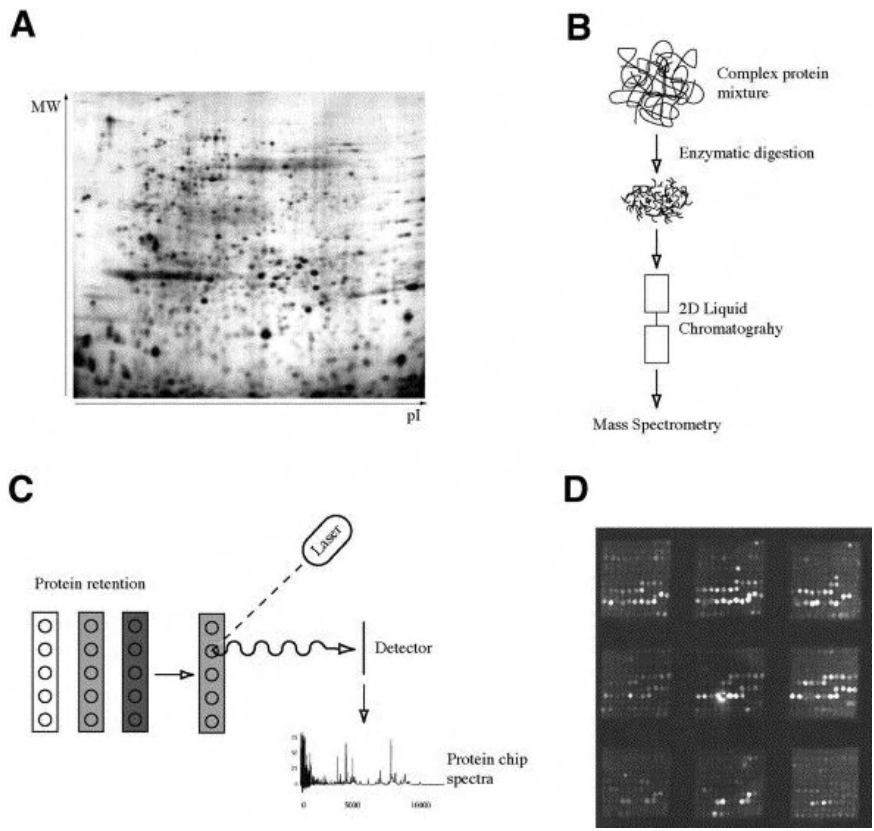

Fig. 11. Principle of HCC proteomics. Cellular proteins of HCC are separated by two-dimensional SDS-PAGE electrophoresis (2DE), and the results are compared with those of paired adjacent nontumorous liver tissues. Protein spots with differential intensity between HCC and nontumorous liver are directly cut out of gels and processed for matrix-assisted laser desorption/ionization–mass spectrometry (MALDI-MS).[59]

approach is based on the identification of proteome patterns that could be used as disease signatures. This technique is known as surface-enhanced laser desorption ionization (SELDI), which is based on the selective retention of proteins on modified array surfaces. Once unbound proteins are discarded, proteins retained on the array are analyzed by MS, generating a specific pattern or profile of the analyzed proteome.

Using the MALDI proteomic approach to identify proteins altered in HCC, the chaperone heat-shock proteins (Hsp27, Hsp70, GRP78) were found upregulated in many HCCs,[60] while Hsp27 was associated with metastatic HCC.[61] The proteasome subunits (PSMA6, PSMB4, PSMC2, and PSMD12) were upregulated in tumor tissues of the *p21-HBx* transgenic mice,[62] while altered apolipoprotein E and chloride intracellular channel 1 proteins were found in HCCs of patients with HCV infection.[63] Using proteomics, our group identified the following proteins expressed in HCC: elongation factor 1b, thioredoxin-like protein 4A, 26S proteasome, geminin, SENP8, NF-κB–BIE, calreticulin, HSPA9B, growth arrest–specific protein 1, and peroxiredoxin 2 (Fig. 12) (Lee KKH *et al.*, The Chinese University of Hong Kong, unpublished data).

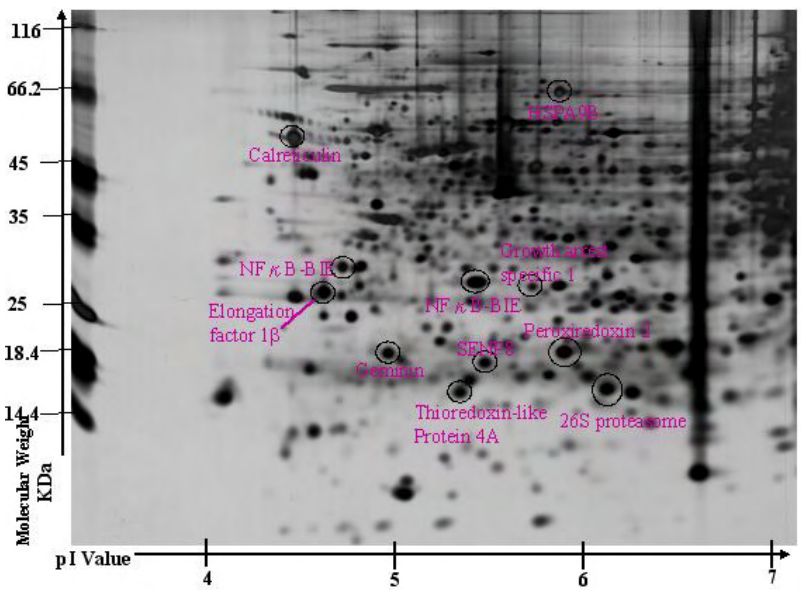

Fig. 12. Proteome of HCC: 2D gel electrophoresis. Two-dimensional gel electrophoresis and MALDI-TOF identified the following proteins that are expressed in HCC: elongation factor 1b, thioredoxin-like protein 4A, 26S proteasome, geminin, SENP8, NF-κB–BIE, calreticulin, HSPA9B, growth arrest–specific protein 1, and peroxiredoxin 2 (Lee KKH *et al.,* The Chinese University of Hong Kong, unpublished data).

Gene Transfer and Immunotherapy in HCC

Gene transfer and gene therapy and immunotherapy are one of the major innovative approaches currently pursued by many investigators to treat HCC.[64–68] Several reports utilizing restriction of tumoricidal gene therapy to selected HCC cells have been documented.[69] The 5′ flanking sequence of the alpha-fetoprotein gene (*AFP*) was constructed as the promoter for the thymidine kinase gene of herpes simplex virus (*HSV-TK*), which was then cloned in an adenovirus vector. AFP-producing cells (HuH7) were specifically killed after transduction of the *HSV-TK* gene, followed by administration of the antiviral TK drug ganciclovir. Another approach was to link the wild-type *p53* gene to the *AFP* gene promoter in a retrovirus vector in order to achieve selective growth inhibition of AFP-producing cells. Introduction of this gene into AFP-positive HCC cells resulted in inhibition of clonal growth and increased the sensitivity of these cells to cisplatin. Thus, restoring wild-type *p53* expression in HCC in combination with chemotherapy can be considered as a strategy for the treatment of HCC. However, retrovirus vectors suffer from the drawback of low frequency of gene transfer and the need of hepatocyte proliferation to allow the vector to replicate.

Another novel method is to first transduce hepatocytes with an adenovirus that transiently expresses the urokinase gene, resulting in a high rate of asynchronous liver regeneration. This approach resulted in a 10-fold increase in the efficiency of subsequent transfection with retrovirus. Other methods of improving gene transfer in the liver include the liposome-encapsulated DNA-mediated gene transfer with intravenous injection, and the use of the Moloney murine leukemia virus long terminal repeat (MoMLV LTR) encapsulated in multilamellar liposomes of egg phosphatidylcholine. Chloroquine and colchicine pretreatment increases the levels of plasmid DNA in the liver. Although adenovirus-based vectors are capable of transducing a high percentage of cells, the effects are transient and usually last no more than a few weeks. Other difficulties include the low rates of penetration of these vectors in solid tumors. The recent failures of gene therapy in treating other diseases including cancer have hampered the continuation of further trials. Another approach is to link the liver-targeting circumsporozoa (CS) protein with drugs or drug-metabolizing enzymes to treat liver tumors.[70]

New discoveries in molecular genetics and the significant potential of utilizing these findings to treat HCC, together with improved vectors and vehicles that are targeted to HCC cells and membranes, will make molecular therapy of HCC possible in the foreseeable future.

Conclusions

Recent molecular studies have revealed a great deal about the role of proto-oncogenes, tumor suppressor genes, and hepadnaviruses in the development of HCC. The diagnosis and therapy of neoplastic diseases using molecular biology techniques is just beginning. The first rays of light on what promises to be a glorious period in the history of medicine are on the horizon. The only limitation of this technology to the potential benefits it will bring is our imagination to develop and apply it.

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11

Staging

Justin M. Burns and Frederick L. Greene

Introduction

The observation that survival rates were higher for individuals with localized cancer compared to individuals with spread of the disease led to the development of staging systems in the early 20th century.[1] The use of cancer staging systems provides many advantages in the treatment of cancer. Staging systems provide a common language between institutions to facilitate the exchange of information and allow for the randomization of similar patient cohorts in ongoing clinical trials investigating cancer therapies.[1–3] The ultimate goal is to provide an accurate prognosis and to allow for the initiation of appropriate therapy for the individual while enabling the comparison of end results of therapeutic interventions for the entire cohort. For a staging system to be universally efficacious, it must be prospectively validated and reproducible in all patient populations.

The importance of cancer staging is highlighted by the fact that, in the United States, the use of the American Joint Committee on Cancer (AJCC) tumor–lymph node–metastasis (TNM) staging system

has increased from less than 30% of newly diagnosed cases of cancer in 1985 to more than 90% in 2001.[2,3] Since 1987, the TNM system has been used worldwide and is the recommended staging strategy of the AJCC and the International Union Against Cancer (UICC).

Liver cancer is the fifth most common cancer in the world and the third highest cause of cancer-related death.[4] Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, and it presents unique challenges to the development of an ideal cancer staging system. The ability to stratify HCC patients into homogeneous cohorts is more complex than with any other cancer. Most cases of HCC develop in a cirrhotic liver; thus, prognosis as well as potential therapeutic intervention is dependent on the function of the residual liver and the anatomic extent of the disease. Therefore, patients may present with an early HCC, but have poor underlying synthetic function of the liver. In this scenario, the global prognosis of the patient is more dependent on the synthetic function of the liver than on the tumor burden. This phenomenon has prevented the creation of a universally accepted staging system for HCC.

In 1988, the AJCC/UICC adopted the TNM classification derived from the Liver Cancer Study Group (LCSG) of Japan for evaluation of the prognosis of HCC.[5] The TNM classification is based on pathologic analysis of the surgical specimen; however, less than 30% of patients are candidates for resection at initial presentation. Therefore, the TNM system did not provide accurate prognostic information for the majority of patients with HCC. Further drawbacks included a complex T-classification including 10 subcategories, a controversial 2-cm–size threshold, and overlap in prognosis between the T subcategories.[6] Additionally, the early TNM staging system did not take into account the synthetic function of the residual liver.

As the limitations of the TNM system became evident, many staging systems were introduced in an attempt to more accurately stratify patients based on survival predictions for newer therapies. Unfortunately, the use of multiple staging systems undermines the randomization of patients into clinical trials, prevents outcome measurement comparisons among centers for various treatment modalities, and makes prognostic discussions with individual patients difficult — all of which

are key advantages of a universal system. The current staging systems can be placed in two broad categories: clinical staging systems and staging systems based on histopathology. This chapter will describe popular staging strategies that are used today, including the strengths and weaknesses of each system.

TNM

The TNM staging system is a histopathology-based system derived from a cohort of patients undergoing resection or liver transplantation. The current 6th edition (Table 1) includes a simplified TNM system for HCC[1,7] as well as tumor characteristics and liver function, which have been cited as underlying weaknesses of the 5th edition. The International Cooperative Study Group on Hepatocellular Carcinoma conducted a multi-institutional, international study that evaluated the survival of 557 patients who underwent resection of HCC. This work identified five independent predictors of mortality from HCC: (1) major vascular invasion (major branch of the portal vein or hepatic veins); (2) microvascular invasion; (3) severe fibrosis/cirrhosis of the nontumorous liver; (4) multiple tumors; and (5) tumor size greater than 5 cm.[8] An overlap in the existing T-categories was observed, which was previously reported by Izumi *et al.*[6] There was no statistical difference of 5-year survival for patients in the T_1 group compared with the T_2 group ($p = 0.6$), or in the T_3 group compared with the T_4 group ($p = 0.5$).[8] These findings led to a simplification of the T-system by stratifying patients into three groups based on the extent of vascular invasion (T_1, no vascular invasion; T_2, microvascular invasion; T_3, major vascular invasion), in addition to tumor size and number (Table 1). The importance of vascular invasion has been documented in several series,[9–11] including Izumi *et al.*[6] who reported that the presence of vascular invasion was the main factor affecting mortality following operative resection of HCC.[6] Furthermore, Vauthey *et al.*[8] investigated the significance of residual liver function. Major fibrosis, defined as a score of 5 or 6 (Ishak scoring system[12]), significantly decreased the 5-year survival rate for all three T-categories (Table 2). Subsequently, the current 6th edition includes a fibrosis designation (F0 or F1) in each T-category.[1]

Table 1. TNM staging system for HCC (6th ed.).[1]

T-classification	Morphology
T_1	Single tumor without vascular invasion
T_2	Single tumor with vascular invasion or multiple tumors, none >5 cm
T_3	Multiple tumors, any >5 cm or tumor involving a major branch of the portal or hepatic veins
T_4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
	Regional lymph nodes (N)
N_X	Regional lymph nodes cannot be assessed
N_0	No regional lymph node metastasis
N_1	Regional lymph node metastasis
	Distant metastasis (M)
M_X	Distant metastasis cannot be assessed
M_0	No distant metastasis
M_1	Distant metastasis

Stage

Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage III A	T_3	N_0	M_0
Stage III B	T_4	N_0	M_0
Stage III C	Any T	N_1	M_0
Stage IV	Any T	Any N	M_1

Fibrosis (severe or cirrhosis) downgrades any stage

An essential attribute of a cancer staging system is the ability to accurately apply its prognostic capability to different patient populations. A fundamental difference in the etiology of HCC in China compared with Western populations is the underlying hepatitis serologies. In China, HCC occurs predominately in patients with hepatitis B, while this represents a minority of patients in Western populations.[8,13,14] The validity of the TNM system in predicting the prognosis of patients with HCC resulting from hepatitis B was investigated by Poon and Fan.[11] They retrospectively reviewed 518 patients (hepatitis B surface antigen

Table 2. Prognosis of T-categories of the TNM staging system.[43]

	Group	Fibrosis[a]	5-year survival (%)
T1	Solitary without	F0	64
	vascular invasion	F1	49
T2	Solitary with vascular invasion	F0	46
	Multiple tumors ≤ 5 cm	F1	30
T3	Major vascular invasion[b]	F0	17
	Multiple tumors ≥ 5 cm	F1	9

[a]F0: fibrosis grade 0–4; F1: fibrosis grade 5–6.[12]

[b]Invasion of the major branch of the portal vein or the hepatic veins.

[HBsAg]-positive serology in 443 patients) who underwent hepatic resection for HCC from 1989 to 2000 at the University of Hong Kong.[11] Major and minor vascular invasions were reported to be independent prognostic factors, and were the two factors with the most significant impact on survival. Furthermore, the authors supported both the change in tumor size criteria from 2 cm to 5 cm, and the importance of designating the presence of fibrosis in the classification scheme.[11]

Despite these similarities, there were a few discrepancies between the two studies. Vauthey *et al.*[8] reported similar survival between patients with multiple tumors (any greater than 5 cm) and patients with major vascular invasion[8]; this led to the integration of these two subsets into a single category (T_3) in the 6th edition of the TNM system.[1] In contrast, Poon and Fan[11] observed that major vascular invasion (portal vein or hepatic veins) carried a poorer prognosis than multiple tumors (any greater than 5 cm). Additionally, Poon and Fan[11] demonstrated that invasion of adjacent organs, bilobar tumors, and perforation of visceral peritoneum were independent predictors of a poor prognosis on multivariate analysis; while Vauthey *et al.*[8] eliminated these factors from the current T-classification. Poon and Fan[11] subsequently reported no significant difference in stage IIIA and stage IIIB patients in the 6th edition of the TNM staging system. Subset analysis demonstrated that patients with major vascular invasion had a poorer prognosis than the other patients grouped in the T_3 and T_4 categories.[8,11]

The results reported by Poon and Fan[11] were significant in providing external validation for the new TNM system in a different patient population. Furthermore, the authors confirmed that vascular invasion is the most important prognostic factor for survival, and they reiterated the importance of the underlying liver function on prognosis in HCC.

Okuda

The Okuda staging system is a clinical staging scheme based on tumor size, presence of ascites, total bilirubin, and serum albumin (Table 3). This staging strategy was introduced in 1985, and was the first system to incorporate liver function into the stratification of patients with HCC. The authors performed a retrospective analysis of 850 patients with HCC treated during an 8-year period. The median survival of 229 patients who received no treatment was 1.6 months, 8.3 months for stage I patients, 2.0 months for stage II patients, and 0.7 months for stage III patients. The median survival of stage I patients who underwent hepatic resection ($n = 115$) was 25.6 months; and for stage II patients with resection ($n = 42$), 12.2 months.[15]

Table 3. The Okuda staging system for HCC.[15]

Parameter	Value	Points
Tumor size	>50%	1
	<50%	0
Ascites	Present	1
	Absent	0
Serum albumin (g/dL)	>3	0
	<3	1
Serum bilirubin (mg/dL)	<3	0
	>3	1
Stage		
1	0 points	
2	1–2 points	
3	3–4 points	

The Okuda staging system was used for many years, but contains several weaknesses. A prospective validation of the system was not performed. Furthermore, patients with early and advanced disease are stratified into the same cohort, resulting in a poor ability to differentiate patients by duration of survival.[7] These weaknesses have been repeatedly demonstrated in studies that will be discussed later in this chapter.

Groupe d'Etude de Traitement du Carcinome Hepatocellulaire (GRETCH)

The GRETCH is a clinical scoring system proposed in 1999 by Chevret *et al.*[16] A total of 761 patients who presented with HCC were enrolled over a 30-month period. Patients were randomly assigned to either a training sample ($n = 506$) from which a classification system was established or a test sample ($n = 255$) for validating its prognostic significance. Variables included for cohort stratification were the Karnofsky index, serum bilirubin, serum alkaline phosphatase, serum alpha-fetoprotein, and ultrasonographic evidence of portal venous obstruction. In this study, only 56 patients were treated with surgical resection; while 304 patients were treated with locoregional therapy, systemic chemotherapy, or hormonal therapy. The remaining 401 patients did not receive therapy. Patients were stratified into three groups based on the cumulative score (Table 4): low risk of death, score = 0 (group A); intermediate risk of death, score = 1–5 (group B); and high risk of death, score $\geq$ 6 (group C). These groups were reported to have a 1-year survival of 74%, 34%, and 7%, respectively, in the test group compared with 79%, 31%, and 4%, respectively, in the validation sample.[16]

Cancer of the Liver Italian Program (CLIP)

The CLIP staging system is a clinical scoring system that accounts for both liver function and tumor characteristics. This system was originally developed in the early 1990s, and was the result of a retrospective analysis of 435 patients with HCC diagnosed at 16 Italian institutions.[14] This system includes Child–Pugh stage, tumor morphology and

Table 4. Groupe d'Etude de Traitement du Carcinome Hepatocellulaire (GRETCH).[16]

Variable	Score			
	0	**1**	**2**	**3**
Karnofsky index (%)[a]	≥80			<80
Serum bilirubin (μmol/L)	<50			≥50
Serum alkaline phosphatase (ULN)[b]	<2		≥2	
Serum alpha-fetoprotein (μg/L)	<35		≥35	
Portal venous obstruction	No	Yes		
Risk	*Score*		*1-year survival*	
Low risk of death	0		74%	
Intermediate risk of death	1–5		34%	
High risk of death	≥6		7%	

[a] Karnofsky index ≥80% = complete autonomy of the patient.
[b] ULN = upper limit of normal.

Table 5. Cancer of the Liver Italian Program (CLIP) staging system for HCC.[14]

Variable	Points		
	0	**1**	**2**
Morphology	Single <50%	Multiple <50%	Massive or >50%
Child's Score	A	B	C
AFP (ng/mL)	<400	≥400	
Portal vein thrombosis	No	Yes	

Score = sum of points for 4 variables

AFP = alfa-fetoprotein.

extension, serum alpha-fetoprotein (AFP) levels, and portal vein thrombosis (Table 5).[14,17]

One of the major advantages of this system is that it has undergone external validation in different patient populations.[7,17–20] Two years following their initial description of this staging system, the CLIP investigators conducted a prospective randomized study to validate the CLIP score in 196 patients with HCC. The authors concluded that the

CLIP score had greater prognostic efficacy when compared with the traditional Okuda staging system.[17] Survival rates at 1 and 2 years were 84% and 65%, respectively, for a CLIP score of 0; 66% and 45% for a score of 1; 45% and 17% for a score of 2; 36% and 12% for a score of 3; and 9% and 0% for the 4–6 category.[17] Ueno *et al.*[18] investigated the predictive power of the CLIP system compared with the Okuda stage and the TNM stage in 662 Japanese patients with HCC. The authors reported that the CLIP system had independent prognostic value equal to (if not greater than) that of the Okuda and TNM staging systems. One group reported less than favorable prognostic results for the CLIP system compared with the Chinese University Prognostic Index (CUPI) in a study with 926 Chinese patients[21]; however, the patient population was not similar to the population in the original reports by the CLIP study group.[7]

Despite external validation of the CLIP system, one limitation of it is that other staging systems were not included in the analysis of these cohorts.[22] Additionally, the CLIP system is criticized for overlap of patients in the early stages, which was a potential weakness recognized by the CLIP investigators.[17,22,23] Critics have pointed out that, in many studies, the majority of patients are grouped into a CLIP score of 0–2,[18,19,24–26] which results in poor stratification and prognostic ability.[24] Furthermore, it is important to note that few of the patients in this study underwent surgical resection due to the advanced state of disease at presentation,[27] and that alkaline phosphatase has not been shown to be a sensitive measure of liver function.[22]

Barcelona Clinic Liver Cancer (BCLC)

The BCLC system is a clinical staging system in which the prognostic model for HCC is based on four characteristics: (1) tumor stage, (2) degree of liver function, (3) the patient's general condition, and (4) treatment efficacy.[4] Patients are stratified into four major categories, which simultaneously link staging with treatment indication (Table 6).[13] Patients placed into the *early stage* (stages A_1–A_4) are likely to benefit from radical therapies such as surgical resection, liver transplant, and percutaneous injection.[4,7] Long-term survival for these

Table 6. Barcelona Clinic Liver Cancer (BCLC) staging system for HCC.[13]

Stage	Performance status	Tumor stage	Liver function
Stage A (early HCC)			
A_1	0	Single, < 5 cm	No portal HTN; normal bilirubin
A_2	0	Single, < 5 cm	Portal HTN; normal bilirubin
A_3	0	Single, < 5 cm	Portal HTN; elevated bilirubin
A_4	0	Up to 3, < 3 cm	Child–Pugh class A-B
Stage B (intermediate HCC)	0	Large multinodular	Child–Pugh class A-B
Stage C (advanced HCC)	1–2	Vascular invasion or hepatic spread	Child–Pugh class A-B
Stage D (end-stage HCC)*	3–4	Any of the above	Child–Pugh class C

*At least one of the conditions should be met.
HCC = hepatocellular carcinoma; HTN = hypertension.

patients is reported to be 50%–75% over 5 years. Patients grouped into the *intermediate stage* (stage B) are believed to benefit from palliative therapy with chemoembolization, and have a 50% 3-year survival rate. The *advanced stage* (stage C) includes patients who are symptomatic from their disease with an associated decrease in performance status and/or who have an aggressive tumor pattern (vascular invasion or extrahepatic spread). Patients in this group have a 3-year survival of approximately 10%. Finally, patients with severe disease based on performance status and underlying liver function are grouped into the *terminal stage* (stage D).[4]

The BCLC staging system has several strong points. It takes into account tumor characteristics (vascular invasion, number and size of nodules), the underlying liver disease (Child–Pugh score and presence of portal hypertension), and overall performance status of the patient, while ultimately providing a guide to therapy. Minor criticisms of this scoring system are that assessment of portal hypertension is not precise and that the overall scheme is difficult to administer.[7] Additionally, some authors have stated that the BCLC system is used to justify treatment algorithms implemented at individual centers as opposed to being a prognostic model that can be universally applied to patients with HCC.[17,24]

The most important weakness of this system is the lack of prospective validation. However, there have been several recent reports in the literature that have attempted to justify the BCLC scoring system. Cillo *et al.*[28] reported a retrospective analysis of 187 patients at a single institution from 1990 to 1999. This analysis compared the Okuda, CLIP, French, CUPI, and BCLC scoring systems using survival as the only measure of performance for each system. The study contained a large number of patients with early HCC, with 43% of patients treated with a surgical resection — higher than in reports describing the other staging systems.[14,15,21] The authors concluded that the BCLC system offered the best discrimination of prognoses for early HCC categories, and was similarly efficient in distinguishing between intermediate and advanced stages compared with the other scoring systems.[28]

A second retrospective review comparing the different prognostic models was published in 2005 by Marrero *et al.*[22] This study reviewed 239 consecutive patients with cirrhosis and HCC between January 2000 and December 2003. In this study, 25% of patients received surgical intervention (resection, 4%; transplantation, 21%), 19% underwent radiofrequency ablation, 9% received chemoembolization, 6% received radiation, and 12% were treated with systemic chemotherapy.[22] This study demonstrated a significant difference in the probability of survival across the different stages. The TNM (stages II and III), Japanese Integrated Staging (JIS) (stages 1–3), CLIP (stages 1–3), and GRETCH (stages B and C) systems were reported to have poor stratification of survival at the intermediate stages. Of all the systems reported, the BCLC

system was shown to have the highest homogeneity, the highest discriminatory score, and the best monotonicity of gradients. Furthermore, the BCLC model was the only scoring system to have a significant impact on the Cox survival model, indicating that it had independent predictive value on survival in the cohort. Based on these findings, the authors concluded that the BCLC system is superior to the other prognostic models and should be implemented when treating patients with HCC. Critics of this retrospective review have highlighted the fact that patients were placed into cohorts on the basis of treatment, and that the prognosis was based on the therapeutic intervention and not on the actual disease state.[29] This is a common criticism that has been applied to the BCLC system since its initial introduction into the literature.

In a follow-up study based on their earlier retrospective review, Cillo *et al.*[23] conducted a prospective validation of the BCLC staging system. This study evaluated 195 consecutive patients with HCC from June 2000 through June 2004, using survival as the measure of performance when comparing different staging systems. BCLC, CLIP, and Okuda were included in the prospective analysis; and the U.S. United Network for Organ Sharing (UNOS) TNM, JIS, and AJCC TNM 2002 staging systems were retrospectively applied to the subgroup of surgical patients. Forty-eight percent of patients underwent surgical intervention (resection, 27%; transplant, 21%); 42% underwent percutaneous ablation; while the remaining 10% were treated with transarterial chemoembolization (TACE), systemic chemotherapy, or supportive care. This study again demonstrated the overlapping survival prognosis of patients in the early stages of the CLIP scoring system (0–2). The authors stated that the BCLC was also more accurate in distinguishing between intermediate and advanced stages of disease compared with the CLIP and Okuda systems. Subset analysis excluded patients undergoing liver transplant; this improved the prognostic performance of both the Okuda and CLIP systems, although they were still determined to be inferior to the BCLC system. In the retrospective analysis by Cillo *et al.*[23] of surgical patients, only the BCLC system was a significant predictor of survival; these observations again led this group to endorse the BCLC staging system.[23]

However, even authors that support the use of the BCLC system have pointed out a major flaw in this study. The BCLC system is based on a

defined treatment algorithm, which was not followed in this study; thus, the study is not a true validation of this prognostic model.[30] Despite this flaw in the study, Marrero[30] felt that it was important to note the better predictive power of the BCLC system compared with the AJCC TNM system in retrospective reviews of patients who have undergone surgical therapy.

Chinese University Prognostic Index (CUPI)

The CUPI is a clinical staging system based on a study from 1996 to 1998 examining 926 patients at a single institution in Hong Kong (Table 7). The group sought to derive a new prognostic index and, furthermore, to compare the proposed index with other scoring systems (TNM, Okuda, and CLIP). The CUPI takes into account six variables: the TNM staging system, total bilirubin, ascites, alkaline phosphatase, AFP, and asymptomatic disease on presentation. A score is given to

Table 7. Chinese University Prognostic Index (CUPI) staging system for HCC.

Variables		**Points**
	Stages I & II	−3
TNM	Stage III	−1
	Stage IV	0
Asymptomatic disease		−4
Ascites present		3
AFP ≥500 (ng/mL)		2
	<2	0
Bilirubin (mg/dL)	2–3	3
	>3	4
ALP ≥200 (IU/L)		3
Risk	*Score* *	*Mortality*
Low risk	≤1	3 months, <30%
Intermediate risk	2–7	3 months, 30%–70%
High risk	≥8	3 months, >70%

*Score: sum of points from the 6 variables.
AFP: alfa-fetoprotein; ALP: alkaline phosphatase.

each variable, and then the scores are added to stratify patients into three different mortality risk groups. The low-risk group has a 3-month mortality of less than 30% (score ≤ 1), the intermediate group has a 3-month mortality of 30%–70% (score 2–7), and the high-risk group has a 3-month mortality of greater than 70% (score ≥ 8). Surgical resection for the primary tumor was only performed in 96 patients (10.4%), nonsurgical interventions were administered to 289 patients (31.2%), while the remaining 541 patients (58.4%) were treated with supportive care. An important characteristic of the study population was the high incidence (79%) of hepatitis B; this is in contrast to most other staging systems that have been proposed based on a predominance of patients with hepatitis C serology. The authors concluded that the CUPI was more discriminant in stratifying patients into different risk groups and was better at predicting survival than the TNM staging system, the Okuda staging system, and the CLIP prognostic score.[21]

The strengths of the CUPI are that it is easily applicable and incorporates both measures of tumor biology and liver function. The disadvantages of the system are the large number of variables used to stratify patients into a staging group and the lack of prospective validation. Furthermore, there is a difference in the patient population between the CUPI and other Western-derived staging systems. This major discrepancy may prevent direct comparisons between the CUPI and other patient cohorts with different disease serology.[7]

Japanese Integrated Staging (JIS)

The JIS system was proposed by Kudo *et al.*[24] in 2003. The purpose of this staging system was to improve the prognostic ability of the Japanese staging system developed by the Liver Cancer Study Group of Japan (LCSGJ),[31] which did not account for the underlying function of the diseased liver. In developing the JIS system, Kudo *et al.*[24] included the Child–Pugh classification to the TNM stage based on the LCSGJ criteria (Table 8). The authors performed a retrospective analysis of 722 consecutive patients treated for HCC at two institutions, and compared the CLIP score with the JIS score. The authors reported significant differences in survival curves for nearly all JIS scores (0–5), whereas

Table 8. Japanese Integrated Staging (JIS) system for HCC.[24]

Variable	**Score**[b]			
	0	1	2	3
Child–Pugh	A	B	C	—
TNM stage by LCSGJ[a]	I	II	III	IV
JIS Score	*Survival (%)*			
	3-year	5-year	10-year	
0	87	73	48	
1	72	52	20	
2	56	33	10	
3	25	13	3	
4	13	2	0	
5	1	0	0	

[a]LCSGJ: Liver Cancer Study Group of Japan.
[b]Score obtained by adding the TNM stage and the Child–Pugh score.

there were no differences between CLIP scores 3 and 4–6. Additionally, the JIS score was reported to be superior in discriminating the best prognostic group. The JIS system demonstrated a 10-year survival of 65% for patients with a score of 0 compared with a 23% 10-year survival for patients with an equivalent CLIP score.

This staging strategy was introduced in 1985, and was the first system to incorporate liver function into the stratification of patients with HCC in other patient populations.[24] Of note, the authors did not include the BCLC staging system in their analysis for several reasons. First, they pointed out that evaluation of performance status is subjective and impossible to determine retrospectively; and second, that clinically relevant portal hypertension is not a predictive variable and should not be included in staging systems. Finally, they believe that this system is a validation of the institution's treatment algorithm as opposed to a true prognostic scoring system.[24]

In 2004, the original authors published a follow-up retrospective study with the aim of validating the JIS prognostic system.[26] A total of 4525 consecutive patients were analyzed at five different institutions from 1990 to 2002. This study reported findings similar to their previous

work in that survival curves showed significant differences among all JIS scores; however, in contrast, there was no significant difference in survival curves for CLIP scores 3–6. Furthermore, the CLIP system was again found to group a large number of patients into the low categories (63% with a CLIP score of 0–1) compared with the JIS system (45% with a JIS score of 0–1). Finally, the authors stated that the Akaike information criteria (AIC) proved that the JIS scoring system was statistically a better model for predicting outcome than the CLIP scoring system.[26]

In both of the previous studies, the JIS system was compared with the widely implemented CLIP system but did not include the BCLC system.[24,26] Toyoda *et al.*[32] published a retrospective review comparing all three strategies in 2005. This study reviewed 1508 patients diagnosed with HCC from 1976 to 2003, and performed subset analyses during the periods 1976–1990 and 1991–2003. The authors reported that, during the period 1976–1990, patients were equally distributed in each category of the CLIP system and BCLC system, whereas the percentages in the JIS scores 0 and 1 were small. In contrast, in the latter time period, more than 50% of patients were grouped into CLIP scores 0 and 1 and the BCLC class A, while patients were evenly distributed across categories except for the JIS score 5.[32] This reflects the fact that patients with HCC are being diagnosed at an earlier stage of disease compared with previous decades. The authors concluded that the JIS system had the best discriminatory ability, followed by the CLIP system, while the BCLC system was last. It is important to remember that this is a retrospective review; the BCLC system is not easily implemented in retrospective analyses, especially a review dating back several decades. Furthermore, this system requires a specific treatment algorithm that was likely not followed over the course of this study.

The studies have a common weakness in that they are all retrospective in nature, and they are all based on similar patient populations in Japan. As previously noted, other retrospective analyses and one prospective study based on Western populations have drawn different conclusions.[22,23] Furthermore, it is difficult to include Western staging systems (e.g. BCLC), which include hepatic transplantation as a therapeutic intervention, since this is rarely used in Japan.

Modified CLIP and JIS Staging Systems

As previously noted, the CLIP staging system uses the AFP level as one of the variables. However, this variable has been shown to be an insensitive marker in terms of prognosis. Subsequently, some authors have advocated changes to the CLIP system as it was originally described. Nanashima *et al.*[33] studied the relationship of protein induced by vitamin K absence or antagonist II (PIVKA-II) on prognosis compared with AFP level. This study reviewed data on patients undergoing surgical resection between January 1990 and April 2002 ($n = 91$). The pathological TNM classification, the CLIP, and the modified CLIP (using PIVKA-II) were compared with regard to patient survival and tumor recurrence. When the predictive level of PIVKA-II was set at 400 mAU/mL, this marker more closely correlated with postoperative tumor recurrence and patient survival compared with AFP.[33] The modified CLIP appeared to be better at discriminating between certain groups than the traditional CLIP; however, both had significant overlap in survival curves. Furthermore, this study was based solely on patients undergoing surgical resection, which contrasts with the original CLIP study in which the majority of patients presented with advanced disease. The significance of this study is the authors' suggestion that making certain modifications may enhance the prognostic ability of the CLIP system.

In a follow-up to the previous pilot study, Nanashima *et al.*[34] performed a retrospective analysis of prognosis in 210 Japanese patients comparing the TNM, JIS, CLIP, and their modified CLIP scores. This study again only considered those patients who had undergone hepatic resection. Many of these patients received preoperative chemoembolization ($n = 65$), alcohol injection ($n = 3$), or both ($n = 4$) prior to resection. In this patient population, the authors reported that the modified CLIP score demonstrated the lowest AIC compared to the other prognostic systems.[34]

In addition to studying modifications of the original CLIP system, Nanashima *et al.*[35] have also proposed changes to the JIS scoring system. The original JIS system uses a combination of the Japanese TNM system and the Child–Pugh classification. However, the authors noted

that the majority of patients undergoing resection had Child–Pugh class A disease; thus, use of the original JIS system may not be optimal for patients undergoing resection. The authors conducted a retrospective analysis on 101 Japanese patients undergoing hepatic resection and evaluated a modified JIS system, which uses the liver damage grade proposed by the LCSGJ.[31,35] Liver function was assessed by determining the indocyanine green retention time at 15 minutes; this has been reported to be an accurate measure of liver function.[36] The authors reported that the liver damage grade demonstrated better discrimination of disease-free and overall survival compared with the Child–Pugh classification.[35] This is likely a reflection of the ability of the liver damage grade to stratify patients with Child–Pugh class A disease into smaller cohorts.

In a follow-up study, Nanashima *et al.*[37] then performed a retrospective analysis on 230 patients undergoing surgical resection for HCC, comparing the JIS system, the modified JIS system using liver damage grade, the CLIP system, and the modified CLIP system using PIVKA-II. The authors observed that the modified CLIP score was a superior prognostic model to the CLIP score, and that the modified JIS score was superior to the JIS score. Furthermore, the modified JIS score score had the lowest AIC statistic, leading the authors to conclude that the modified JIS score score should be used as the prognostic model for HCC patients undergoing hepatic resection.[37]

The potential weakness of using the Child–Pugh classification in the JIS score and the CLIP score has been further investigated by other groups. Wiesner *et al.*[38] investigated replacing the Child–Pugh classification with the Model for End-stage Liver Disease (MELD) score, which has been demonstrated to be a better predictor of mortality for cirrhotic patients. This group reported on two retrospective analyses, comparing the traditional JIS score and CLIP score to similar models using the MELD score.[39,40] The patient population in each study included patients undergoing locoregional therapy, but did not include patients undergoing surgical resection. Huo *et al.*[39,40] concluded from both analyses that a MELD-based JIS and MELD-based CLIP scoring system demonstrated improved predictive ability compared with the original systems.

2002 Consensus Conference

The American Hepato-Pancreato-Biliary Association (AHPBA) and the AJCC sponsored a consensus conference in November 2002 that was organized to identify the best staging strategy for HCC. The four stated goals of the conference were to (1) educate participants about the process and purpose of staging systems for cancer; (2) evaluate existing data and review the current state of knowledge regarding the natural history of HCC and its response to treatment as related to cancer stage; (3) identify the best current staging system for HCC; and (4) identify deficits in HCC staging and come to some consensus on how to improve future systems.[41]

Based on the evidence presented for each staging system reviewed at the consensus conference, the panel made five recommendations:

1. Clinical staging should be the primary staging system and applied to all patients. Currently, the CLIP system is the staging system of choice because it is applicable to all patients, is easily applicable, and has been prospectively validated; however, the panel pointed out the potential shortcoming of the CLIP system in application to patients with chronic hepatitis B.
2. A secondary staging system for patients undergoing resection or liver transplantation is needed. The pathologic system recommended is the TNM system, which has undergone validation.
3. Neither of these staging systems is free of limitations, and other factors may be important in determining prognosis, including treatment-directed variables, the etiology of disease, and factors affecting tumor biology.
4. All studies on HCC, where it is appropriate to use staging, should include one or both of these staging systems (CLIP or TNM) to define patient populations.
5. Further studies on the validation of staging systems are needed.[7]

Discussion

Hepatocellular carcinoma has presented unique challenges in creating the perfect staging system. The prognosis of HCC is clearly the

result of both tumor characteristics and residual liver function. Over the past two decades, many different prognostic models have been proposed. These scoring systems were developed on the basis of different patient populations, inclusion criteria, tumor characteristics, and therapeutic interventions, thus making it difficult to compare models. Consequently, different regions and even different institutions in the same region implement different staging systems.

The 2002 consensus conference by the AHPBA and the AJCC advocated the use of the CLIP scoring system for preoperative staging, and recommended that the TNM system should be implemented as a pathological system following resection. These recommendations were made in an attempt to unite different centers into a single staging strategy. However, the recommendations were not accepted by many centers because investigators believed that their own staging systems were superior. Furthermore, newer studies and systems have been published since the committee convened.

Bruix *et al.*[42] proposed four main factors affecting prognosis: (1) the stage, aggressiveness, and growth rate of the tumor; (2) the general health of the patient; (3) the liver function of the patient; and (4) the specific intervention. These authors have suggested that the staging systems either omitting some factors or using only one factor will have poor predictive power.[42] However, use of the fourth factor (specific intervention) has led to a great deal of disagreement. Some authors believe that this model justifies its therapeutic algorithm and is not a true prognostic model.

Unfortunately, it is impossible to initiate a randomized control study to develop a single staging system for all patient populations. Thus, currently, the ideal prognostic model does not exist.[43] There will continue to be newer systems developed based on biological, molecular, and genetic markers.

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12

Selection of Patients for Liver Resection

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Introduction

The goal of liver resection in hepatocellular carcinoma (HCC) is to cure the patient with minimal operative risk.[1–4] The major causes of hospital mortality are postoperative hepatic failure, bleeding, and postoperative septic complications. In the past two decades, an increased understanding of liver segmental anatomy as well as improvements in surgical techniques and perioperative care have led to a dramatic decrease in operative mortality and improvement in surgical outcome. Currently, the reported 5-year survival after resection of HCC in cirrhotic liver is 30%–60%, with an operative mortality of less than 3%.[1–4] These good results can also be attributed to better patient selection for surgery.

Well-defined and generally accepted staging systems are available for most cancers; however, in HCC, there is still no universally accepted staging system that can be used to guide treatment. In fact, the selection of patients with HCC for hepatectomy has evolved into a complex task that incorporates information regarding tumor extent, the severity

of the underlying liver disease, liver functional reserve, and general medical condition of the patient. The general, commonly employed criteria for unresectability of HCC include large-sized tumor with insufficient hepatic remnant after liver resection, extensive and multifocal bilobar tumors, extrahepatic metastases, and main portal vein/hepatic vein/inferior vena cava tumor thrombus.

This chapter illustrates the approach used to select patients with HCC for liver resection.

Assessment of Tumor Extent

Patients who are deemed to have resectable HCCs on initial clinical assessment via ultrasonography (USG) examination, and without any evidence of lung metastases on chest X-ray, are subjected to further radiological staging for resectability.

Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are used most commonly in HCC (see Chapter 8). High-resolution triple-phase CT scan (CT in noncontrast, hepatic-arterial, portal-venous, and delayed phases) is a mandatory investigation.[5] Similarly, if MRI is used, precontrast, arterial, venous, and delayed phases are essential. The recent implementation of multislice CT (MSCT) with 4- and 16-row detectors has permitted the acquisition of images of the liver with 1.25-mm slice thickness during a single breathhold (10–12 seconds). These thinner images not only provide increased resolution and improved lesion detection, but also permit the production of excellent multiplanar reconstruction without the stair-step artifact of thicker slices. The hypervascular nature of the primary tumor makes imaging a critical feature in the detection and characterization of this tumor.

The variable appearance on different planes of contrast is critical to appreciate in staging this tumor. This is especially important in patients who are candidates for surgical resection. In triple-phase CT scan, after infusion of the contrast agent at a rate of 4–8 mL/s, the hepatic arterial phase is obtained at 20–30 s, the early parenchymal phase at 40–55 s, and the portal phase at 70–80 s. HCC characteristically shows maximal contrast enhancement during the arterial phase, and becomes

hypoattenuating compared with the surrounding liver in the portal venous phase as a result of rapid washout of contrast. Of importance to the surgeons operating on patients with HCC is the information a CT scan provides on the size and site of the tumor as well as on its relationship to the portal and hepatic veins, the size of the whole liver, and the amount of liver tissue that can be left behind after resection. Vascular invasion can also be assessed. The distinction of benign thrombus from tumor thrombus is not always possible, but enhancement of the thrombus during the earlier phases following contrast administration is highly suggestive of tumor thrombus (see Chapter 33).

Extrahepatic metastases of HCC are not rare. The possibility of extrahepatic metastases and the clinical features of extrahepatic metastases should be considered when examining patients with HCC, particularly those in advanced T-stage, to enable precise evaluation of the spread of HCC and determination of the appropriate treatment method. The lung, abdominal lymph nodes, and bone are the most common sites of extrahepatic metastatic HCC.[6,7] Therefore, CT scans of thorax, abdomen, and bone are also required for advanced T-stage HCC cases to look for any extrahepatic metastases.

Positron emission tomography (PET) using F-18 fluoro-2-deoxy-D-glucose (FDG) is now well established as a noninvasive diagnostic tool for the detection of a variety of malignant tumors. FDG-PET has been established as a useful diagnostic method for metastatic liver tumors because it can detect these lesions with a high sensitivity. However, the role of FDG-PET in HCC remains controversial, and several investigators have reported an inadequate sensitivity for PET (20%–55%) because HCC accumulates FDG to various degrees.[8–10] This could be explained by differences in the activity of the enzyme glucose-6-phosphatase (G-6-Pase), which converts FDG-6-P to FDG. The activity of G-6-Pase is reported to be high in normal liver and nearly zero in metastatic liver tumors; in contrast, G-6-Pase activity has been reported to vary widely in individual HCCs. Well-differentiated HCCs have a low detection rate at FDG-PET because their metabolic activity is similar to that of the surrounding liver parenchyma. Poorly differentiated HCCs are more likely to be detected with FDG-PET because of the increase in metabolic activity. With respect to the prognostic value of FDG-PET,

recent reports suggest that preoperative FDG-PET reflects tumor differentiation and is useful for predicting the outcome in patients with HCC.[11–15] Further prospective evaluation of FDG-PET is necessary. Its efficiency in detecting distant metastases from HCC has not been well investigated. At this moment, the role of FDG-PET can merely be regarded as an adjunct to conventional imaging.

Size of HCC

The size of the tumor is not a clear-out limiting factor for partial hepatectomy with curative intention. Recently, the implementation of screening programs using alpha-fetoprotein (AFP) and USG in high-risk populations has identified an increasing number of patients with small HCC. The 5-year and 10-year survival rates of patients who underwent hepatectomy for small HCC have been reported as 55%–70% and 18%–46.3%, respectively.[16,17]

The role of hepatic resection for large HCC (>10 cm) remains controversial. However, in view of the absence of an effective treatment for advanced T-staged HCC, some clinicians consider liver resection to be the treatment of choice when the tumor is still confined to the liver. The 5-year survival after hepatectomy for large HCC has been reported as 26.2%–38.7%.[18–25] Such treatment should only be carried out in experienced centers on selected patients with low operative risks and good liver function.

HCC with adjacent organ involvement

Involvement of adjacent organs by HCC is no longer considered as a contraindication to resectional surgery with curative intent. The adjacent organs include diaphragm, adrenal gland, abdominal wall, stomach, colon, and spleen. Nonrandomized controlled studies showed that patients with HCC with adjacent organ involvement had survival, operative morbidity, and operative mortality rates comparable with those of patients without adjacent organ involvement.[26–29]

In a case-control study by our group,[28] we showed that patients with tumors which have invaded the diaphragm have operative mortality,

operative morbidity, and long-term survival rates similar to those without such an invasion (5-year survival of 28% vs. 32%, respectively). The operative procedures were the same as those in patients with HCC without diaphragmatic invasion, the exception being that a rim of diaphragm of at least 1 cm was excised around the area of invasion *en bloc* with the tumor. No attempt was made to dissect the tumor from the diaphragm because this might cause bleeding, tumor rupture, or implantation of the tumor in the diaphragmatic wound. The diaphragm was repaired with continuous nonabsorbable sutures after tumor resection. A small infant feeding tube was put under water seal and placed through the diaphragmatic wound into the pleural cavity. At the end of suturing of the diaphragmatic wound, the anesthetist was asked to expand the lungs fully with positive ventilation. The infant feeding tube was withdrawn as the suture was tightened and the knot tied. No chest drain was required, and routine chest X-ray at the end of the operation was performed to assess the amount of residual pneumothorax.

HCC with vascular invasion

Vascular invasion of HCC is traditionally regarded as a poor prognostic factor. HCC usually spreads intrahepatically through the portal vein branches. The optimal treatment for patients with HCC and major vascular invasion remains controversial. According to the treatment algorithm proposed by the Barcelona Clinic Liver Cancer staging system,[30] patients with HCC and vascular invasion are to receive only palliative or investigational treatment and not to undergo hepatectomy. When the tumor thrombus extends to involve the main portal veins, the prognosis is extremely poor because of the likely spread of HCC intrahepatically through the portal vein. In general, liver resection is advocated only in patients whose tumor thrombi are limited to the first branch of the portal vein without extension to the portal bifurcation.[31–34] When tumor thrombi extend to the portal bifurcation or main trunk, the role of liver resection becomes controversial (see Chapter 33).

Involvement of the hepatocaval confluence or inferior vena cava (IVC) is traditionally considered a contraindication for liver resection, due to the risks of gas embolism and massive hemorrhage.

The development of innovative surgical techniques, such as total hepatic vascular exclusion, venovenous bypass, and *ex vivo* hepatic resection, have made curative resection of tumors involving the IVC possible. IVC involvement by HCC does not necessarily preclude resection.[35–37] If the tumor involvement of the IVC is small, control of the IVC can be achieved simply by placing a vascular clamp tangentially to the vena cava. The resected IVC can be repaired primarily if the segment of IVC resected is small; larger resections of the IVC require interruption of IVC flow. The method of vascular control depends on whether the involvement of IVC is below or above the hepatic veins. Liver resection with reconstruction of the IVC should only be performed in centers with experience in both liver resection and liver transplantation.

Assessment of General Condition of Patient

Preoperative investigations should include a chest X-ray, full blood count, liver and renal function test, and full clotting profile. Cardiopulmonary assessment should be routine in patients over 65 years of age.[1]

The amount of intraoperative blood loss has repeatedly been shown to be an important factor associated with operative mortality in liver resection. Modern developments in liver surgery have allowed adequate hemostasis to be made even in the presence of liver cirrhosis.[38] In our experience with cirrhotic liver resection, a platelet count of <50 and a prolonged prothrombin time of >4 s over the control are associated with an adverse outcome following liver resection; but an isolated abnormality would not necessarily deter us from proceeding with hepatic resection, using platelet concentrates and fresh frozen plasma to correct the coagulopathy. However, we decline surgical intervention in patients with both abnormalities.[39]

Assessment of Liver Functional Reserve

There is little controversy regarding the amount of liver that can be resected in noncirrhotic patients. A normal liver can tolerate up to 75% of resection of functional liver parenchyma (preserve at least two segments of functional liver). The major risk of cirrhotic liver resection

is the development of postoperative liver failure and death. The amount of liver that can be safely resected depends on the degree of cirrhosis, the functional liver reserve, and the regenerative response to the surgical insult. Patients without cirrhosis or with well-compensated cirrhosis can regenerate the resected liver parenchyma within weeks. However, patients with decompensated cirrhosis have difficulty in maintaining hepatic function immediately after hepatectomy. Cirrhotic livers are also less able to regenerate.

Preoperative assessment of liver function as well as prediction of postoperative residual functional liver remnant and reserve are of paramount importance to minimize the surgical risk. This should start with clinical assessment, i.e. conventional biochemical blood tests (liver function test, clotting profile, and platelet count). In addition, there are numerous quantitative liver function tests that have been evaluated (see Chapter 3). No single method of liver function assessment has been universally accepted as the standard in patients with liver cirrhosis, and no particular test has been demonstrated to be clearly superior to the others in predicting postoperative outcome. Any test on its own cannot take into account the complexities of all aspects of liver function.

Using a point scoring system based on the levels of serum bilirubin, serum albumin, presence or absence of ascites and encephalopathy, and nutritional status, a classification system for hepatic functional reserve for cirrhosis was created. This system, Child's classification, was originally used to assess the operative risk in cirrhotic patients with portal hypertension undergoing shunting operation.[40] Pugh later modified the original classification by substituting prothrombin time for nutritional status.[41] There is a general agreement that the Child–Pugh classification is the most simple, reliable, and reproducible method to identify patients at risk. The parameters measured in this classification give an estimation of the gross synthetic and detoxification capacities of the liver. The Child–Pugh classification indicates whether the cirrhotic liver is compensated (grade A), decompensating (grade B), or decompensated (grade C); and acts as a prognostic index. The Cancer of the Liver Italian Program (CLIP) score, the Japanese Integrated Staging (JIS) score, and the Barcelona Clinic Liver Cancer (BCLC) staging classification incorporate the Child–Pugh classification as a variable for measurement

of liver function. The Okuda staging system also incorporates similar parameters (serum bilirubin, serum albumin, presence or absence of ascites) as its variables.[42] In general, Child–Pugh class A patients can be considered for resection of up to 50% of liver parenchyma, whereas Child–Pugh class B patients tolerate resections of up to 25%; Child–Pugh class C cirrhosis is considered as an absolute contraindication for liver resection. We generally offer liver resection to Child–Pugh class A and selected Child–Pugh class B patients.

However, not all Child–Pugh class A patients have the same degree of liver functional reserve. To compensate for the limitations of the Child–Pugh classification in predicting the risk of posthepatectomy liver failure, various quantitative liver function tests and tests for measurement of residual liver volume by imaging techniques have been designed. Each of these tests assesses only a specific aspect of liver function; as a consequence, when used alone, these tests have their limitations. A combination of these tests is usually necessary. While some centers depend on liver biochemistry and Child–Pugh classification in assessing the liver function of patients, other centers employ more sophisticated quantitative liver function tests such as indocyanine green (ICG) retention test, galactose elimination capacity, or a combined functional and volumetric method.

The principles of quantitative liver function tests are based on the pharmacokinetics of an exogenous substance being eliminated by the liver. The hepatic clearance of the exogenous substance is related to the liver perfusion and extraction ratio. The ICG retention test at 15 min (ICG-R15) has been useful to predict the safe limit of liver resection and posthepatectomy liver failure. The normal values of ICG-R15 range from 3.5% to 10.6%. Most units consider an ICG-R15 value of $>14\%$ to preclude major liver resections, as it indicates a significant reduction in the liver reserve.

Many Japanese groups rely on ICG-R15. Makuuchi and Sano[43] established an algorithm for decision making in surgical treatment based on three parameters: the presence or absence of ascites, total bilirubin level, and ICG-R15. Operability is assessed by the former two parameters, and the maximum resectable liver volume is restricted by the third parameter: patients with ICG-R15 of $<10\%$, 10%–20%,

20%–30%, and >30% are subjected to hepatectomy with the extent of the liver resected equivalent to trisectoriectomy or bisectoriectomy, one sectoriectomy, one segmentectomy, and limited resection (less than one segment), respectively.

In Western countries, the selection of surgical candidates for hepatectomy is usually based on the assessment of the presence/absence of portal hypertension and the bilirubin level. According to the treatment algorithm proposed by the BCLC staging system, hepatectomy is considered for patients with a single tumor, absence of clinically relevant portal hypertension, and normal bilirubin level.[30,44]

Other methods of assessment of liver functional reserve, such as galactose elimination capacity (GEC) and technetium-99m–galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy, were evaluated in some centers.[45–47] However, they are still in an investigatory phase.

For patients undergoing major hepatectomy, CT volumetry is useful in evaluating whether the remnant liver volume is adequate. A small liver remnant volume was shown to be associated with postoperative hepatic dysfunction.[48,49] In selected patients with small remnant liver, attempts have also been made to improve the safety of liver resection by embolizing the portal vein that supplies the part of the liver containing the tumor. Preoperative portal vein embolization (PVE) can be used in patients with limited functional hepatic reserve to increase the resectability and the safety of liver resection. PVE induces hepatocytes in the embolized liver to go into apoptosis and hepatocytes in the unembolized liver to enter into a highly active phase of proliferation, resulting in hyperplasia of the unembolized liver. Nonrandomized studies showed that preoperative PVE is a safe and effective method of increasing the remnant liver volume before hepatectomy.[50–53] Increasing the remnant liver volume in patients with insufficient postresection liver volume appears to reduce postoperative liver dysfunction.[53] Tanaka *et al.*[51] showed that preoperative PVE improved the prognosis after right hepatectomy for HCC in patients with impaired hepatic function, although it did not prevent tumor recurrence. On the other hand, Azoulay *et al.*[50] and Wakabayashi *et al.*[52] showed that PVE during major hepatic resection neither improved nor worsened long-term prognosis,

but allowed resection in a patient group that was previously considered as unresectable (see Chapter 14).

Conclusion

The tumor extent, the general condition of the patient, and the liver functional reserve are the most important factors determining the results of liver resection for HCC.

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Problems Associated with Liver Resection in Cirrhotic Patients

Cheng-Chung Wu

Introduction

Although many nonoperative modalities have been proposed for treating hepatocellular carcinoma (HCC),[1,2] partial liver resection remains the best option for curing the disease.[3–7] Liver resection is also used for other primary or secondary liver malignancies and some benign hepatobiliary diseases.[8–10] Liver resection is a complex procedure.[11] It is recommended to be performed in a large medical center with high volume experience to reduce morbidity and mortality.[11,12] The major risks of liver resection are bleeding, sepsis (mainly due to bile leakage and intra-abdominal abscess), ascites, and liver failure.[13] Resection of a cirrhotic liver is even more complex, as the aforementioned risks become more severe.[3–6,13] Generally, the morbidity and mortality of liver resection in patients with a cirrhotic liver are higher than those for a normal liver.[1,5–7,11–14] Because HCC usually arises from a cirrhotic liver,[1–8] reduction of mortality and morbidity in cirrhotic liver resection is a major task for liver surgeons.

Recently, several surgeons in different institutions have reported liver resection without mortality.[15,16] To achieve this goal, the problems associated with cirrhotic liver resection should be adequately dealt with. Complications that do not occur in normal liver resection may occur in cirrhotic liver resection.[13] Moreover, cirrhotic patients are less tolerant to complications than patients with a normal liver. In this chapter, the problems of liver resection in cirrhotic patients and their solutions will be discussed. For the sake of clarity in the nomenclature of liver anatomy and liver resection, the Brisbane 2000 international consensus of the terminology for liver anatomy and resection[17] is used.

Problems Associated with Cirrhotic Liver Resection for HCC

There are many differences between liver resection in cirrhotic and normal livers. Knowledge of these differences allows more appropriate patient selection and more correct decision making during liver resection in cirrhotic patients. The problems associated with cirrhotic liver resection interreact with one another.[13] Being unaware of these problems causes cascade-like complications, thus increasing postoperative morbidity and mortality and even adversely affecting long-term survival in cancer patients.

The problems associated with cirrhotic liver resection are as follows:

1. The cirrhotic liver cannot tolerate liver ischemia as in the normal liver.[7,18] Although the effectiveness of liver inflow blood occlusion in liver resection remains controversial,[10,14] the author and other investigators[16,18,19] intermittently occlude inflow blood during liver transection to reduce operative blood loss even in cirrhosis. However, the influence of ischemia on the cirrhotic liver is different from that in the normal liver.[7,14,18]
2. As the cirrhotic liver is usually surrounded by many thin-walled dilated collateral vessels and dilated lymphatic ducts in the perihepatic ligaments (coronary ligament, triangular ligament, and round ligament), and liver mobilization for liver resection requires division of these ligaments, bleeding and/or ascite formation may result.[7,19,20] The more severe the degree of cirrhosis, the more

dilated the perivascular vessels.[13] Moreover, bleeding tendency and coagulation defects are more frequent in cirrhotic patients.[13,20–22] Jaundice inevitably occurs in the cirrhotic patient after blood transfusion.[18,20,22]

3. The cirrhotic patient is usually intolerable to sepsis, which may occur after liver resection, because cirrhosis itself is an immunocompromised state.[13] In cirrhotic patients who undergo liver resection, blood transfusion increases the rate of bacterial translocation from the bowel and thus increases the postoperative infection rate.[23] Moreover, blood transfusion may affect the immunity of the host. In patients with primary or secondary malignancy, the prognosis becomes poorer if they receive blood transfusion.[8,24,25]
4. As much as 80% of the original volume of a normal liver can be resected.[26] A normal liver tolerates a massive liver resection and recovers in the postoperative period, gradually regenerating to its original size within 6 months.[26,27] However, the regenerative power of a cirrhotic liver is less than that of a normal liver.[13,26,27] When a large volume of a cirrhotic liver is resected, the remaining liver rarely regenerates to its original size.[7,26] A cirrhotic patient may die of liver failure in the early postoperative period or may fall into chronic liver failure with a poor quality of life.[13] Because there is no data for the difference in regeneration ability between the different degrees of liver cirrhosis, the residual nontumorous liver after partial hepatectomy should be as large as possible in cirrhotic patients.[19,21]
5. Liver cirrhosis associated with portal hypertension[4,13,20–22] may hinder liver resection. A long-standing portal hypertension may result in hypersplenism and thrombocytopenia with bleeding tendency.[21] Because liver resection increases portal vein resistance, if esophageal varices are present, these varices may rupture if portal hypertension is aggravated.[4,13,26,28] For this reason, Bruix *et al.*[4] rejected such HCC patients for liver resection.
6. Grossly, regeneration nodules in cirrhotic liver, especially in posthepatitic macronodular cirrhosis, are sometimes difficult to differentiate from small HCCs.[29] Thus, removal of HCC by inspection or palpation during operation is not reliable. Moreover, HCC usually has a soft consistency[29] such that, when hidden in a hard cirrhotic liver, the actual location and extent of the tumor are difficult to determine.

These nodules are difficult to detect during operation; thus, total removal of these nodules is difficult.

7. The nutritional status of cirrhotic patients is usually not similar to that of patients with a normal liver. The nutritional status is included as an item of the Child–Pugh criteria, which are used to evaluate the prognosis of cirrhotic patients.[30] Poor nutrition may cause a poor postoperative course.[31] Postoperative care for patients with poor nutrition is usually more difficult. Pulmonary, renal, and septic complications occur more commonly in the postoperative period. Therefore, nutritional support in the early postoperative period is very important after cirrhotic liver resection.[3,10,31]

Strategies and Solutions for Problems in Cirrhotic Liver Resection

To improve the results of HCC resection, the aforementioned problems should be overcome. Appropriate assessments should also be performed.

Preoperative assessment

Patient selection criteria

General liver function tests and imaging studies are routinely performed before liver resection for HCC. The data from the indocyanine green (ICG) clearance test are essential for liver resection in cirrhotic patients.[3,18–21,32] The general condition and comorbid diseases of the patient should be carefully evaluated and treated before liver resection. At present, there is no general agreement on the severity of the degree of an individual organ dysfunction to be used as a contraindication for HCC resection. The author and colleagues[32] use the American Society of Anesthesiology classes I and II in selecting patients for liver resection. This system is easy to use on patients before any type of surgery. Chronological age is no longer considered a contraindication to liver resection.[33] Routine preoperative gastroduodenal endoscopy is recommended because of the high incidence of associated peptic ulcer in cirrhotic patients.[34] The presence of esophageal and/or gastric varices can also be detected.

Treatment of severe varices, i.e. presence of red-colored sign or F3,[34] before liver resection is needed. As liver resection aggravates portal hypertension, there is a high chance that such varices may rupture after the operation.[3,13,18,32] Since hepatectomy may also cause stress ulcer bleeding, treatment of peptic ulcer disease in the perioperative period is needed. Although some authors favor concomitant portosystemic shunt[35] during hepatectomy, the author and others[32,34] suggest that a better treatment option is endoscopic variceal ligation or sclerotherapy before hepatectomy. Moreover, antacids, H_2 blockade, or proton pump inhibitors should be used if peptic ulcer is present. Using these strategies, we had no patients who suffered from gastrointestinal bleeding in the early postoperative period.[3,32]

For HCC patients with end-stage renal diseases, they should be treated by hemodialysis in the perioperative period.[36] One day before the scheduled operation, heparin-free hemodialysis should be carried out; and the dialysis should continue for 1 week after the operation.[36] In patients with thrombocytopenia with a resectable HCC, if the liver function fulfills the patient selection criteria as listed in Table 1, liver resection and concomitant splenectomy should be performed.[3,21,32]

Determination of extent of liver resection

Based on imaging studies, the size of the remnant liver after liver resection can be predicted preoperatively. As the regeneration power of a

Table 1. The liver volume that should be preserved after liver resection.

ICG R15 (%)	Preserved liver parenchyma*
40–50	≥7.5
30–39.9	≥7
20–29.9	≥6
10–19.9	≥5
<10	≥3

*No. of Couinaud's liver segments (normal = 8) that should be preserved.

cirrhotic liver is less than that of a normal liver,[27] the liver remnant after resection should be as large as possible to reduce the possibility of hepatic failure in the early postoperative period.[13] The blood inflow and outflow of the liver remnant should be well preserved. There is no general consensus on the patient selection criteria and on the extent of liver resection in cirrhotic patients. Many proposals have been suggested to predict the safe extent of resection and to increase the safety of cirrhotic liver resection.[13,35,37–39]

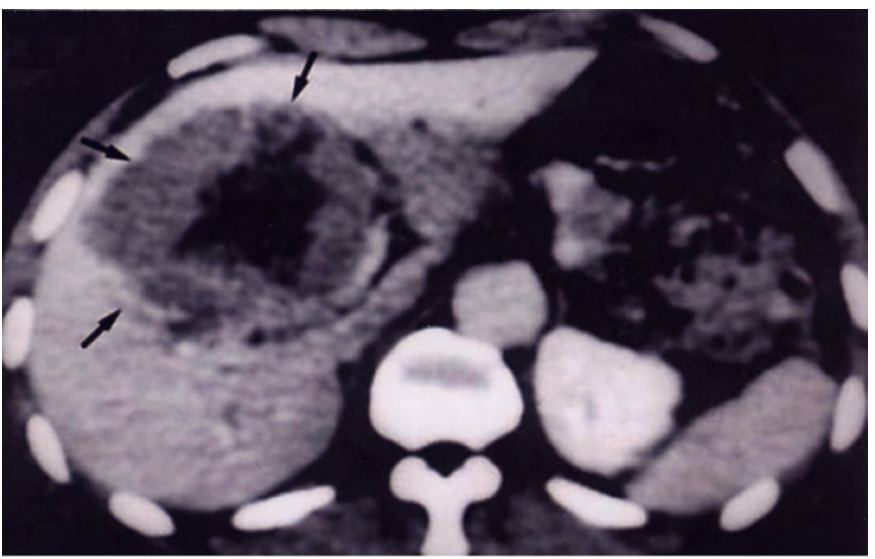
In the past, it was considered safe to carry out left hemihepatectomy, but not right hemihepatectomy, in cirrhotic patients[7]; however, extended right and left hemihepatectomies have been reported to be possible even in cirrhotic liver.[10] Most surgeons select Child–Pugh class A patients for liver resection,[1,5–9,12,40] but our experiences show that Child–Pugh class A patients have variable liver functions.[3,20] Extensive liver resection in Child–Pugh class A patients with a high ICG retention rate may result in death due to postoperative liver failure.[13]

Many investigators have proposed criteria to help decide the extent of hepatectomy for safe liver resection in cirrhotic patients.[37,38] However, these formulas are very complex to use. In 1993, Makuuchi *et al.*[39] proposed that the presence of ascites, the serum bilirubin level, and the ICG clearance rate were the main criteria in deciding the extent of liver resection; the unit for liver resection was based on Couinaud's liver segment.[41] Using their criteria to determine the number of liver segments to be resected, they achieved 1056 consecutive hepatectomies without any mortality in 8 years[16]; however, the size of each Couinaud's segment of the cirrhotic liver was not identical.[41] Wu *et al.*[3,32] modified Makuuchi's criteria to determine the minimum number of liver segments to be preserved, instead of the number of liver segments to be resected (Table 1). Under radiological volumetric evaluation, the percentage of liver volume that could be preserved after resection could be predicted.[38] Using this criteria, with careful patient selection, hospital mortality after cirrhotic liver resection (including reresection for recurrent HCCs) approached 0%.[3,32] If the predicted liver remnant volume fell below the criteria, the patient was selected to undergo other nonoperative treatment modalities.[2] These selection criteria make safe hepatectomy feasible if the liver resection is carried out with good preservation

of the liver parenchyma and related structures (including branches of portal vein, hepatic artery, bile duct, and hepatic vein).

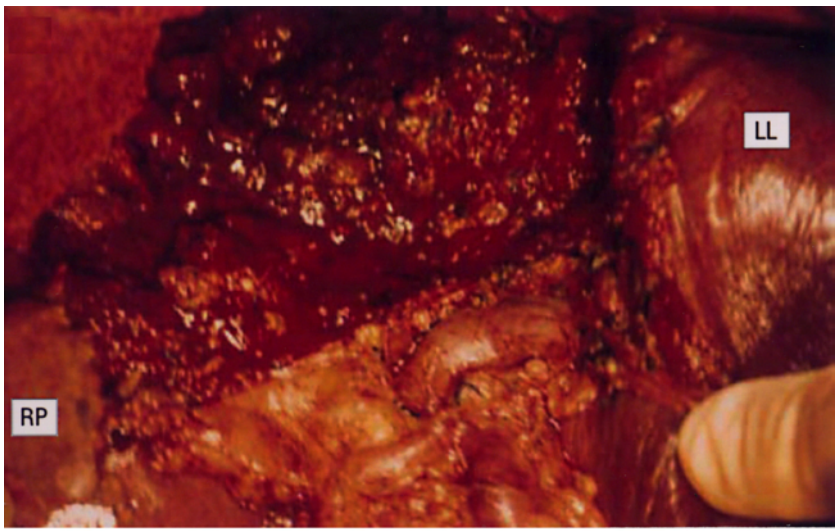
When HCC presents with a pushing border (especially in well-encapsulated tumors),[42] and when it locates just adjacent to the major intrahepatic vasculatures (defined as the left portal vein; the right anterior and right posterior portal veins; and the three major hepatic veins, i.e. right, middle, and left hepatic veins), the tumor remains resectable. The tumor can be carefully dissected from these vessels without damaging them. Despite a large tumor with a narrow resection margin, long-term survival is still possible (Fig. 1).

The extent of the resection margin for HCC is controversial. Many authors recommend that the resection margin for HCC should be as wide as possible (at least greater than 1 cm), like for other malignant

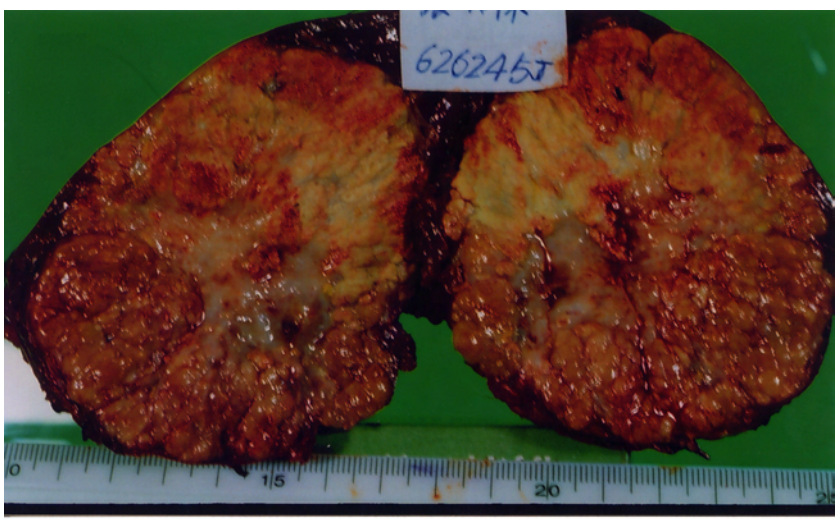


(A)

Fig. 1. (A) A centrally located large HCC (arrows). (B) Liver transection plane after mesohepatectomy (segmentectomy IV, V, and VIII). LL: left lateral section (segments II and III). RP: right posterior section (segments VI and VII). (C) The specimen of the resected HCC. Although the resection margin was very narrow (<3 mm), the patient survived and was disease-free for more than 10 years. (A,B) Reprinted from *Arch Surg*, 2002 (Dec), **137**, 1369–76, copyright ©2002 American Medical Association.



(B)



(C)

Fig. 1. (*Continued*)

diseases.[4–7,40] In patients with a dysfunctioning cirrhotic liver, some centrally located HCCs will not be selected for resection if a wide resection margin is contemplated. However, the author and others[20,43,44] have found that the prognosis of HCC is mainly impacted by its

biological behavior and tumor staging than by the resection margin. This concept is essential for patient selection in HCC with a cirrhotic liver for resection. A pathological study showed that a wide resection margin did not guarantee the total removal of all tumors.[45] Such resectional policies for HCC in cirrhotic liver expand the indication and safety for HCC resection without compromising the long-term survival rates.

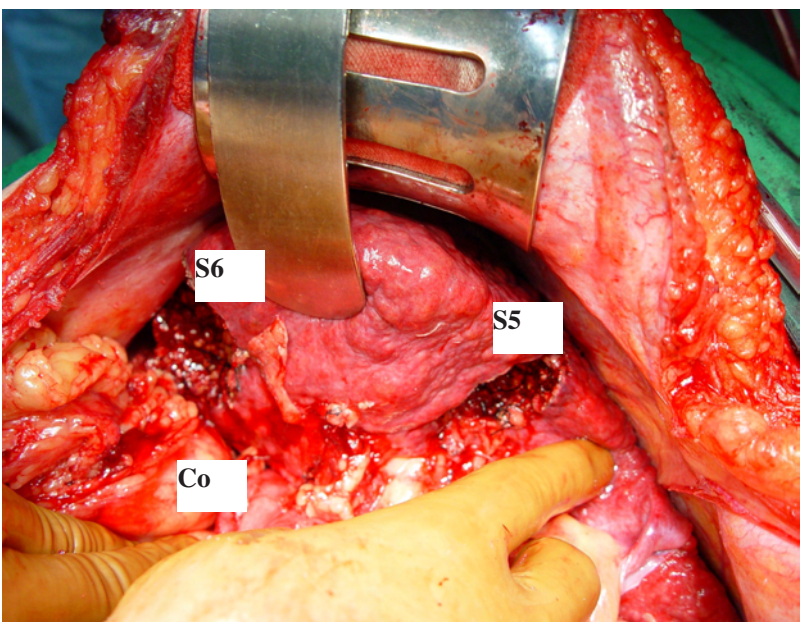
Intraoperative assessment

Although some authors do not advocate the routine use of intraoperative ultrasonography (IOUS),[46] the author and others[3,5,10,16,32] suggest that IOUS is an indispensable tool for liver resection in cirrhotic patients. HCC is usually a fragile tumor.[1,4,29] For an invisible, impalpable, deeply seated soft tumor hidden in a hard liver, the location of the tumor cannot be easily defined by intraoperative palpation and inspection. In contrast, in resection of a deeply seated hard tumor such as a colorectal metastatic cancer or a cholangiocellular carcinoma, the tumor can be easily defined by palpation because these cancers occur in soft normal livers and rarely in cirrhotic livers. Moreover, a blind wide liver resection is hazardous in a cirrhotic patient whose liver function is compromised. Furthermore, the relationship of the tumor to the main intrahepatic vessels can be determined by IOUS; preservation of these vessels is important in cirrhotic liver resection. The liver parenchymal transection plane can be monitored by real-time IOUS during surgery. The relationship of the transection plane to the major hepatic vessels can be seen. In addition, for patients with a posthepatitic cirrhotic liver when an HCC develops in a background of many regeneration nodules, the differentiation of these nodules from HCC during operation can be determined by IOUS findings (Fig. 2), due to the different echogenic patterns between HCC and regeneration nodules. IOUS is therefore essential for the resection of HCC in cirrhotic livers.

Controlling bleeding and limiting blood transfusion in cirrhotic patients

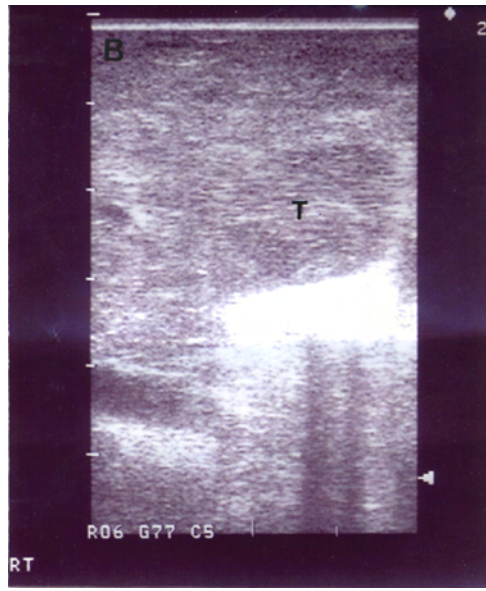
Blood transfusion usually results in high postoperative morbidity and mortality after liver resection.[4–6,13] Blood transfusion also causes poor

long-term outcomes after HCC resection because it compromises the immunity of the hosts.[3,24–26] It is well known that cirrhotic patients have bleeding tendency. Coagulation defects due to poor liver function, thrombocytopenia due to hypersplenism, and development of perihepatic collaterals due to portal hypertension can cause operative bleeding in cirrhotic liver resection.[4,6,18,20] Operative blood loss is generally estimated by the sum of the blood in the suction container and in the gauze.[18,19,24,25]

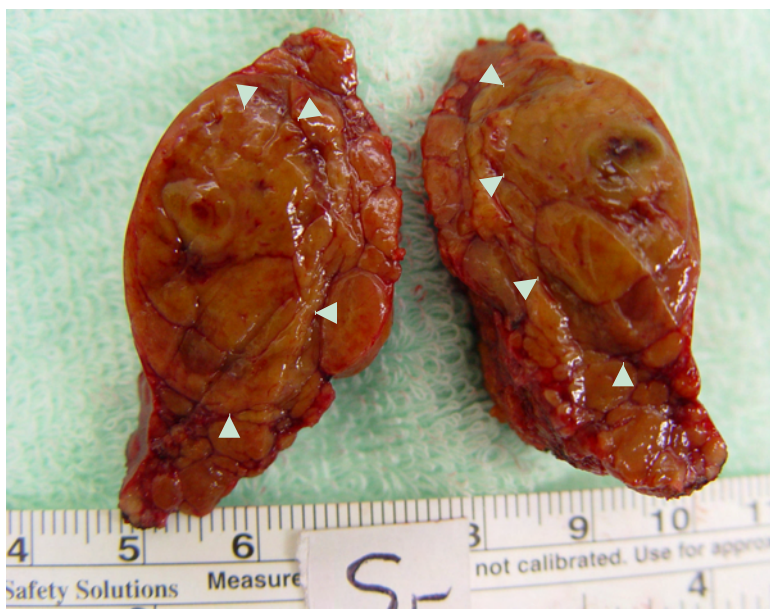


(A)

Fig. 2. The patient had hepatitis B virus (HBV)-related macronodular liver cirrhosis. His platelet count was 35 000/mm^3, and his ICG 15-min retention rate was 37.5%. He underwent a concomitant splenectomy and two wedge resections of the liver for two HCCs. (A) The liver cut surface over S5 and S6. Co: colon. Please note multiple regeneration nodules on the liver surface. (B) Both tumors were impalpable and invisible from the liver surface. They were shown as hypoechoic lesions (T), which could only be detected by IOUS. (C) The resected specimens: (C-1), S5 tumor; (C-2), S6 tumor (arrowheads). Both tumors were well-differentiated HCCs. Grossly, they were difficult to differentiate from the surrounding cirrhotic nodules.

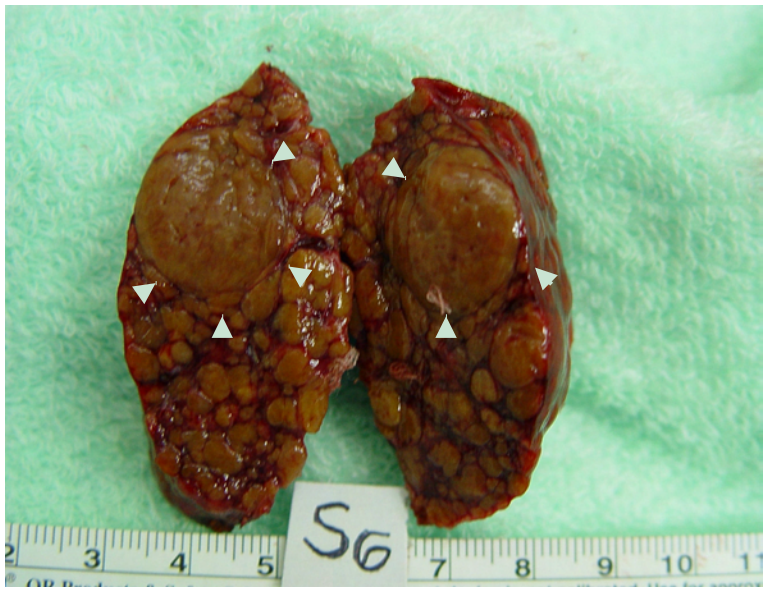


(B)



(C-1)

Fig. 2. (*Continued*)



(C-2)

Fig. 2. (*Continued*)

The policy for blood transfusion in general surgical procedures is to replace the operative blood loss,[6,25] which cannot be estimated accurately if there are ascites in the abdomen.[18,19,22] A cirrhotic liver is usually surrounded by many thick lymphatic ducts.[13,19] If the hepatectomy requires mobilization of the liver, these lymphatic ducts are divided. The leaked lymph may be considered as blood loss.[18,19] Moreover, if hepatectomy is performed under the hepatic inflow blood occlusion technique, intestinal congestion is inevitable to occur, with subsequent ascite formation.[19,22] The amount of ascites increases with the total inflow occlusion time; thus, the actual amount of operative blood loss is overestimated. If the blood transfusion policy in cirrhotic liver resection follows the policy for the general surgical procedures, the amount of transfused blood will be more than the actual blood loss.[18–22] In addition, blood transfusion in cirrhotic liver inevitably results in an increase of total bilirubin in the early postoperative period.[18,19,22] Restriction of blood transfusion is an important policy in cirrhotic liver resection.[22] Actually, blood transfusion is not necessary in most cirrhotic liver resections when the estimated blood loss is less than 1500 mL.[19]

To reduce operative bleeding, several techniques have been used. Although some authors are reluctant to use intermittent hepatic inflow occlusion — 15-min occlusion and 5-min release in total occlusion; 30-min occlusion and 5-min release in hemihepatic occlusion[18,47] — due to the fear of ischemia-reperfusion injury,[10,14,46,48] this technique is easy to use in liver resection[1,3,5,16,18] and reduces intraoperative blood loss. Our experiences showed that cirrhotic patients tolerated prolonged intermittent liver ischemia with an overall ischemia time of over 200 min.[18] Recently, other surgeons have extended the intermittent clamp time to over 300 min in a diseased liver.[49]

There are many techniques and tools for liver parenchymal transection. During the early days of liver surgery, Lin *et al.*[7] advocated the finger fracture technique; however, this technique is rough and experience-demanding. Nowadays, most surgeons prefer to use the Cavitron ultrasonic dissector and aspirator (CUSA) for parenchymal liver transection[10]; it is very effective for noncirrhotic liver resection,[49] but less so for cirrhotic liver resection. In experienced hands, a randomized trial did not show any benefit of the CUSA when compared with the Kelly crush method.[50] Clinically, we use the Kelly crush method for liver parenchymal transection, as the power of crush of the liver parenchyma can be controlled by the surgeons according to the severity of cirrhosis.[3,18,51]

Reduction of central venous pressure and decrease of ventilation volume by the anesthesiologist during liver transection are also important to reduce bleeding from the backflow of blood.[3,10,32,51] Since both the cirrhosis and the liver resection can result in a hyperfibrinolytic state, bleeding in liver resection can be reduced by using an antifibrinolytic agent. Blood-transfusion–free hepatectomy in a large group of patients has been reported by Wu *et al.*[51]

Postoperative assessment

Patient management

In the postoperative period, low-dose dopamine (3–5 μg/kg body weight/min) can be given[52]; this increases portal blood flow and improves the recovery of liver function.[32,52] Wu *et al.*[3,32] use this treat-

ment strategy until the bowel function resumes completely. Branched-chain amino acid (BCAA)-enriched fluid should be administered to maintain a positive nitrogen balance after cirrhotic liver resection. Nutritional support may prevent postoperative pulmonary complications and other septic complications,[31] resulting in an early recovery.[53] Albumin should be infused to avoid ascite formation if the postoperative serum albumin level is less than 3 g/dL.

Infection control

Controlling infection after liver resection is important because liver resection results in a large dead space with necrotic tissues on the cut surface of the liver.[53] Cirrhosis on its own is an immunocompromised state,[13,23] and infection is dangerous in the postoperative period.[54] Although postoperative prophylactic antibiotics after liver resection are used routinely by many liver surgeons,[10,13,15,16] the inappropriate use of antibiotics causes problems. The routine use of postoperative antibiotics as prophylaxis is not necessary in liver resection for liver tumors if preoperative bowel preparation has been performed.[53]

Policy of intra-abdominal drain

Since liver resection results in a large dead space into which fluid accumulates, a drainage tube is routinely used by many surgeons. In addition, if bile leakage occurs, the drainage tube may prevent the formation of an intra-abdominal abscess.[54] However, some prospective randomized studies suggest that the placement of drains after liver resection is unnecessary or even contraindicated in cirrhotic liver resection.[55–57] With the advancements in interventional radiology, intra-abdominal fluid collections can be aspirated totally.[55–57] Moreover, the inappropriate placement of a drain results in problems.[57] A total of 100 consecutive living donor liver resections for liver transplantation (all had a normal liver) without the need for drainage has been reported.[58]

Drainage tubes may not be necessary if an anatomical right or left hepatectomy is performed. However, for Couinaud's segment-oriented

liver resection, especially in central liver resection (segmentectomy VIII), mesohepatectomy (resection of segments IV, V, and VIII; Fig. 1), anterior sectionectomy (segmentectomy V and VIII), or segmentectomy IV in which a big transection plane is required,[47] drainage should be used. Such liver transection planes are bigger than those in right or left hepatectomy.[47] As the exact boundaries of each Couinaud's segment are not consistent and identical, some bile ductules of the removed segments may remain in the liver remnant; thus, the possibility of bile leakage is higher. In our practice, soft drains are placed around the liver transection plane and are removed within the next 3 to 4 days when the drainage becomes serous, clear, and with no evidence of bile leakage.[3,32]

The correct placement of drainage tubes prevents fluid accumulation and abscess formation.[54] Nevertheless, prospective randomized trials to test the efficacy, side effects, and cost-effectiveness of drains after such types of liver resection should be performed.

Conclusions

Liver resection should be considered as a treatment option for HCC in a cirrhotic liver. Adequate knowledge on the problems associated with cirrhosis leads to management strategies with good patient selection, logical decision on the safe extent of hepatectomy, and appropriate postoperative management. Cirrhotic liver resection is no longer considered as a risky operation. Although liver transplantation has been advocated for HCC in a cirrhotic liver, in the circumstances of insufficient liver donation, liver resection remains the best treatment option for patients with HCC and even recurrent HCC.

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14

Preoperative Portal Vein Embolization

Takuya Hashimoto and Masatoshi Makuuchi

Introduction

Currently, hepatic resection is considered to be the only curative treatment for large and/or multiple hepatocellular carcinomas (HCCs) because liver transplantation or ablative therapy is not indicated for most of these tumors. In patients with large and/or multiple HCCs, major hepatic resection (the resection of three or more Couinaud segments)[1] is often required to achieve good results. Moreover, since HCC frequently metastasizes via the portal venous system, anatomic hepatic resections including right or left hemihepatectomy provide better long-term results.[2–5]

Although recent advances in hepatobiliary surgical techniques have improved both the short- and long-term outcomes after hepatic resection for liver tumors, coexisting impaired hepatic functional reserve is still a major cause of operative morbidity after extensive hepatic resection. Because most patients with HCC have impaired hepatic functional reserves due to hepatitis B or C virus–associated liver cirrhosis, the

amount of liver parenchyma that can be safely resected in these patients is extremely limited. This dilemma limits the number of HCC patients who can benefit from hepatic resections and results in a low resectability rate.[6,7]

In 1982, Makuuchi *et al.*[8,9] first carried out preoperative portal vein embolization (PVE) in a patient with hilar bile duct carcinoma who was scheduled to undergo a major hepatic resection in order to increase the safety of this procedure. This approach is based on the concept of the hepatic atrophy–hypertrophy complex. This concept dates back to 1920, when Rous and Larimore[10] demonstrated that ligation of a major branch of the rabbit portal vein resulted in atrophy of the ipsilateral hepatic lobe and hypertrophy of the contralateral lobe. Later, in 1975, Honjo *et al.*[11] ligated the ipsilateral portal venous branch in patients with HCC in an effort to suppress tumor growth. Although this approach did not succeed in preventing tumor growth, it did produce marked atrophy of the occluded part of the liver. Likewise, patients with hilar bile duct carcinoma involving a branch of the portal vein that caused partial liver atrophy and corresponding hypertrophy of the contralateral portion of the liver[12] experienced an uneventful postoperative clinical course after extensive hepatectomy.

Major hepatectomy produces volume reduction of the liver and an incremental increase in portal pressure immediately after the operation. If PVE is performed preoperatively, increase in portal pressure has already occurred at the time of PVE and an increase in size can be observed in the other part of the liver. PVE dramatically increases the safety of hepatic resection; consequently, the indication of PVE is extended to diseases such as HCC, intrahepatic cholangiocarcinoma, and metastatic liver tumors. At present, PVE is recognized worldwide as a standard preoperative interventional procedure in patients with HCC with a borderline size of the future remnant liver (FRL).[13–18]

However, the indications for PVE in patients with HCC continue to be debated for the following reasons: (1) the livers of most HCC patients are compromised by an underlying liver disease, and the capacity for liver regeneration after PVE may be impaired under such conditions[19–21];

(2) because most HCCs are hypervascular tumors fed mainly by arterial blood flow, cessation of the portal flow induces a compensatory increase in arterial blood flow in the embolized segments,[22] resulting in rapid progression of the tumors after PVE; and (3) arterioportal shunts are frequently found in cirrhotic livers and in HCC, and these shunts may attenuate the effects of PVE and there is even a risk of spread of the embolic material to the FRL.

In this chapter, we first make some general remarks on PVE and then focus on PVE for HCC patients.

General Remarks on PVE

Technique of PVE

PVE can be performed through one of three standard approaches: the intraoperative transileocolic venous approach, the transhepatic contralateral approach (i.e. portal access via the FRL), and the transhepatic ipsilateral approach (i.e. portal access via the liver to be resected). These approaches are chosen on the basis of the type of hepatic resection planned, the location of the tumor, the extent of embolization, the type of embolic agent used, and the availability of surgical and radiological facilities. For every one of these procedures, portal vein anomalies should be looked for by ultrasound (US) or computed tomography (CT) prior to PVE (Fig. 1) and by direct portography at the commencement of embolization (Fig. 2), paying particular attention to whether or not second-order branches originate close to or independently of the main portal trunk. Right anterolateral fluoroscopy is recommended during embolization of the branches to segments 6 and 7.

Rare technical failures are usually associated with catheterization difficulty due to severe angulations between the portal branches, and migration of embolization materials. To overcome narrow angulations, several preshaped catheters have to be prepared. The use of a balloon-tipped catheter is advocated to avoid the latter complication.

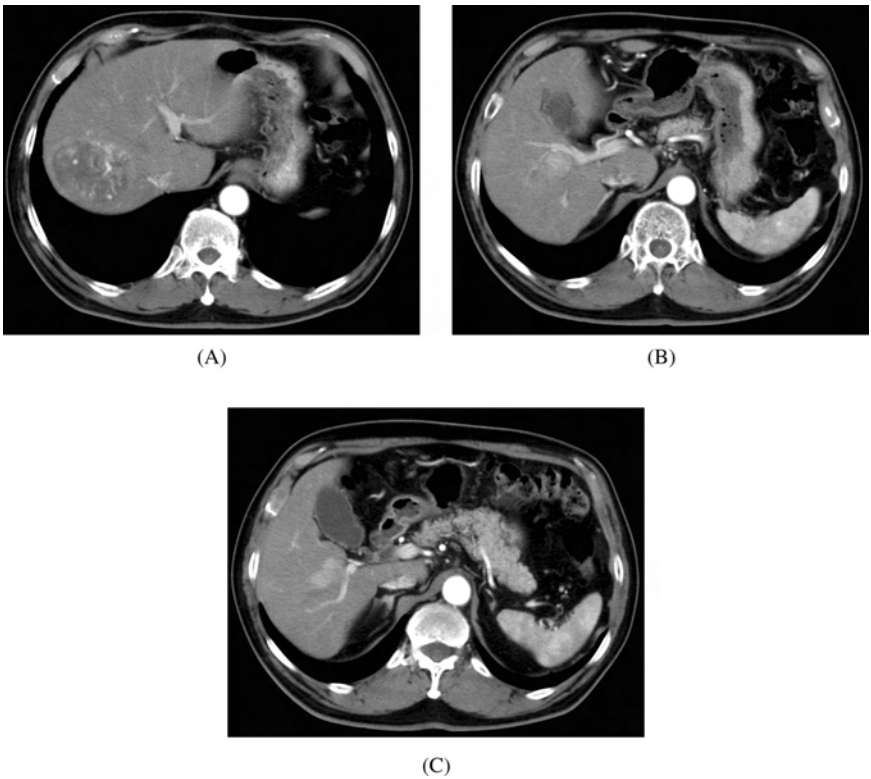
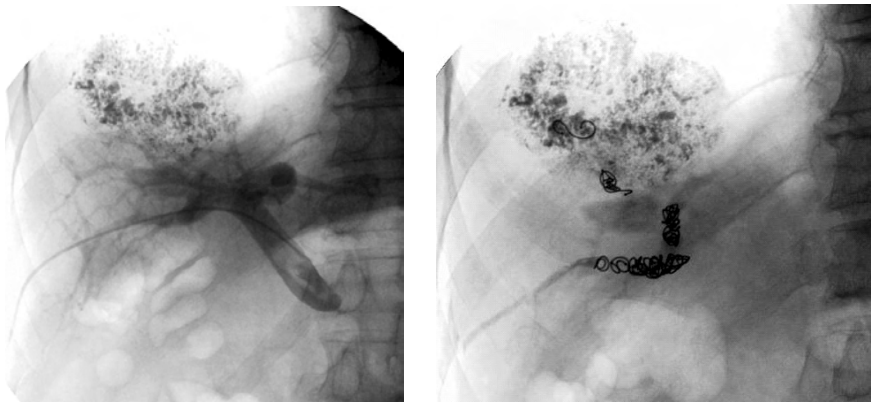


Fig. 1. CT scan images of a 74-year-old man with HCC. (A) The tumor is located in segments 8 and 7. (B,C) The tumor is budding near the hepatic hilum between the right paramedian and right lateral portal branches. The percentage of the volume of the left liver to the volume of the whole liver without the tumor is 46.9%. The indocyanine green retention rate at 15 minutes (ICG-R15) was 11%. A right hepatectomy was planned.

Transileocolic venous approach

The transileocolic venous approach is performed during laparotomy under general anesthesia by direct cannulation of the ileocolic vein through the introduction and advancement of a balloon catheter into the portal vein for subsequent embolization under fluoroscopic guidance.[8,9] This approach is often performed when an interventional radiology suite is not available, when the percutaneous approach is not feasible,



(A) (B)

Fig. 2. Transhepatic ipsilateral right PVE with gelatin sponge particles, thrombin, and coils in a 74-year-old man with HCC in segments 8 and 7. (A) Anteroposterior flush portogram obtained before right PVE with the use of a 6-F vascular sheath in the segment 6 portal branch and a 5-F flush catheter in the main portal vein. Iodized oil, which had been administrated during a previous transcatheter arterial chemoembolization (TACE), has accumulated in the tumor. (B) Completion of PVE. Embolized material remains in the portal veins and can be faintly visualized. Coils were placed at the root of the portal branches.

or when additional treatment is needed during the same surgical exploration.[23]

One advantage of this approach is the full evaluation of the extent of the tumor at the time of PVE, including the detection of peritoneal dissemination and hilar lymph node metastases.[24] Catheterization of all the portal tributaries is simple, even with anatomical variations. However, open laparotomy under general anesthesia is required, and this technique is not suitable for patients with a history of previous lower abdominal surgery. Intestinal ileus has been reported.[24]

Transhepatic approach

The transhepatic procedure can be performed under local anesthesia with or without intravenous sedation. US examination of the liver is performed to determine the best access route to the portal venous

system. Under aseptic conditions, access to the portal venous system is gained under ultrasonic and fluoroscopic guidance. The contralateral approach (access through the FRL) is technically easier than the ipsilateral approach (access through the portion of the liver to be resected), especially in the presence of the tumor at the puncture line or of anatomical variations.[25]

The transhepatic contralateral approach was initially the most commonly used technique.[26] For embolization of the right portal branches, a branch of the left portal system is accessed and a balloon occlusion catheter is advanced through an introducer into the branches of the right portal tree for embolization. The major advantage of this approach is the operative ease of catheterization of the desired right PV branches from the left side. However, the shortcoming of this method is that the portal vein in the FRL is punctured. Iatrogenic lesions of the FRL lobe, including hematoma, portal vein wall dissection, and portal vein thrombosis, have been described in a multicenter review.[27]

The transhepatic ipsilateral approach was first described by Nagino *et al.*[28] For this approach, a peripheral portal venous branch in the liver to be resected is accessed and a sheath is advanced into it. One apparent advantage of the ipsilateral approach is that the FRL is not injured. Embolization materials or coils can be placed along the puncture line upon completion of the procedure to prevent post-PVE hemorrhage. However, this approach is technically more demanding than the contralateral approach. A balloon occlusion catheter that has a side lumen opening just proximal to the balloon is occasionally required to avoid unintended embolization of the FRL. When there is severe angulation in the right portal branches, the technique usually requires the use of reverse-curved catheters. Furthermore, it is usually difficult to perform post-PVE portography or portal pressure measurement to confirm the efficacy of embolization with this procedure.

Embolization materials

There is no general consensus regarding the ideal embolization material for PVE (Table 1). Biomaterials including gelatin sponge particles with thrombin[24] and fibrin glue (combination of fibrinogen and

Table 1. Hypertrophy of left liver after right liver PVE.

Reference	Year	Underlying liver	Embolizing material	Interval between PVE and operation (or evaluation)	Volume increase (%)[a]
29	1995	Normal	Fibrinogen + thrombin + iodized oil	2	11
32	1997	Fibrosis F1–F4	Absolute alcohol	4	27
24	1999	Normal	Gelatin sponge + thrombin + iodized oil	2	10
15	2000	Normal	*N*-butyl-2-cyanoacrylate + iodized oil	4	11
48	2000	Normal	Gelatin sponge	3	11
		Fibrosis F1–F4			9
37	2001	Normal	Gelatin sponge	3	8
30	2002	Normal	Polyvinyl alcohol + coils	4–6	8
52	2003	Normal	*N*-butyl-2-cyanoacrylate + iodized oil	3–7	16
		Fibrosis F3–F4			9

[a] Increase in the future remnant liver volume–to–total liver volume (FRLV/TLV) ratio.

thrombin),[28,29] synthetic glue (*N*-butyl-2-cyanoacrylate),[25] synthetic embolization particles (polyvinyl alcohol),[30,31] coils, iodized oil, and absolute ethanol[32] are used. These materials have yielded different rates or degrees of hypertrophy of the unembolized segments, and the choice of the embolization material usually depends on the surgeon's or institute's preference.

Biomaterials are absorbable and thus allow recanalization, while unwanted outcomes induced by migration of embolization materials into the portal branches of the FRL are minimal or absent.[24] *N*-butyl-2-cyanoacrylate immediately polymerizes upon contact with blood and has a permanent embolizing effect. Despite the long-lasting embolization effect, accompanying massive peribiliary fibrosis and portal vein casting[25] can lead to difficulty in hilar dissection or discrimination of tumor invasion.[33] Polyvinyl alcohol particles have a smaller diameter (150–100 μm) than gelatin sponge particles (500–100 μm). This material is selected because of its safety, minimal periportal reaction, and enduring embolization effect when used in combination with coils.[31] Coils and iodized oil are usually used in combination with this material. In particular, iodized oil produces a long-lasting portal cast, which can be viewed on follow-up CT scans. PVE with absolute ethanol has been proposed because of its strong coagulation effect.[32] The hypertrophy appears to be more significant than with other materials (Table 1), but PVE with absolute ethanol has been associated with a marked increase in serum aspartate transaminase (AST) and alanine transaminase (ALT) levels, secondary to liver necrosis.[32] We have to consider the time between PVE and liver regeneration because liver regeneration is not complete until a certain time period after PVE.

Portal pressure after PVE

Total portal venous flow (mL/min) is thought to be unchanged after PVE because the liver does not have an intrinsic ability to modulate portal flow, which is a function of extrahepatic and systemic factors. In a human PVE study, this principle was confirmed using Doppler US.[34] Because the same volume of portal blood flows through the nonembolized part of the liver after PVE as the portal flow to the whole liver prior to

PVE, portal pressure in the nonembolized liver is elevated immediately after PVE by 4.9 ± 2.7 cm H_2O.[35] A similar increase was observed in cirrhotic patients with a higher baseline portal pressure.[17] The elevation of portal pressure is thought to be transient, with pressure gradually returning to the baseline value in 2–3 weeks, as indicated by the portal flow velocity (cm/s) changes measured using Doppler ultrasound.[36]

Clinical course after PVE

Signs and symptoms of postembolization syndrome due to PVE itself, such as pain, fever, nausea, and vomiting, are milder and lighter than transcatheter arterial embolization (TAE). Most patients experience a mild fever following PVE that subsides within 2–3 days. Changes in liver function as reflected by an increased total bilirubin value and prolonged prothrombin time are mild and transient, returning to their baseline values 2–3 days after PVE. Serum AST and ALT values are stable in around 50% of patients; and for the remaining patients, the values are mildly elevated on day 1, returning to baseline values 4–7 days after PVE.

These findings suggest that inflammatory and/or necrotic reactions after PVE are minimal, if present.[24] The exceptions are when absolute ethanol is used for embolization[32] and when PVE is carried out after TAE.[17,18] In both situations, PVE is followed by marked AST and ALT elevations that tend to return to their baseline values at the end of 2 weeks, when hepatectomy can then be scheduled.

Volumetric changes after PVE

In order to determine whether PVE is necessary before hepatic resection and to assess the degree of FRL hypertrophy, the ratio of FRL volume to total liver volume (the FRLV/TLV ratio) is a widely used parameter. CT scan with contrast is the most commonly used method to calculate noncancerous total liver and FRL volumes. CT examination should be performed before and after PVE. Multislice helical CT scanning with contrast administration allows accurate volumetric measurement

by subtracting the small tumor volumes and the vasculobiliary structures, even down to the Couinaud's segment level.

PVE leads to an increased segmental volume in the nonembolized liver and a decrease in that of the embolized liver, homogeneously maintaining a constant total liver volume. The regeneration rate in the noncirrhotic liver was reported to be 12 cm^3 per day 2 weeks after PVE,[13,29] then fell to 11 cm^3 per day at 4 weeks[29] and 6 cm^3 per day at 32 days.[25] In general, a 30% increase in nonembolized liver volume as an absolute value and a 10% increase, as expressed by the FRLV/TLV ratio, are seen 2 weeks after right PVE (Table 1; Fig. 3).

Various factors have been reported to affect the regeneration rate after PVE. The greater the FRL volume before PVE, the smaller the volume increase after PVE.[14,24,37] Various materials used for embolization resulted in somewhat different magnitudes of hypertrophy (Table 1). Hypertrophy appeared to be modest when biological materials such as Gelfoam and fibrin glue were used, most probably due to the occurrence of progressive recanalization. Absolute alcohol was reported to achieve

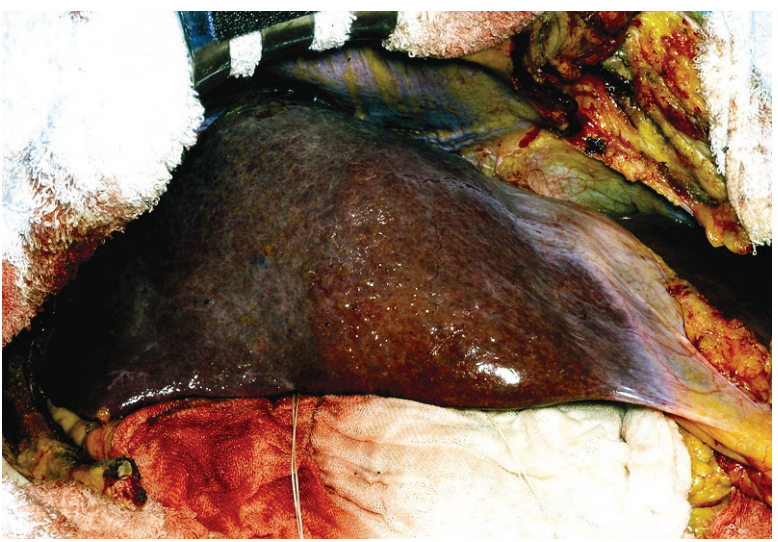


Fig. 3. Gross appearance of the liver of a 74-year-old man with HCC after selective TACE and right PVE. The left liver is hypertrophied, whereas the right liver is atrophied with a darker-colored and wrinkled surface.

the highest degree of regeneration with marked increases in AST and ALT levels, secondary to liver necrosis. Diabetes, obstructive jaundice, and active hepatitis have been reported to hamper the regeneration process.[24,29] In cirrhotic patients, the regeneration rate is slower than in noncirrhotic patients. The reported regeneration rate was 9 cm^3 per day at 2 weeks.[13,25]

Histological changes after PVE

In a human study, liver tissues obtained 3 weeks after PVE showed an almost normal microscopic structure in both the embolized and nonembolized lobes. However, in the embolized lobe, dilatation of sinusoids with decreased hepatocyte density and hepatocyte apoptosis, especially in the pericentral area, was observed.[38] There were no signs of necrosis or inflammation in the embolized lobe. Exceptionally, liver tissue in the embolized lobe has shown clear evidence of necrosis when the embolizing material was absolute ethanol[32]; when cyanoacrylate was used, it produced peribiliary fibrosis.[25] In contrast, microscopic findings in the nonembolized liver showed hepatocyte replication, as evidenced by the increased mitotic figures and other parameters of cell proliferation such as the levels of proliferative cell nuclear antigen and Ki-67.[38,39] Hepatocytes in this liver were histologically characterized by basophilic cytoplasm and abundant binuclear cells, and they were small — the observation of which provided indirect evidence of hepatocyte proliferation.[38]

Functional changes after PVE

Cellular hyperplasia and the resulting partial hypertrophy do not necessarily signify functional gain in the corresponding part of the liver, considering that proliferating isolated hepatocytes lose their differentiated hepatocyte-specific functions. Most former reports investigating liver function after PVE assessed whole-liver function, including both the embolized and nonembolized lobes. The overall functional hepatocyte number, as estimated by the clearance of antipyrine (a prototype low-extractable drug), showed similar values before and 2 weeks after

PVE.[40] When the ATP concentrations and hepatic energy reserves per gram of liver tissue were assessed in the nonembolized lobe 3 weeks after PVE, these values were similar to those of the control tissue.[41] Likewise, the nonembolized lobe uptake of technetium-99m–galactosyl human serum albumin (^{99m}Tc-GSA), a ligand bound to asialoglycoprotein receptors on the hepatocyte cell membrane, showed a rapid increase 1–2 weeks after PVE.[42,43] These findings demonstrated the volume increase in the nonembolized liver to be accompanied by a parallel increment in liver function in the corresponding part.

PVE for HCC

Indication of PVE for HCC patients

For large and/or multiple HCCs, major hepatic resection is often required to achieve a successful cure. Likewise, segment-oriented anatomical resection is recommended even for small HCCs to prevent postoperative recurrence.[4,5,44] When selecting the surgical procedure (especially the extent of functional liver parenchyma to be resected), one should consider the hepatic function of the patients, which is often impaired because of hepatitis B or C virus–associated liver fibrosis/cirrhosis. If the scheduled FRL volume seems to be insufficient to maintain the patient's metabolic demand, the performance of PVE is considered. The indication and selection criteria of hepatectomy for an HCC patient vary from institution to institution.

In general, because right hemihepatectomy for HCC patients requires surgeons to remove approximately two thirds of the functional liver mass, preoperative PVE for the right portal vein is often considered in most institutions. Right hemihepatectomy is scheduled when (1) there is a large tumor in the right liver, (2) there are multiple tumors in the right liver, (3) the tumor is close to the bifurcation of the right portal vein, and (4) macroscopic vascular invasion to the first-ordered branches of the portal vein or bile duct is revealed. Other major resections, including extended right or left hemihepatectomy and left hemihepatectomy,

are also thought to be indications for PVE of the corresponding portal veins.

Kubota *et al.*[45] proposed the indication for PVE according to the patient's condition and liver function. In brief, PVE is indicated when the remnant liver is expected to be less than 40% of the preoperative liver volume in patients with normal liver function (no jaundice, ICG-R15 <10%), or less than 50% in patients with liver dysfunction (obstructive jaundice, ICG-R15 10%–19%).

Role of transcatheter arterial chemoembolization (TACE)

Transarterial chemoembolization (TACE) is one of the treatment options for nonresectable HCCs. Minagawa *et al.*[46] reported that hepatic resection with preoperative TACE was an effective therapy in selected patients who had HCC with portal venous tumor thrombus. However, it is controversial as to whether TACE should be performed preoperatively for all HCC patients. In several reports on PVE in HCC patients, most patients underwent selective or nonselective TACE before PVE and hepatectomy.[14–18,32,47,48]

One of the aims of using TACE is to enhance the effect of PVE. Sugawara *et al.*[47] showed that, by using a multiple linear regression analysis, only previous TACE significantly predicted the atrophy effects of PVE. Recently, the effect of previous TACE on the regeneration of nonembolized liver in cirrhotic patients was also confirmed by Ogata *et al.*[18] The combination of TACE and PVE resulted in more damage to the embolized liver and a better hypertrophy ratio. Examination of the resected specimens revealed that the necrosis of the noncancerous liver parenchyma was minimal in most cases, although the necrosis of the HCC tumors was marked.[17] Moreover, TACE strengthened the effect of PVE by first embolizing any arterioportal shunt, which is frequently found in cirrhotic livers and HCC tumors.

The other aim of TACE before PVE is to prevent tumor progression during the period between PVE and the planned hepatectomy. During the waiting period, the tumor volume calculated from CT tended to decrease and tumor markers did not increase.[17] Sequential TACE

and PVE produced a remarkable antitumoral effect, but caused only a transient inflammatory effect, on the liver parenchyma.

The reported intervals between TACE and PVE range from 1 week to 6 weeks (Table 2). Given that a shorter interval between these two interventions results in more damage to the embolized liver, PVE is performed at least 2 weeks after TACE in most institutions. However, Aoki *et al.*[17] proposed that, for HCC patients with chronic hepatitis (ICG-R15 <20%), PVE is deliberately performed after a shorter interval of 7–10 days because the effect of TACE is reduced as time passes. In this protocol, the ICG-R15 values before and after the sequential TACE and PVE procedures were similar in most cases, thus showing that liver function was not adversely affected by these procedures.[17] Ogata *et al.*[18] also used this sequential TACE and PVE strategy in cirrhotic patients with HCC before a right hemihepatectomy. They recommended that PVE be performed at least 3 weeks after TACE in cirrhotic patients.[18]

Effect of PVE on diseased liver

The regeneration of the nonembolized liver is summarized in Table 2. In general, the hypertrophy ratio in injured liver patients is inferior to that in the normal liver. The interval between PVE and hepatic resection varies. In Europe, evaluation after PVE is made after 4–8 weeks, while the interval is 2–4 weeks in most of the institutions in Japan. It is predicted that the longer the observation time after PVE, the larger the volume increase after PVE. Considering a number of reports on successful liver resection after PVE with short intervals, an interval of 2–4 weeks appears to be sufficient.

Unfortunately, some patients failed to show FRL hypertrophy after PVE and hepatectomy had to be abandoned. The lack of hypertrophy, despite a technically successful PVE, is most probably explained by the failure to increase portal flow to the FRL due to the presence and/or development of collateral vessels from the portal to the systemic circulation. In such patients, portal venous pressure was remarkably high before the PVE, suggesting that severe cirrhosis was present.[17] Similar phenomena have been reported by our group and others[48–50] after embolization in patients with portal hypertension. Based on these

Table 2. Results of PVE for HCC patients.

Reference	Year	Number of HCC patients	TACE	Interval between TACE and PVE	Embolization material	Interval between PVE and operation (or evaluation)	Volume increase (%)[a]
14	1997	23	Scheduled	2–6 weeks	Absolute alcohol	4–8 weeks	18
32	1997	7	Scheduled	2 weeks	Absolute alcohol	4 weeks	27
48	2000	26	Scheduled	2 weeks	Gelatin sponge	3 weeks	11
15	2000	10	Not scheduled	At least 2 weeks	*N*-butyl-2-cyanoacrylate + ionidized oil	4 weeks	16
16	2000	33	Scheduled	2 weeks	Gelatin sponge	3 weeks	12
47	2002	66	Not scheduled	4–8 weeks	Gelatin sponge (+ thrombin)	2–3 weeks	13
17	2004	17	Scheduled	7–10 days	Gelatin sponge + thrombin	2 weeks	11
18	2006	16	Scheduled	At least 3 weeks	*N*-butyl-2-cyanoacrylate + iodized oil	4–8 weeks	12
		16	Not performed		*N*-butyl-2-cyanoacrylate + iodized oil	4–8 weeks	8

[a]Increase in the FRLV/TLV ratio.

observations, Kianmanesh *et al.*[51] proposed that, in Child–Turcotte–Pugh class A patients, PVE preoperatively tested the capacity of the injured liver to regenerate and the absence of hypertrophy after PVE was a contraindication to major hepatic resection.

Results of hepatic resection after PVE

The main aim of preoperative PVE is to extend the indication of hepatic resection in those patients in whom resection would be impossible without PVE. The reported morbidity of hepatic resection after PVE ranges from 25% to 50%, while the mortality rate ranges from 0% to 10%.[15–18,48] From the viewpoint that PVE enables unresectable HCC to become safely resectable, these results appear to indicate the success of this procedure. Several reports have reported the long-term results after hepatectomy with PVE, with the 5-year overall survival rate ranging from 32.2% to 55.6% and the 5-year disease-free survival rate ranging from 17% to 46.7%.[15–18,48]

Farges *et al.*[52] conducted a randomized trial to evaluate the effect of PVE on right hemihepatectomy using patients with various diseases, including those with normal liver function. In their series, they obtained improvements in terms of total bilirubin, prothrombin time, and hospital stay by conducting PVE in patients with chronic liver disease ($n = 14$ each).[52] Based on these findings, they recommended the routine application of PVE in patients with diseased livers.

There are several retrospective studies comparing patients who have undergone hepatectomy with and without PVE to prove the effect of PVE for HCC patients. Azoulay *et al.*[15] performed PVE for 10 HCC patients scheduled for major hepatic resection in whom the estimated FRL volume ratio was less than 40%. They compared the surgical results of the 10 HCC patients who also had PVE with those of 19 HCC patients who had not met the PVE criteria and had undergone major hepatic resection without PVE. Nine of the 10 patients were able to undergo hepatic resection after PVE with zero mortality and 45% morbidity. On the basis that the long-term results were comparable between the two groups, they concluded that more patients with previously unresectable HCC in an injured liver could benefit from

resection. Tanaka *et al.*[16] reported results of the comparison between patients who underwent right hepatectomy for HCC with and without PVE. The postoperative mortality rate of the patients with PVE was similar to that of the patients without PVE. The tumor-free survival rate was similar in the two groups, while the 5-year survival rate of the patients with PVE was superior to that of the patients without PVE. Thus, although PVE did not prevent tumor recurrence after right hepatectomy for HCC patients with impaired hepatic function, it improved the prognosis, preserved hepatic function, and allowed treatment of tumor recurrence.

In contrast, another report expressed the opinion that PVE would not contribute to any improvement in the long-term results. Wakabayashi *et al.*[53] reported that, in 69 advanced HCC patients receiving major hepatic resection, multivariate analysis failed to show that PVE was a significant prognostic factor. In addition, remote metastasis involving lung, bone, or stomach was more frequently seen postoperatively in patients with PVE than in patients without PVE. However, this study was not a randomized trial and the interpretation of the results may be difficult. From the point of view that PVE can extend the operability for HCC patients who are considered to be unresectable without it, PVE should improve the long-term prognosis of advanced HCC patients.

Tumor progression during the waiting period after PVE is one of the problems. To overcome this problem, the concept of sequential TACE and PVE is applied. Aoki *et al.*[17] proposed the sequential TACE and PVE method with a short interval (7–10 days) between these two procedures. The procedures were safe and induced satisfactory hypertrophy of the nonembolized segments within approximately 2 weeks, with no deterioration in basal hepatic functional reserve or tumor progression. The 5-year disease-free and overall survival after curative hepatic resections in 17 patients with advanced HCC were 46.7% and 55.6%, respectively; these results would appear to represent a remarkable improvement. Recently, Ogata *et al.*[18] compared the patients with sequential TACE and PVE and the patients with PVE alone. In their protocol, the interval between TACE and PVE was 3–4 weeks. The short-term results, including morbidity and mortality of these two groups, were comparable; on the other hand, the disease-free

survival rate of patients who received sequential TACE and PVE was significantly higher than that of patients treated with PVE alone before hepatectomy. They concluded that this double preparation could achieve a higher complete necrosis rate of the tumor and a longer recurrence-free survival.

Conclusions

PVE induces atrophy of the embolized liver to be resected with compensatory hypertrophy of the contralateral part of the liver to be preserved. Total liver volume is changed not only for patients with normal liver function, but also for patients with chronic hepatitis and cirrhosis. By decreasing the risk of liver failure, the complication rate, and hospital stay, PVE is thought to widen the indications for liver resection for HCC patients who would otherwise be poor candidates for hepatectomy due to the inadequate estimated liver size and function after hepatectomy. TACE is a feasible preparation prior to PVE for HCC patients because it strengthens the effect of PVE and prevents tumor progression during the waiting period. A larger number of patients should be investigated to clarify the long-term benefits obtained from PVE.

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15

Intraoperative Ultrasound

Guido Torzilli and Henri Bismuth

Introduction

Hepatic surgery performed without a parenchyma-sparing policy carries significant risks of mortality, due to the not-negligible occurrence of postoperative liver failure. In particular, the coexistence of liver cirrhosis in most cases of hepatocellular carcinoma (HCC) has a considerable adverse effect on the surgical results: recent series are still associated with mortality rates above 5%.[1] For this reason and for the widely accepted ultrasound-guided percutaneous therapies,[2] surgical treatment of HCC has become less important in its role as the first-choice treatment for HCC.

On the other hand, imaging techniques have been introduced as aids for surgeons in performing liver resection. In fact, since the early 1980s, intraoperative ultrasonography (IOUS) has been employed in hepatic surgery on the cirrhotic liver.[3–5] Now, even cirrhotic liver resections can be carried out with no mortality, while at the same time the goals of oncological radicality and liver parenchyma sparing are achievable

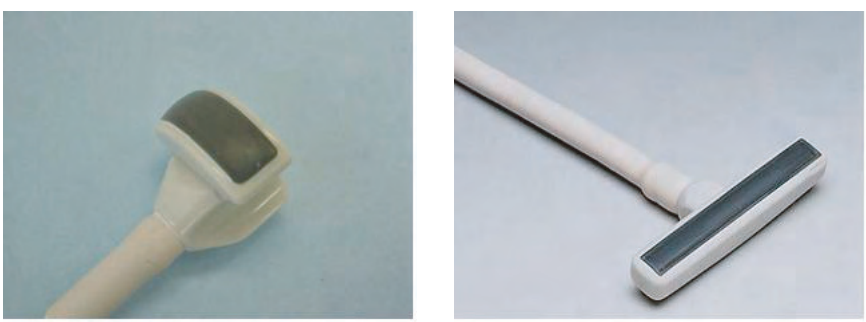
with the use of IOUS.[6,7] The recent demonstration of the feasibility and efficacy of contrast-enhanced intraoperative ultrasonography (CE-IOUS) has further added the relevance of IOUS in liver surgery.[8,9]

In this chapter, the technical aspects and the impact of IOUS during HCC surgery for staging and resection guidance are discussed.

Technical Aspects

For a proper IOUS, high-frequency echoprobes (7.5–10 MHz) are necessary and should have a flat shape to allow their use in deep and narrow spaces. For this purpose, T-shaped probes, interdigital probes, and microconvex probes are commercially available (Fig. 1). The main factors for probe selection are its volume, its stability, and the width of the ultrasonographic scanning window. The best probe should be small, thin, short in transverse length, stable, and with a wide ultrasonographic scanning window. In this sense, the microconvex probe represents the best compromise for all of these requirements (Fig. 1A). Indeed, the T-shaped probe (Fig. 1B) is more stable, but has a lower ratio between the lateral length and the ultrasonographic scanning window compared to the microconvex probe.

For CE-IOUS, we use a convex 3–6-MHz frequency and 1.88–3.76-MHz harmonic frequency transducer from Aloka (Aloka Co., Tokyo,



(A) (B)

Fig. 1. (A) Microconvex ultrasound probe for intraoperative use. (B) T-shaped ultrasound probe with the scanning area perpendicular to the wire axis.

Japan). In all patients, 4.8 mL of sulphur hexafluoride microbubbles (SonoVue®, Bracco Imaging, Italy) is injected intravenously through a peripheral vein by the anesthesiologist. For HCC, CE-IOUS is used to characterize any lesions that are newly detected at IOUS.[8] The rationale is to check the vascular pattern during contrast enhancement for each of the new lesions. It is very important to identify the arterial vascularization, which lasts from 20 to 30 seconds for HCC. As each nodule has to be carefully evaluated, multiple injections need to be carried out for multiple nodules. Intraoperative high-frequency probes, although retaining the advantages of small volume and stability, have less evident contrast enhancement effects and have limited value for CE-IOUS.

Ultrasound liver anatomy

A background of perfect knowledge of the liver anatomy (see Chapter 2), surgically and ultrasonographically, is required to perform IOUS properly. For surgical anatomy, the Brisbane 2000 terminology[10] is used. After entering the abdominal cavity, liver mobilization by dividing the round and falciform ligaments as well as freeing of all the adhesions to the anterosuperior and inferior surfaces of the liver should be carried out before liver exploration with IOUS (Fig. 2). Obviously, adhesions with other organs or structures should not be divided because of the possibility of tumor infiltration into these structures. IOUS is helpful in ruling out or confirming tumor invasion, and the planned surgical strategy may have to be changed accordingly.

By pulling onto the round ligament, the liver can be dragged inferiorly and posteriorly and the surface of the liver is widely exposed. The entire liver can be studied ultrasonographically by following the portal branches and the hepatic veins (HVs). The probe should be handled using just enough pressure to ensure good contact with the liver surface without compressing the intrahepatic vascular structures, in particular the HVs. The three main HVs are readily identified. By positioning the probe and tilting it upwards, the HVs can be traced to the confluence of the HVs into the inferior vena cava (IVC). Then, gently withdrawing the probe, the HVs can be traced individually inside the liver. HVs appear as echo-free zones in the liver parenchyma, and the vessel wall appears

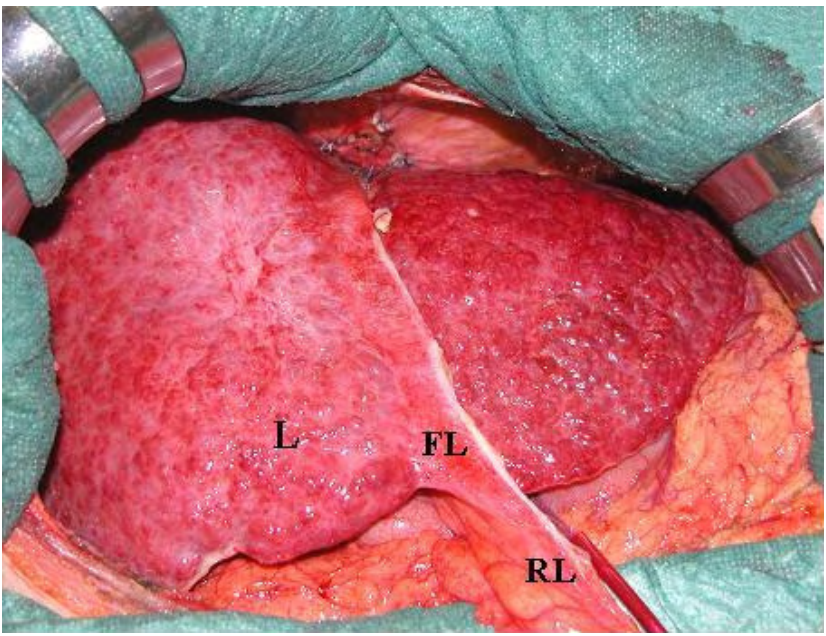
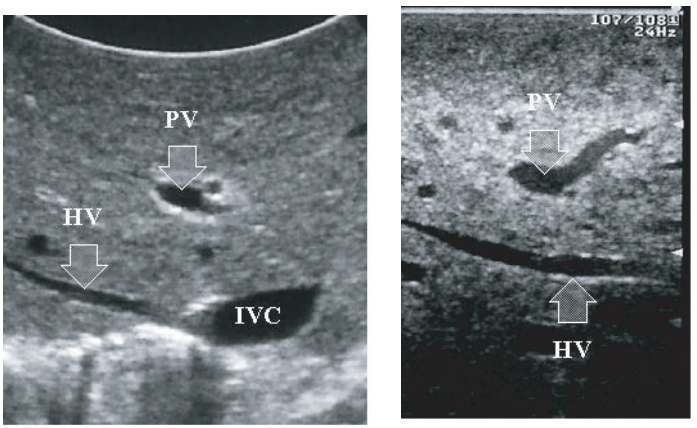


Fig. 2. Liver (L) exposure for IOUS. FL, falciform ligament; RL, round ligament.

as a thin hyperechogenic line (Fig. 3A). The HV wall can be thicker and its lumen thinner in the cirrhotic liver because of the stiffness of the liver (Fig. 3B).

The portal vein branches can be followed by positioning the probe horizontally on segment 4 to visualize the first-order bifurcation; then, the first-, second-, and third-order portal branches can be followed using the probe. Because of the presence of Glisson's capsule, the portal branches that run together with the arteries and the bile ducts have a thicker wall when compared with the HVs. These portal branches appear at IOUS as echo-free zones surrounded by a thicker hyperechogenic layer (Fig. 3A), and adjacent parallel thinner vascular structures which are visible are the arteries and bile ducts of the Glissonian triad. However, in principle, the distinction between HVs and portal branches should be based not only on their appearance, but also on their anatomical relationships. Indeed, in the cirrhotic liver, as already mentioned, the vessel wall of HVs can be thick and not immediately differentiable from that



(A) (B)

Fig. 3. (A) The portal vein (PV) and the hepatic vein (HV) — in this picture, the inferior right hepatic vein — have different thicknesses in their walls. In particular, the wall of the portal branch is thicker as it commonly happens. (B) Appearance of a cirrhotic liver at IOUS, with a portal vein (PV) and a hepatic vein (HV) visible in the same scan. Both vessels have similar wall thicknesses, which is not infrequent in the presence of a cirrhotic liver. IVC, inferior vena cava.

of peripheral portal branches (Fig. 3B). Following the portal pedicles at the sectional, segmental, and subsegmental levels and positioning them in relation with HVs, it is possible to precisely define the locations of the liver sections and segments by using IOUS.

The appearance of the bile ducts at IOUS is worth mentioning because of their peculiarity. Normally, bile ducts appear as thin echo-free zones in the Glissonian triad; once dilated, they appear more evidently as echo-free zones with a serpiginous path pattern (Fig. 4). The difficulty in the IOUS study of bile ducts is the segmental anatomy. Indeed, bifurcation of the sectional and segmental ducts is closer to the hilum when compared with the portal venous branches. Thus, on a single scan, it is possible to visualize more than a single segmental bile duct. If this fact is not recognized, it can be difficult to visualize which part of the liver is not well drained. Conversely, once recognized, IOUS can allow the exact definition of the bile duct anatomy, both under normal and pathological conditions.

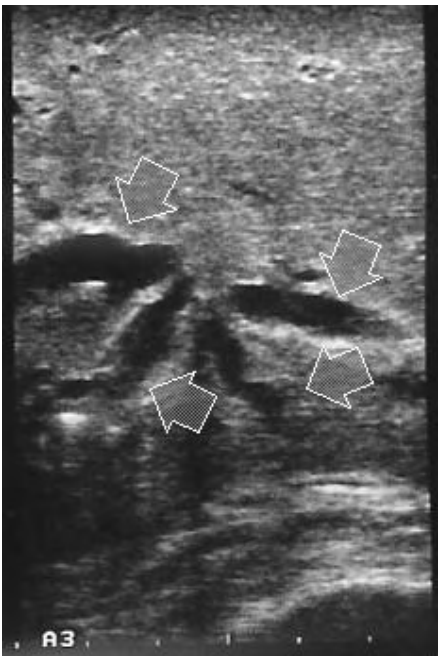


Fig. 4. At IOUS scan, the dilated intrahepatic biliary ducts appear as echo-free serpiginous areas, as shown in the illustration in which dilated segment 1 bile ducts are indicated by arrows.

Indications

The use of IOUS in liver resections can be schematically divided into two principal phases: (1) liver exploration for staging of the disease and planning of the surgical strategy, and (2) guidance of the surgical maneuvers.

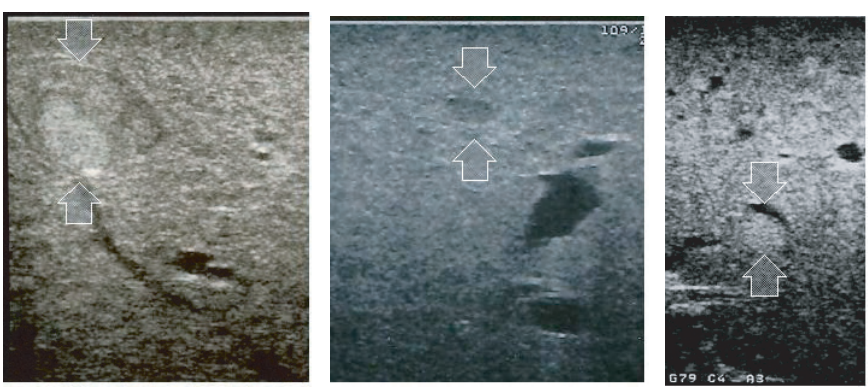
Liver exploration

Detection and differentiation of liver nodules

The hard and irregular surface of the cirrhotic liver makes the detection of small nodules by palpation difficult. IOUS allows the detection of new lesions in around 30% of cases[11]; as a consequence, IOUS has a

great impact on the surgical treatment strategy. However, with improvements in preoperative imaging technology, the impact of IOUS on operative decision making has decreased to around 4%–7% in more recent reports.[12,13]

The impact of IOUS on operative decision making depends on two main factors: the surgical policy of the individual team, and the type of tumor. If the surgical policy is to carry out major hepatectomies in a considerable number of patients, new nodules detected by IOUS within the same hemiliver would not modify the surgical strategy. Recently, because of the extensive use of IOUS to achieve parenchyma-sparing resections, major hepatectomies are carried out in the minority of patients.[6,7] Thus, the detection of new nodules intraoperatively becomes important in changing the surgical strategy. During surgery for HCC, it is usual for IOUS to detect many nodules in the cirrhotic liver. However, the minority of these nodules are tumors, thus adding the risk to overstage the tumors. It is important to be able to differentiate between these lesions at IOUS.[14] While nodules with a mosaic ultrasonographic pattern (Fig. 5A) are malignant in 84% of cases, only 24%–30% of hypoechoic (dark) nodules (Fig. 5B) and 0%–18% of hyperechogenic (bright) nodules (Fig. 5C) are neoplastic.[11,15]



(A) (B) (C)

Fig. 5. (A) A mosaic pattern lesion (arrows) at IOUS. (B) A hypoechogenic lesion (arrows) at IOUS. (C) A hyperechogenic lesion (arrows) at IOUS.

Even biopsy is not 100% fool-proof. The only nodule that can be easily differentiated intraoperatively from a HCC or a liver metastasis is a small hemangioma, which is often discovered primarily at IOUS. Liver hemangioma has a typical ultrasonographic pattern and, when compressed, changes its size and appearance (Fig. 6). Further improvements in the differential diagnosis of liver nodules using IOUS can be expected by the introduction and widespread use of CE-IOUS using the later generation of contrast agents.

Recently, the use of CE-IOUS has changed the operative strategy in 30%–40% of cases.[8,9] Tumor vascularity as a criterion for differentiating regenerative or dysplastic nodules from HCCs correlates well with histology. There is a progressive increase in unpaired arteries from dysplastic to neoplastic nodules in a cirrhotic liver.[16] Certainly, the pattern of vascular enhancement alone is not sufficient in differentiating

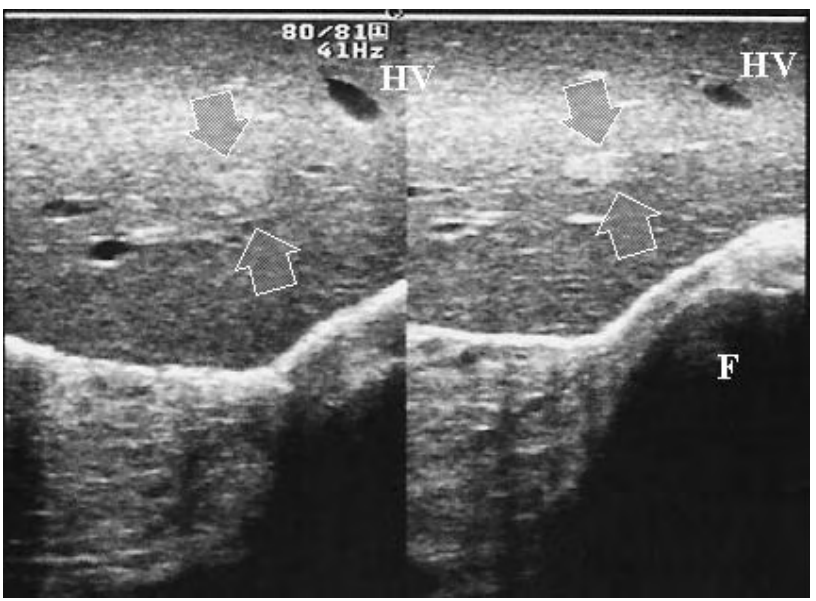


Fig. 6. Left: at IOUS, a small hyperechogenic nodule is found (arrows). Right: IOUS-guided liver compression modifies the size and shape of the nodule (arrows), and a hepatic vein (HV) branch is also compressed. This behavior at IOUS-guided compression and its echogenicity are compatible with a small hemangioma. F, finger.

malignant from nonmalignant nodules in a cirrhotic liver with 100% specificity. However, CE-US provides a differential diagnosis of focal liver lesions with 95% specificity.[17] A word of caution should be made here that this high specificity should not be extrapolated to CE-IOUS. Indeed, in IOUS, high resolution of ultrasonography can be achieved by putting the probe in direct contact with the liver; liver nodules smaller than 1 cm are often seen and need to be differentiated. For these nodules, the vascularity as a criterion for differential diagnosis is less specific. However, some further improvements can be expected.

In the early 1990s, attempts were made to carry out CE-IOUS using carbon dioxide as a contrast material. However, the need for arterial catheterization made this technique too invasive to be generally accepted.[18] In our preliminary experience, CE-IOUS provided remarkable results, either by adding information on the nodular vascularity in patients with HCC or by detecting nodules that were not visible at IOUS in patients with colorectal carcinoma with liver metastases.[9] Focusing on patients operated for HCC, the specificity of CE-IOUS was around 69%.[8] This value is not that high when compared with that reported for CE-US[17]; however, as we have mentioned, the small lesions in the CE-IOUS study can explain the discrepancy.

For tiny nodules, the neovascularity as a criterion for differentiation between malignant and benign lesions has limitations. A specificity of 69% is encouraging, as it means that we can provide proper information using this new technique in 7 out of 10 lesions detected at the time of laparotomy. For the remaining 3 lesions, even using histology may be difficult, as we know that there is no consensus between Western and Eastern pathologists on the definition of early HCC and dysplastic lesions.[16,19]

In practice, at CE-IOUS, we can follow in real time the enhancement of the liver parenchyma, with vessels appearing hyperechogenic instead of the echo-free pattern at nonenhanced US. Any lesion that remains hypoechogenic with or without inner vessels and with arterial enhancement before the remaining liver parenchyma should be resected (Fig. 7). Those lesions that disappear once the contrast enhances the liver are not considered neoplastic, and should not be resected.

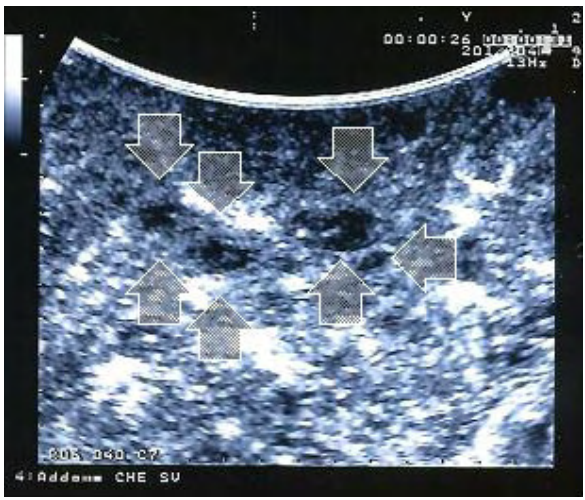


Fig. 7. At CE-IOUS, 31 seconds after contrast agent injection (see the time shown at the upper-right corner of the picture), 4 nodules in a cirrhotic liver are evidently shown as black holes (arrows). The central 2 nodules show hyperechogenic signals inside each of the nodules, which represents inner vessels; while the 2 lateral nodules show no hyperechogenic signals within the nodules. However, these latter 2 nodules are clearly distinguishable from the surrounding parenchyma.

Tumor location

IOUS allows an accurate three-dimensional reconstruction of the relationship between the tumor and the portal branches and HVs. This is a fundamental step in deciding on the proper surgical strategy. Indeed, a surgical decision should only be made using the portal branches and HVs as landmarks to reduce the risk of major postoperative morbidity and mortality. Defining the relationship between the tumor and the major vessels is relevant in planning the type of resection.[6,7] IOUS allows the surgeon to recognize if a HCC is (1) separated by some liver parenchyma from the vessel (Fig. 8); (2) in direct contact with the vessel but without invading its wall (Fig. 9); (3) invading the vessel wall or invading into a bile duct, causing proximal bile duct dilatation (Fig. 10); or (4) associated with a venous tumor thrombus (Fig. 11).

Hepatectomy involving the whole liver segment should always be considered if the portal venous branch of that liver segment has been involved by the tumor.[6] In the case of tumor infiltration of a HV, the

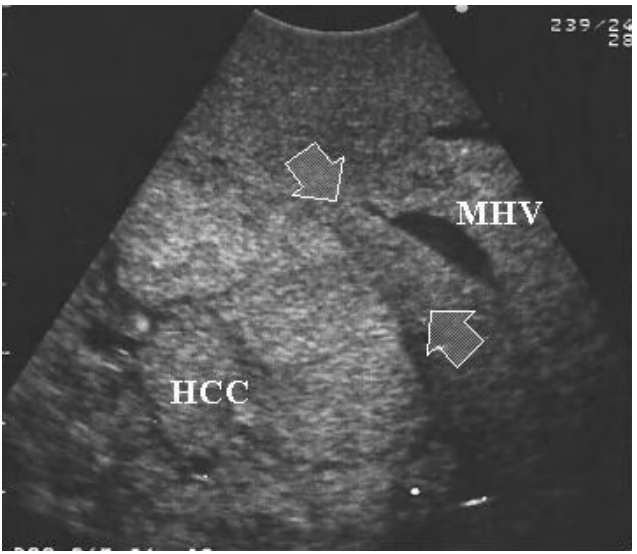


Fig. 8. This HCC is clearly separated by some liver parenchyma (arrows) from the middle hepatic vein (MHV). Due to invasion of the right hepatic vein and coexistence of an inferior right hepatic vein, this patient underwent segments 7 and 8 resection with sparing of segments 5 and 6.

liver parenchyma drained by this vein should only be resected if there are no accessory HVs at IOUS (Fig. 12) and if color Doppler IOUS shows hepatofugal blood flow in the feeding portal branch once the HV is trial-clamped.[7]

Resection guidance

Types of surgical approaches

1. Systematic segmentectomy

In a cirrhotic patient, the liver volume to be resected must be determined with particular care, aiming to have a right balance between surgical radicality and noncancerous liver parenchyma sparing. Liver function tests and liver volumetry on CT scans help in this decision. Tumor dissemination from the main lesion through the portal branches cannot be detected with certainty by preoperative and intraoperative

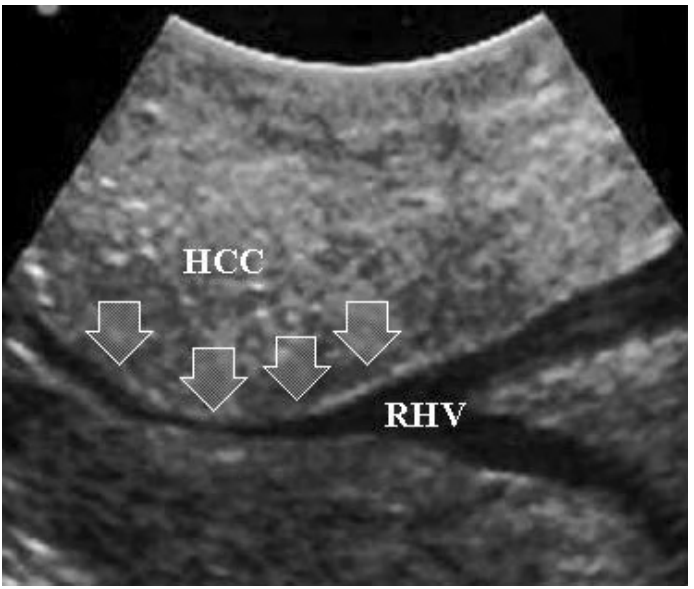


Fig. 9. A HCC in contact with the right hepatic vein (RHV) without any sign of infiltration. The arrows indicate the vessel wall (thin hyperechogenic line), which is always visible. The operation consisted of a limited resection of segments 7 and 8 with sparing of the RHV.

imaging modalities.[20] As a consequence, some authors argue that the resected specimen should consist of the liver parenchyma together with the lesion supplied by the portal venous branch.[20] This is impossible to identify without the use of IOUS, especially in a cirrhotic liver where there are wide variations and abnormalities in the distributions of the portal branches. For this, ultrasonically guided segmentectomy and subsegmentectomy were reported in the early 1980s[21]; and its technique, indications, and results are detailed in Chapter 20.

We have recently established the following alternatives to this approach for tumors located in the left hemiliver:

a. Hooking of the portal branch

The segmental portal branches to segment 4 are divided into superior and inferior branches, but this most common of branching patterns can

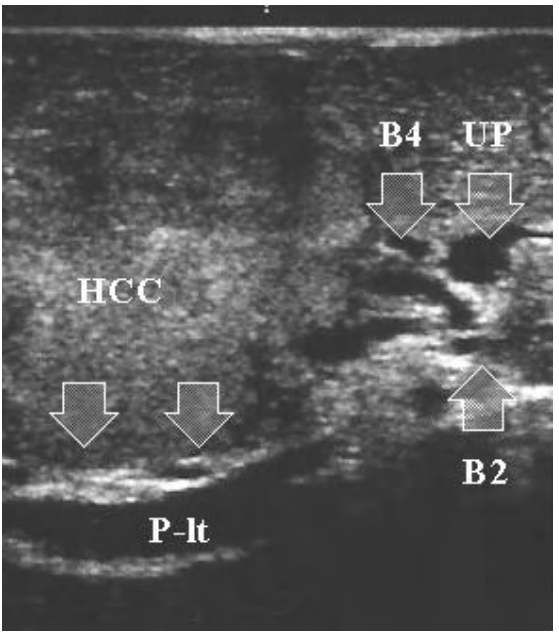


Fig. 10. A HCC in contact with the left portal branch (Plt) without signs of direct infiltration, but with bile duct dilatation in the left liver. The arrows indicate the vessel wall (hyperechogenic line), which is always visible; but bile ducts from segment 4 (B4) and segment 2 (B2) are dilated. The operation consisted of a left hepatectomy. UP, umbilical portion.

be recognized in just about half of the cases.[22] Instead of puncturing these branches under IOUS guidance, these branches can be approached by dissecting the umbilical portion of the vein. Once exposed, the vessel can be encircled with a suture and pulled under IOUS control to verify whether it is the branch to S4 inferior or not. Then, the portal branch can be ligated and divided, and the discolored area that appears on the liver surface should correspond to S4 inferior, which can be marked with electrocautery before proceeding with the liver dissection. This is a special application of the hooking technique.[23] Furthermore, subsegment 4 superior can be outlined by just clamping the portal branch to subsegment 4 inferior in order to identify the discolored subsegment 4 inferior by the hooking technique. The lateral border of S4 superior

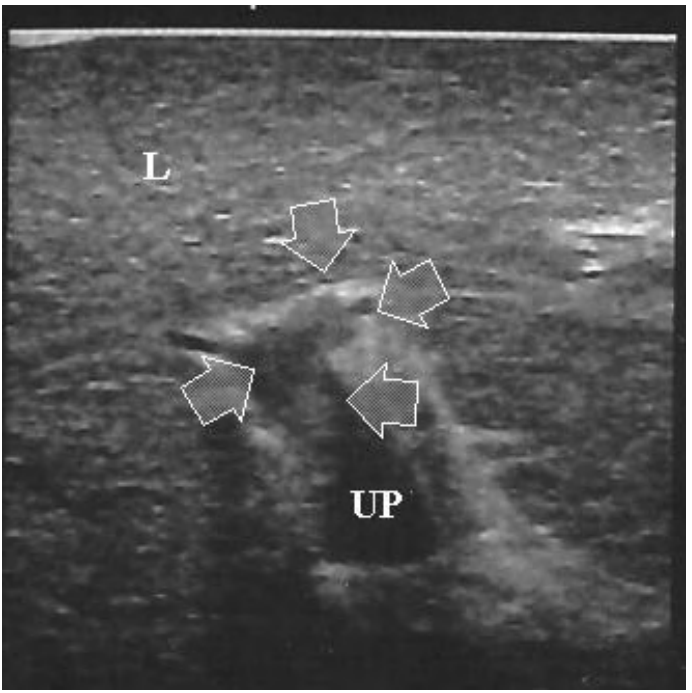


Fig. 11. Multiple HCCs in the right hemiliver. IOUS demonstrated a tumor thrombus (arrows) in the umbilical portion (UP). L, liver.

is then identified by IOUS to be along the left border of the middle hepatic vein, and the falciform ligament marks the medial limit of S4 superior.

b. Compression of the portal branch

In addition to the hooking technique, a new technique has been proposed to perform segmental resections of segments 2 and 3 without clamping the hepatic artery and puncturing the feeding portal branches.[24] Once the feeding portal branch has been identified at IOUS, it is compressed using the IOUS probe on one side of the left liver and a finger on the opposite side (Fig. 13). In this way, it is possible to induce a transient ischemia of the segmental portion of the liver distal to the

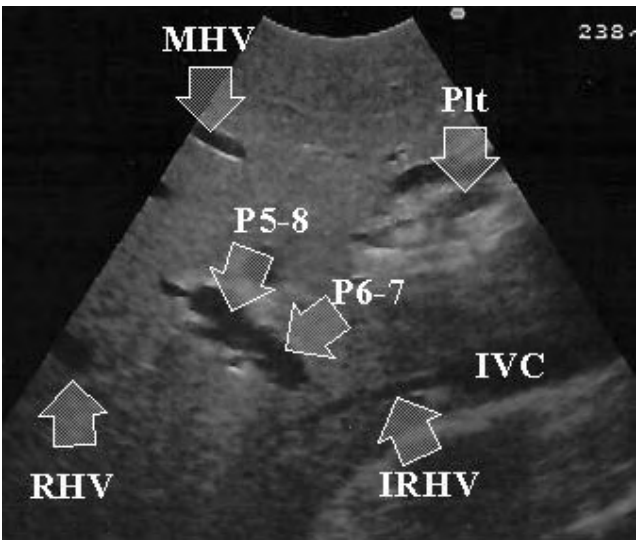


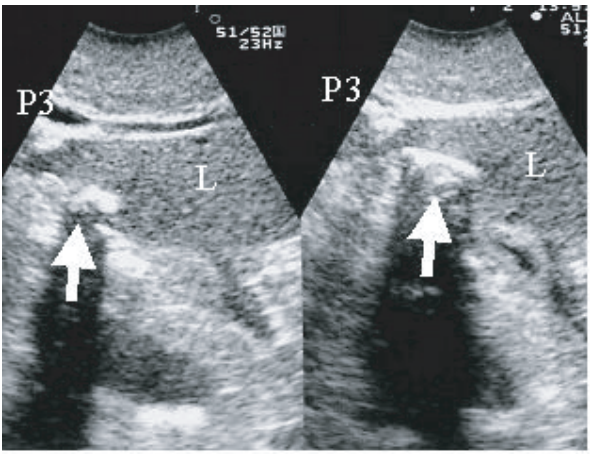
Fig. 12. An inferior right hepatic vein (IRHV) is visible flowing into the inferior vena cava (IVC). This vessel typically runs behind the first- and second-order right portal pedicles. Plt, left portal branch; P6–7, portal branch to segments 6 and 7; P5–8, portal branch to segments 5 to 8; MHV, middle hepatic vein; RHV, right hepatic vein.

compression site. This portion can be marked with electrocautery; then, the compression is released and the segmentectomy is carried out.

This technique is simple, fast, noninvasive, and reversible. The possibility to modify the site of compression and the amount of liver volume resected allows fexibility for different tumors with different backgrounds of the degree of cirrhosis. Together with the S4 subsegmentectomies, these operations represent an alternative to the puncture technique, which is not as reproducible as these two operations.

2. Limited resection

The issue of whether to use anatomical or nonanatomical liver resection in HCC is still controversial.[20,25] There are no randomized studies to compare these two operations. However, recent reports suggest adequacy in the oncological radicality of limited resections for HCC when IOUS is used.[6,7] IOUS-guided limited resection is technically simpler



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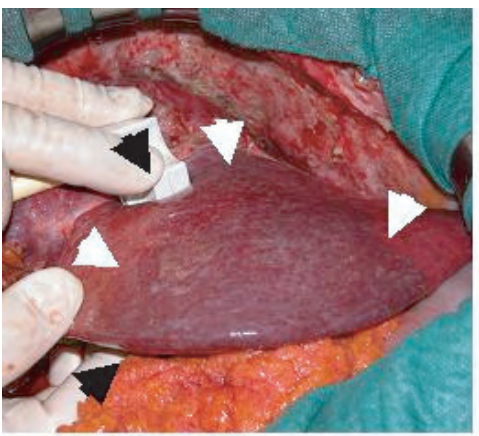

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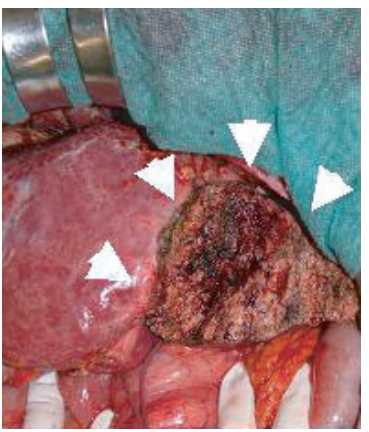


(C)

Fig. 13. (A) At IOUS, the portal branch to segment 3 (P3) is visualized and the surgeon's finger is positioned (arrow) (right), and P3 is compressed (arrow) (left). (B) The hepatic ischemic area generated by the compression with surgeon's finger and probe (black arrows), which corresponds to the area to be resected, is well evident on the liver surface (white arrows). (C) The liver cut surface after segmental resection of segment 3 (arrows). L, liver.

than systematic segmentectomy because there is no need to identify the area of the liver that is fed by the portal branch to be ligated. After identification of the tumor, the surgeon under IOUS control can mark with electrocautery the border of the lesion on the liver surface. The resection margin can then be determined by placing the thin tip of the electrocautery device between the probe and the liver surface. This maneuver results in a shadow in the IOUS image that runs deeply just below the electrocautery device (Fig. 14). In this way, it is possible to define the resection margin for the tumor, which can be marked with electrocautery. The adequacy of the resection margin can be further checked

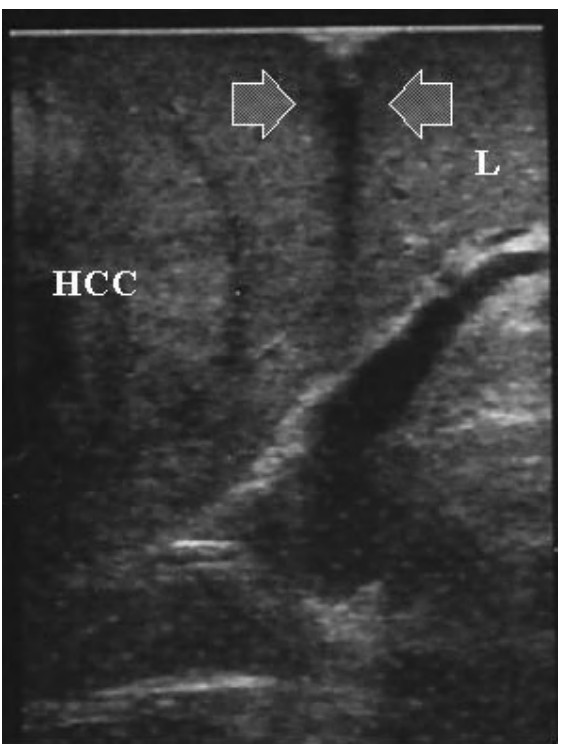


Fig. 14. At IOUS, the electrocautery device positioned between the liver surface and the probe generates a shadow (arrows), which can be related to the tumor. As a consequence, the optimal resection margin can be defined. HCC, hepatocellular carcinoma; L, liver.

with IOUS, as the air trapped between the probe and the demarcation line drawn with the electrocautery device on the liver surface can be visualized at IOUS.

An alternative way to determine the tumor edge with IOUS is to use the fingertips (Fig. 15). With the probe positioned on the liver surface and the surgeon's fingertip pushing on the opposite side of the liver, the relationship between the fingertip and the tumor edge can be seen clearly at IOUS, and the resection margins can be marked on the liver surface.

Liver parenchymal dissection

The main advantage of IOUS is the modification of the traditional way of transecting the liver parenchyma, which is done on a vertical plane to avoid exposing the tumor on the cut surface. IOUS allows real-time visualization of the transection plane, which can be constantly seen in

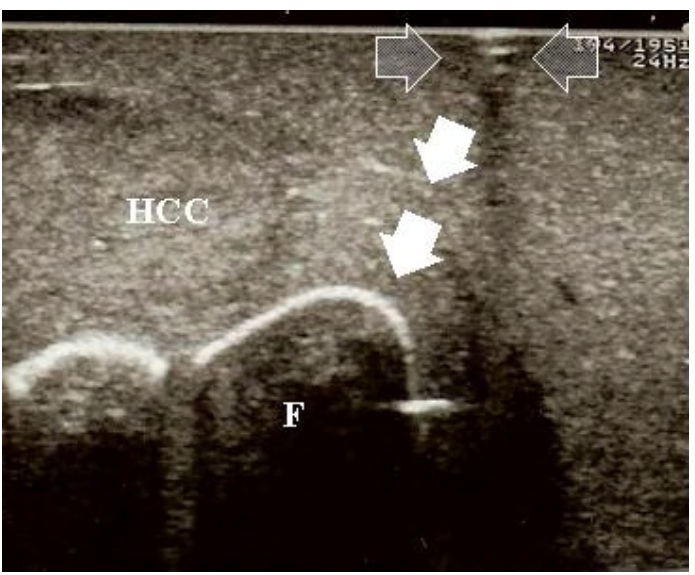
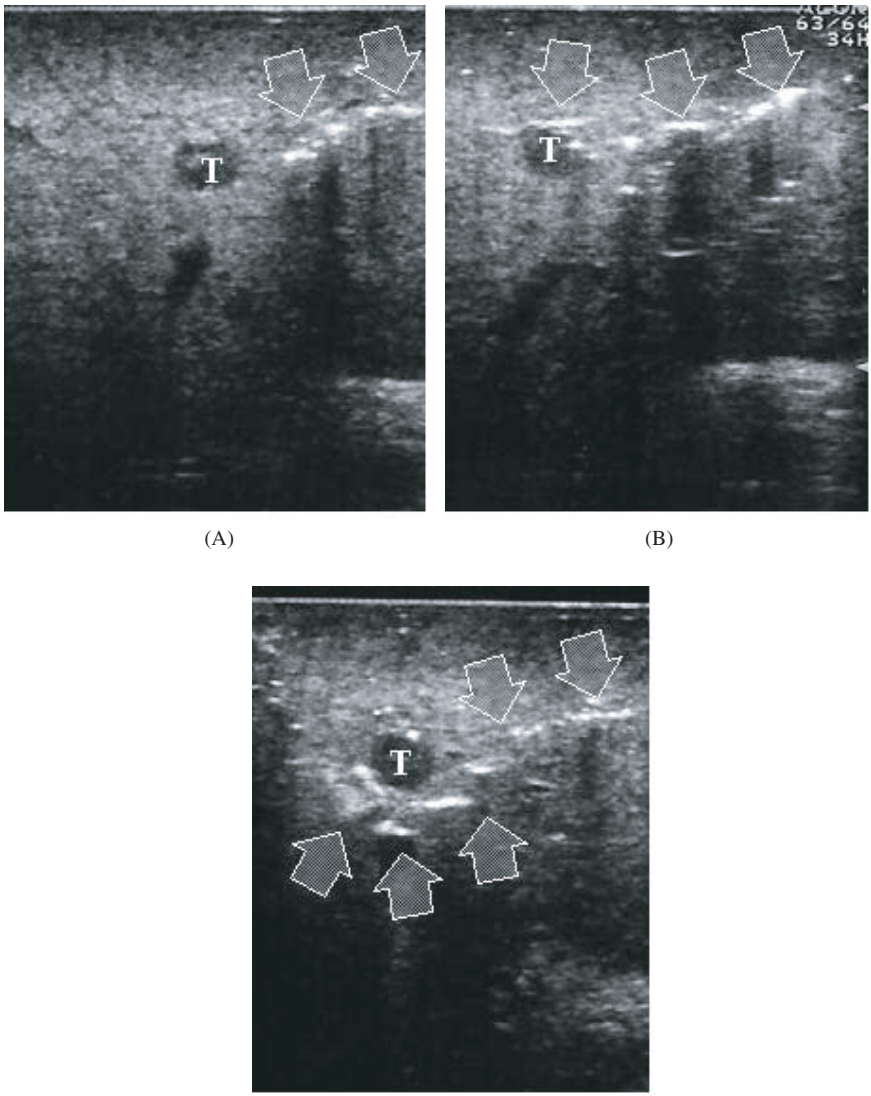


Fig. 15. At IOUS, the electrocautery device positioned on the liver surface (horizontal arrows) and the surgeon's finger (F) positioned on the opposite side of the liver allow the surgeon to draw an ideal plane for transection (white arrows).

relationship to the tumor edge. The transection plane can be modified in its direction when needed. The transection plane appears as an echogenic line due to the entrapment of air bubbles and clots between the cut surfaces of the liver (Fig. 16A). If the transection plane is not clearly visible, it can be better visualized by inserting a gauze or a specifically devised silicon gauze between the cut surfaces of the liver. These techniques allow the surgeon to keep at the proper transection plane. Early recognition of a wrong transection plane allows the surgeon to modify the plane properly (Fig. 16), thus avoiding entering into the tumor inadvertently. In this way, it is possible to carry out a rounded trajectory of the transection plane around the tumor with an adequate resection margin, while at the same time avoiding damage to the important vascular structures. This results in a more conservative but radical treatment, and reduces the rate of major hepatectomies.

The artefacts shown at IOUS on the transection plane can sometimes mask important structures such as the portal branches, which may need to be ligated or preserved. To better visualize the point where the portal branch is, the hooking technique has been devised (Fig. 17).[25] After the Glissonian sheath is exposed and skeletonized, it is encircled with a stitch, which can be visualized by IOUS as an echogenic spot with a posterior shadow. Under sonographic control, the stitch hooking the exposed vessel is gently pulled up to stretch the portal branch slightly, and the traction point is demonstrated clearly on IOUS. If the exposed portal branch is not clearly visible because it has collapsed, the portal triad is unclamped to enable it to fill with blood so that it becomes better visualized on IOUS. If the target site is correct, the portal branch is ligated and divided, and segmentectomy is completed under IOUS guidance; conversely, if the exposed vessel is not the targeted one, it is spared and unnecessary sacrifice of liver parenchyma is avoided.

A practical example in which the hooking technique is used is during ventral or dorsal subsegmentectomy of segment 8. The portal trunk to this segment 8 may bifurcate into its dorsal and ventral trunks just close to the origin of the portal vessel to segment 5. In this situation, there is a risk of ligating and dividing the portal branch of segment 5 instead of the planned subsegmental branch of segment 8, thus causing necrosis



(A) (B)

(C)

Fig. 16. At IOUS, the transection plane (arrows) can be well visualized. (A) IOUS shows that the transection plane is running towards the small tumor (T), and therefore has to be modified. (B) IOUS shows that the transection plane is passing above the tumor (T), and therefore has to be modified. (C) IOUS shows that the modified transection plane is passing under the tumor (T), and therefore resection is now properly carried out.

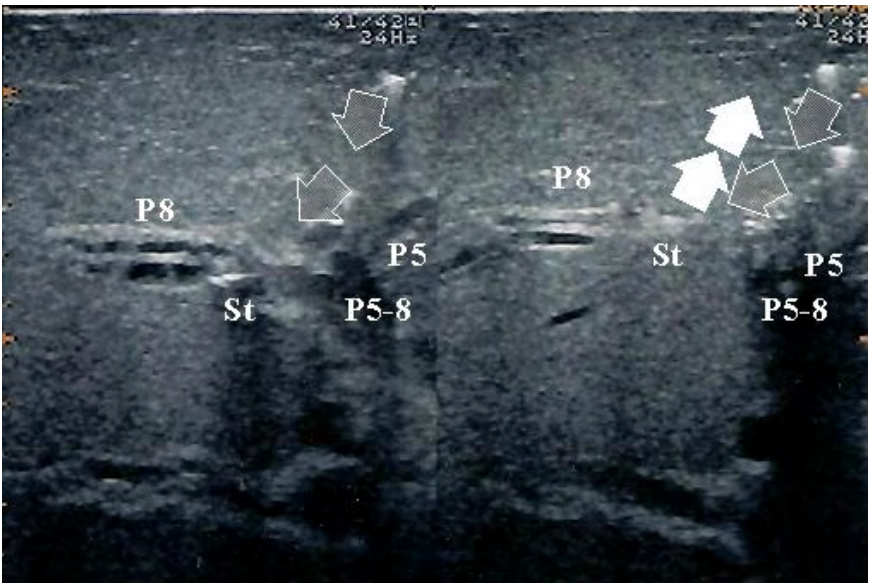
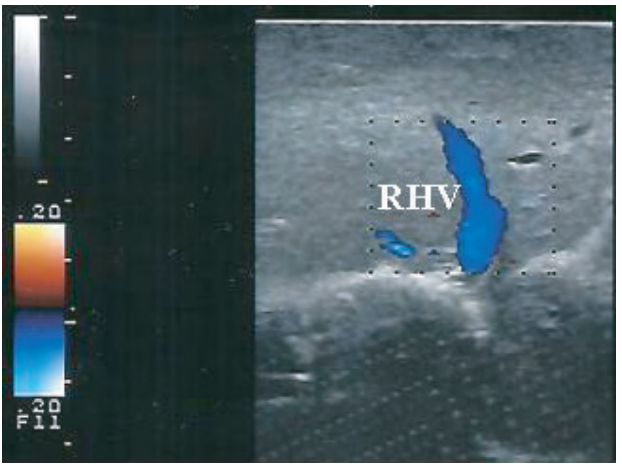


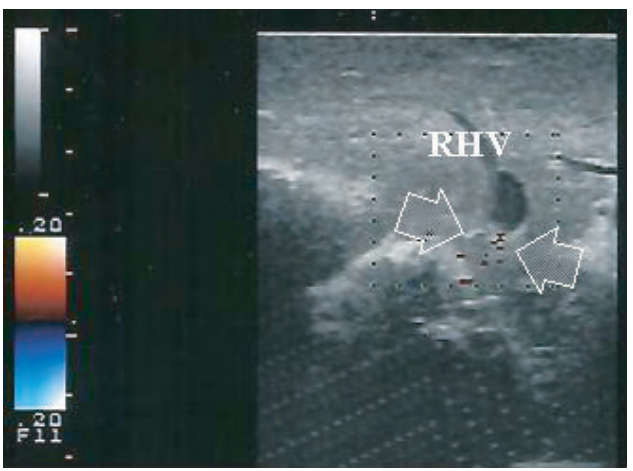
Fig. 17. Left: the portal branch to segment 8 (P8) is dissected (gray arrows) just after its origin from P5–8; at this level, it is encircled and the stitch (St) is visible as a small hyperechogenic spot. Right: traction is applied (white arrows) to pull up the stitch (St), at which level the P8 vessel is no longer visible while P5–8 and P5 are still visible; therefore, it is certain that the encircled vessel is P8 rather than P5 or P5–8, and it is possible to ligate P8 safely.

of segment 5. The hooking technique under IOUS control enables the identification of the branch, which is encircled, and then the surgeon can decide with certainty whether to ligate it. This technique is also useful in patients with tumor thrombus in the major portal branches. In this situation, once the portal branch is skeletonized, it is encircled with a stitch and, under IOUS control, the stitch is gently pulled up. This traction stretches the portal branch slightly, and the traction point is demonstrated clearly on IOUS (Fig. 17). If the traction point is distal to the level of the tumor thrombus, it is possible to ligate the portal branch and proceed with the liver resection, being sure that the thrombus will not migrate because of surgical manipulation.

During liver transection, backflow bleeding from the HVs is an important source of blood loss, and is one of the most important factors

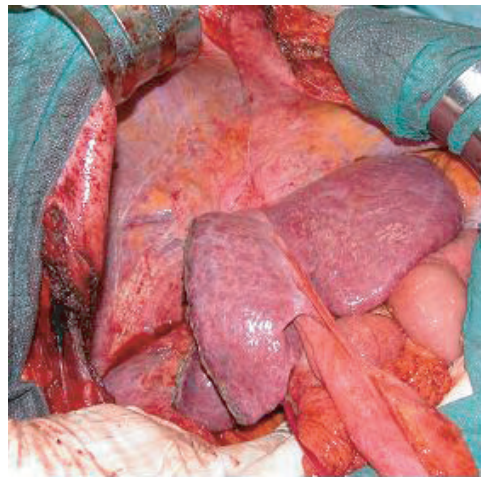


(A)

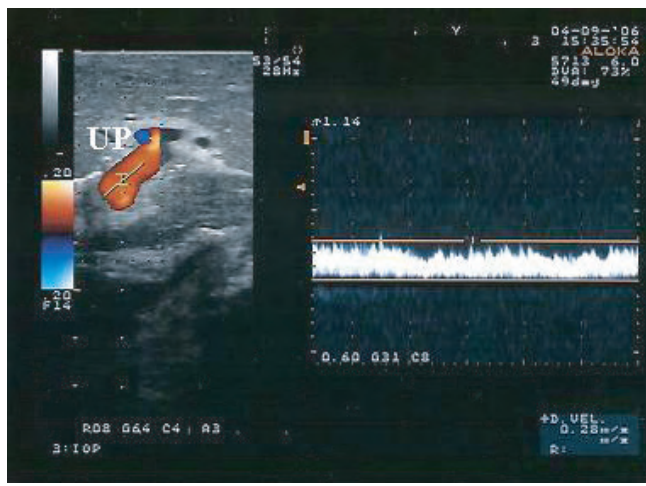


(B)

Fig. 18. (A) At IOUS, the caval confluence of the right hepatic vein (RHV) is visualized. (B) The surgeon positions his fingers at the level of the RHV caval confluence without having to skeletonize the RHV, and with the finger bluntly compresses the RHV; therefore, temporary occlusion of the vessel can be well confirmed at color Doppler IOUS (arrows).

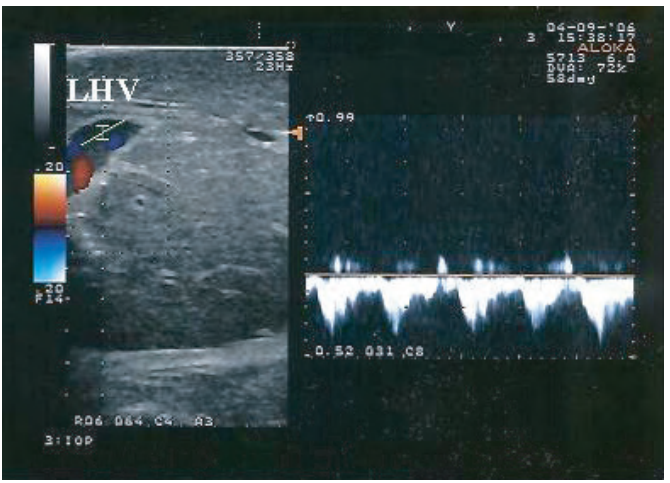


(A)



(B)

Fig. 19. (A) Right hepatectomy has been accomplished, and the cirrhotic liver remnant has to be fixed by suturing the falciform ligament. (B) Color Doppler IOUS allows checking on the patency as well as the acceptable flow pattern and velocity of the portal branch at the level of the umbilical portion (UP). (C) Color Doppler IOUS also allows checking whether an acceptable triphasic hepatic venous flow is present in the left hepatic vein (LHV).



(C)

Fig. 19. (*Continued*)

in determining the short- and long-term outcomes of the patient. Therefore, limiting backflow bleeding from the HVs is important in liver resections. An ultrasound-guided technique for backflow bleeding control from the right HV during right-sided liver resection has been recently described.[26] The technique is very simple: once the right surface of the extrahepatic right HV is exposed to allow for its compression by the surgeon's fingertips, the effectiveness of the finger compression can be checked by IOUS and color Doppler (Fig. 18).

Postresectional control

To confirm that the intended liver nodule has been resected from a patient with multiple liver nodules, two techniques of IOUS can be used. The first one is the "water bath" technique, which consists of verifying the complete removal of the nodule in the resected specimen.[27] The second technique is done by filling the cut liver surface with saline to avoid the artefacts generated by the residual air bubbles and clots, and to look at the remnant liver for completeness of removal of the targeted nodule.

In major liver resections (removal of at least three segments), IOUS allows better determination of the liver transection plane, which should run along a hepatic vein to make the resection truly anatomical. Color Doppler IOUS is a useful aid in these patients because it helps to verify that the vascular supply to the remnant liver has been preserved before irreversibility is done. Furthermore, color Doppler IOUS allows the proper positioning of the remnant liver at the end of the operation by making sure that the blood inflow and outflow are proper in terms of velocity and waveforms at color Dopplering (Fig. 19).[28]

Conclusions

IOUS still remains the best method for staging tumors. New improvements are expected by using CE-IOUS. IOUS helps the surgeon to understand the liver anatomy as well as the relationship between the tumors and the intrahepatic vessels. This information is crucial for planning liver resection. IOUS gives real-time guidance to the surgeon during liver parenchymal transection, thus allowing both anatomical and limited resection to be carried out safely and with a curative intention. IOUS allows operation that would otherwise not be feasible, and it reduces the rate of major hepatectomies.

IOUS should be an instrument used by hepatic surgeons. The American College of Surgeons has recently recognized the need for surgeons with specific training in ultrasound, and similarly in Europe a School for Surgical Ultrasonography has been started. Dedicated monographs have been published almost simultaneously in North America and Europe.[29,30] The time for a wider application of ultrasound in the surgeons' practice has definitely arrived.

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16

Surgical Treatment

Jacques Belghiti

Over the past 10 years, there has been considerable progress in the surgical treatment of hepatocellular carcinoma (HCC).[1–4] The safety of surgical resections has greatly improved because of advances in patient selection, radiological assessment, and perioperative care. Partial resection is safe, with an acceptable overall mortality rate (<5%) in patients with chronic liver disease (CLD).[5,6] However, resection is associated with a 5-year incidence of tumor recurrence of up to 80%.[1,7–9] The main cause of tumor recurrence is the development of new tumors in the remnant liver in patients with CLD; this should be considered as a preneoplastic state.[10] It has been demonstrated that liver transplantation (LT) is the best treatment for patients with CLD who fulfill the Milan criteria.[11,12] The other cause of tumor recurrence after resection is represented by local metastasis due to tumor cell seeding in the adjacent or distal liver segments through the tumor portal venous territory.[6,10] This risk of adjacent metastasis is a strong argument for anatomical resections, including the segmental or subsegmental portal venous drainage areas of the segment containing the tumor.[6,13]

Although the policy of the author and colleagues[14] is to consider LT as a first-line option in selected patients, liver resection remains the major surgical treatment because more than 95% of patients with HCC are not eligible for LT. Furthermore, even in good candidates for LT, the increase in waiting time — which is associated with tumor progression — has led the author and colleagues[14] to consider surgical resection before LT in some patients.

Patient Assessment for Partial Liver Resection

Most patients considered for surgical therapy are asymptomatic. Patients with HCC which is discovered during workup for symptoms including malaise, weight loss, abdominal pain, hepatomegaly, ascites, and jaundice are at an advanced stage and should not be considered for surgery. Asymptomatic patients considered to be at high risk for the development of HCC because of cirrhosis and/or chronic hepatitis B or C status are being increasingly diagnosed by screening programs.[15,16] The suitability of these patients for surgical resection should then be determined by liver function assessment and by radiological tumor staging.

Radiological Imaging

Imaging techniques used for the detection and characterization of liver lesions are also used in the staging of HCC. The most useful and common techniques are percutaneous ultrasonography (US) and multiphasic contrast-enhanced helical computed tomography (CT).

Although highly operator-dependent, US is the most commonly used technique for the assessment and screening of patients. US is a sensitive and specific tool for detecting large HCC nodules, and can detect 85%–95% of lesions 3–5 cm in diameter.[17] When lesions are less than 1 cm in diameter in a cirrhotic liver, sonography often cannot absolutely distinguish HCC from other solid lesions in the liver, including regenerative nodules. Sonography is also very sensitive for the detection of vascular abnormalities that are commonly seen in HCC, including portal and hepatic vein invasion or intrabiliary extension of

the tumor. In addition, the direction of portal blood flow can be assessed by Doppler ultrasound to evaluate the degree of portal hypertension. The recent introduction of microbubble contrast agent has opened new prospects in liver US.[18] Contrast-specific techniques produce images that increase the ability of US to characterize lesions in the setting of liver cirrhosis. HCC typically shows strong intratumoral enhancement in the arterial phase, followed by rapid washout in the portal venous and delayed phases.[19]

With the introduction of spiral scanners, the role of CT in liver imaging has dramatically changed. HCC characteristically shows maximal enhancement during the hepatic arterial phase, and becomes hypodense compared to the surrounding liver in the portal venous phase as a result of rapid washout of contrast.[18] HCC typically appears heterogeneous, which may reflect intratumoral fibrous stranding (mosaic sign), fatty metamorphosis, necrosis, or calcifications. The presence of satellite nodules in close proximity to the lesion is often characteristic. Spiral CT provides detailed mapping and assessment of hepatic arteries, portal veins, and hepatic veins. The anatomical and vascular pathologic details provided by these scans have become extraordinarily useful for surgical planning.[20]

Angiography has been used as a diagnostic tool after the injection of lipiodol (iodized poppy seed oil) into the liver via the hepatic artery. CT is performed 1–4 weeks later. Lipiodol is retained within the HCC, and hence will show up as a densely enhancing lesion. At present, angiography is less used.

The main advantage of magnetic resonance imaging (MRI) over CT is its superiority in distinguishing HCCs from other hepatic lesions, including regenerative/dysplastic nodules in the cirrhotic liver.[21,22] HCC lesions appear hypointense and hyperintense on T1- and T2-weighted sequence images, respectively. The addition of superparamagnetic iron– and gadolinium-enhanced agents produces results that establish MRI as the diagnostic imaging mode of choice for HCC at many institutions worldwide.

Positron emission tomography (PET) is rarely helpful in the diagnosis for HCC. However, a high positive rate of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) accumulation has been reported in patients

with high-grade HCC and in those with markedly elevated alpha-fetoprotein (AFP) levels.[23]

Histological Diagnosis by Fine-Needle Aspiration Biopsy

A needle biopsy is not necessary in the presence of radiological lesions classic for HCC associated with an AFP level of >200 ng/mL. However, imaging-guided biopsy is recommended for small nodules or for lesions without the typical features (arterial hypervascularization) in at least two imaging techniques and normal AFP, especially in candidates for LT. The first goal of biopsy is to limit the risk of unnecessary LT with a false-positive rate that can reach 30% on the explanted specimen.[24] In addition, biopsy helps to assess the histological differentiation of the tumor, since some authors[25,26] have demonstrated that a low grade of histological differentiation is associated with a poor prognosis. Furthermore, the risk of tumor spread from the needle tract exists, but is close to 1%; and the excision of the needle tract in the case of metastasis does not affect long-term survival.[27,28]

Patient Selection

In terms of tumor status, liver resection is usually contraindicated when one of the following criteria exists: (1) extrahepatic metastasis; (2) multiple and bilobar tumors; (3) involvement of the main bile duct; and (4) presence of portal thrombus in the main portal vein and/or the vena cava.

Patients with HCC and tumor thrombus in the vena cava or in the portal trunk have a poor prognosis with a high rate of pulmonary metastases.[29] This major vascular involvement is generally associated with a large tumor, for which treatment cannot be anticipated. It was shown that in a selected group of patients with normal liver function and excellent general status, extensive liver resection associated with removal of the vascular thrombus achieved favorable survival results.[29–31]

The role of hepatic resection for multiple and bilobar HCCs is more controversial.[32–36] Bilobar HCCs may represent either advanced disease with intrahepatic metastasis from one lobe to the other or multifocal

HCCs. However, in some selected patients with good liver function, the presence of a small solitary lesion in the contralateral lobe should not contraindicate resection of the main tumor, and in selected cases major hepatic resection could be associated with wedge resection or local ablative therapy (if the lesion is not superficial).[36,37]

Spontaneous rupture of HCC occurs in 5%–15% of patients.[38–40] This complication is observed particularly in patients with large superficial or protruding tumors, and is associated with hypovolemic shock in less than half of the patients.[38,41] In the case of hemoperitoneum, transhepatic arterial embolization represents the best hemostatic procedure.[39,40,42] In patients with good liver function and single tumor, rupture of HCC should not be regarded as a contraindication to subsequent elective surgical treatment with the intention of cure.[38,40,43]

A great proportion of patients with chronic liver disease continue to present with large advanced tumors. Large tumor size alone should not be considered as a contraindication for hepatic resection.[43–46] It is proven that hepatic resection for HCCs larger than 10 cm in diameter without macroscopic venous invasion is a safe and effective option.[43,44,47] However, the postoperative regenerative process can be impaired in the presence of cirrhosis, especially in the case of small-sized future remnant liver (FRL) (<40% of the functional whole-liver volume).[47,48] Therefore, the use of preoperative portal vein embolization (PVE) — which aims to induce hypertrophy of the FRL — was developed mainly to improve the safety and tolerance of major liver resections in both normal and injured liver parenchyma.[49,50]

Previously, concerns existed about the regenerative capacity of fibrotic or cirrhotic liver parenchyma to hypertrophy after technically successful PVE. Later, studies showed that preoperative PVE induces significant hypertrophy of the FRL, even in patients with CLD.[47,51,52] Furthermore, it was shown that preoperative PVE could improve the safety and tolerance of major liver resections[48,53,54] in patients with CLD.[52] Ogata *et al.*[55] showed that sequential arterial chemoembolization and PVE before right hepatectomy in cirrhotic patients with HCC increased the FRL volume, the rate of complete tumor necrosis, and long-term survival compared to PVE alone. Moreover, the absence of hypertrophy of the nonembolized liver (FRL) following technically successful PVE

is a dynamic test and an indicator for the absence or low capacity of the injured liver to regenerate, and therefore contraindicates major liver resection in these patients.[52,55]

Preoperative Evaluation of Liver Functional Reserve

In addition to the evaluation of tumor status and to avoid postoperative liver failure, preoperative liver functional reserve assessment in cirrhotic patients is critical for the selection of patients.[56] The overall incidence of in-hospital death following liver resection for HCC in studies published in the 1990s ranged between 1% and 10% (Table 1). In most studies, hospital mortality was significantly higher in patients with liver cirrhosis than in patients without cirrhosis. The predominant cause of death in cirrhotic patients is liver failure, which is mainly assessed by Child–Pugh classification,[69] which was originally designed to predict the prognosis of patients with portal hypertension undergoing the shunting procedure.

In the vast majority of Western centers, resection is contraindicated in grade C cirrhotic patients and rarely is limited resection possible in grade B cirrhotic patients.[4] However, even in grade A cirrhotic patients with apparently normal liver function, the risk of liver surgery is increased and more sophisticated quantitative liver function tests have been developed. The indocyanine green (ICG) clearance test seems to be the best single test to predict mortality after hepatectomy.[5,70] It is generally admitted that ICG retention at 15 minutes of less than 15% identifies patients who can tolerate a major resection, while that of more than 20% can only tolerate limited resection.

Other factors predicting postoperative liver failure are (1) FRL volume estimated by CT volumetry at below 40% of the whole-liver volume, (2) grade 4 fibrosis assessed by biopsy of the nontumorous liver, (3) high portal pressure assessed by grade 2 or 3 esophageal varices or measured by transjugular pressure, and (4) the presence of a superimposed active hepatitis assessed by a preoperative elevated transaminase level of more than twofolds normal.[45,71–73] Although these criteria are not commonly accepted, there are strong arguments showing that patients with either one of these criteria should not undergo a major liver resection without preoperative PVE. In patients with CLD, the

Table 1. Series of liver resections for HCC.

Reference	Study period	No. of patients	Cirrhosis (%)	Diameter <5 cm (%)	In-hospital mortality (%)	1 yr (%)	3 yrs (%)	5 yrs (%)
Results after curative surgical resection of HCC in Asian series								
57	1980–1990	229	77	75	11	80	51	26
58	1990–1993	112	68	83	2	92	79	—
59	1985–1993	280	52	—	2	88	70	50
60	1983–1994	382	45	40	4	71	52	46
61	1990–1997	352	—	—	<1	92	73	47
2	1989–1994	136	50	29	13	68	47	36
	1994–1999	241	43	45	2.5	82	62	49
3	1987–2001	135	71	100	2	95	73	55
Results after curative surgical resection of HCC in Western series								
62	1983–1988	72	100	60	7	68	51	—
63	1970–1992	106	33	17	6	—	—	41
64	1985–1995	120	22	—	8	82	44	31
65	1989–1997	77	100	75	—	85	62	51
66	1991–1998	154	65	24	4.5	81	54	37
4	1990–1999	300	82	47	6	81	57	37
67	1983–1999	224	100	81	3	83	63	42
68	1990–2001	164	40	—	4	79	51	40

degree of hypertrophy of the FRL after PVE is variable. Transcatheter arterial chemoembolization (TACE) before PVE could improve the rate of hypertrophy.[56,74]

HCC without Chronic Liver Disease

In the vast majority of cases, HCC develops in the setting of cirrhosis, but 5%–15% of patients have no underlying CLD.[75,76] Usually, the etiology of HCC in normal liver or minimal fibrosis is undetermined, but in some cases a chronic hepatitis B virus infection or hemochromatosis is present.[75] Fibrolamellar carcinoma, which frequently occurs in patients with normal liver, represents a variant of HCC with specific pathological and clinical features.[75] The tumor is hypervascularized with eosinophilic cells surrounded by a dense fibrous stroma. The tumors are frequently observed in the Western hemisphere in white females at a younger age (20–40 years), and are more often located in the left liver with positive lymph nodes; AFP is rarely elevated.[9,77,78]

HCCs in patients with normal liver are often large (>10 cm) and are diagnosed when tumors are symptomatic.[44,47,79] The only curative treatment is major hepatectomy, which is often well tolerated in the absence of underlying liver disease and good regenerative capacity of the remnant liver. The long-term results of HCC resection in patients without CLD are much better than in patients with cirrhosis, with a disease-free 5-year survival rate as high as 50% in the former.[4] These favorable results, observed in both fibrolamellar and nonfibrolamellar HCC, suggest that the absence of underlying liver disease is a major factor of short- and long-term prognosis.[1,4]

HCC with Chronic Liver Disease

The selection of patients with HCC associated with cirrhosis includes two main principles: surgery should be curative, and it should not place the patient at risk of operative death.

Extent of resection

The two main aims of hepatic resection, especially in cirrhotic liver, seem apparently opposite: one is to resect all of the malignant tissue (tumor, satellite nodules, and portal vein territory) with effective clearance; the other is to leave enough nontumorous liver parenchyma in order to prevent postoperative liver failure. This explains the fact that most centers perform limited resections for small HCC, especially in patients with poor liver function. The other argument to perform limited resections is the pattern of postoperative recurrence that results in part from the development of new tumors in the remnant liver.[1,80–84] However, the main risk of limited resections is tumor recurrence by local metastasis, and particularly by tumor cell seeding in the adjacent or distal liver segments through the tumor portal venous territory.[6,56,85]

Anatomical resections, according to the architecture of the portal vein, have the potential to remove undetected cancerous foci (portal vein metastases and satellite nodules) disseminated from the primary gross tumor. The segmental or subsegmental portal venous drainage areas of the segment containing the tumor are identified by intraoperative US (IOUS).[86] Several studies demonstrated that anatomical resections of small, solitary HCC achieve, without increasing the postoperative risk, a significant better overall and disease-free survival than limited resections.[13,66,81,87] Therefore, anatomical resection, when possible, should be the treatment of choice and considered as the reference surgical treatment compared with other treatments. When anatomical resection is not possible, either because of the tumor location and/or the liver function, other therapeutic options such as LT and/or percutaneous treatments should be discussed with the patient.

Improvement of surgical resection

Twenty years ago, the mortality rate of hepatectomy in cirrhotic patients was over 10%. Substantial improvements in the surgical techniques of hepatic resection in the past decade have resulted in a dramatic decline in the operative mortality of hepatic resection for HCC, and have allowed major resections in selected cirrhotic patients (Table 1).

Intermittent inflow occlusion

During liver resection, reducing blood loss and transfusion is essential. Several methods designed to limit the bleeding, from inflow occlusion by portal triad clamping to complete vascular exclusion, have been used.[88] The poor tolerance of cirrhotic liver to warm ischemia led many authors to contraindicate inflow occlusion in patients with cirrhosis. However, it has been demonstrated that intermittent inflow occlusion with 15 minutes of clamping and 5 minutes of unclamping is well tolerated.[89] This method, which minimizes intraoperative blood loss, can be safely repeated for up to 120 minutes in cirrhotic patients with good liver function.[66,87]

Anterior approach

When liver tumors are large, the use of conventional techniques usually requires forceful retraction and mobilization of the liver, with possible disadvantages including compression of both the right and left lobes as well as tumor dissemination. In the anterior approach, after hilar control of the vascular inflow and without prior mobilization of the right lobe containing the tumor, the parenchymal plane is transected directly from the anterior surface of the liver down to the anterior surface of the inferior vena cava (IVC). After the anterior approach to the parenchyma and the control of all venous tributaries including the right hepatic vein, the right lobe is mobilized and resected without forceful retraction of both the right and left lobes. This approach reduces intraoperative blood loss, blood transfusion, hospital death rate, pulmonary metastases, and recurrence compared to the conventional approach.[90–92]

The "hanging maneuver" facilitates the anterior approach (for details, see Chapter 17).[92] During this maneuver, the liver is raised away from the anterior surface of the IVC by a tape. The anteroposterior parenchymal transection is then facilitated by an upward traction on the tape (hanging the liver parenchyma anteriorly) placed in front of the retrohepatic vena cava, thus allowing the following of a direct plane as well as facilitating exposure and hemostasis of the transected posterior parenchyma in front of the IVC. This technique can be used in patients

with normal liver or CLD, and is contraindicated for large tumors invading the vena cava and in the presence of multiple adhesions between the prehepatic liver parenchyma and the anterior surface of the retrohepatic vena cava.[93]

Recurrence Following Resection of HCC

The rate of recurrence following resection of HCC is around 80% at 5 years.[10,34,82,88] The predominant cause of tumor recurrence is metachronous carcinogenesis, since the precursor condition (cirrhosis) persists after surgery.[94] Greater incidence of recurrence is associated with the following factors: presence and severity of an underlying cirrhosis, presence of multiple nodules, tumor of more than 5 cm in diameter, lack of a capsule, moderately or poorly differentiated HCC, presence of daughter nodules, venous invasion, infiltrative rather than expansile tumor, insufficient cancer-free margin, and intraoperative blood transfusion.[66,95–97] Thus, any neoadjuvant or adjuvant therapy that can decrease or delay the incidence of intrahepatic recurrence should be considered after partial hepatectomy.[97,98] In particular, it has been demonstrated that intra-arterial I-131 lipiodol given after curative resection significantly decreases the rate of recurrence and increases disease-free and overall survival.[99]

Although the recurrence following resection of HCC is in most cases associated with a poor outcome, there is growing evidence that some patients benefit from more aggressive approaches, especially if the recurrence is limited to the liver.[61,100,101] Multimodality therapy including TACE, percutaneous ablative therapy, and reresection could result in prolonged survival with an overall 5-year survival rate of 20%.[10,35,61,101–103]

Results of Liver Resection

The largest report of resected patients comes from the Liver Cancer Study Group of Japan, who reported 1-, 3-, 5-, and 10-year survival rates of 85%, 64%, 45%, and 21%, respectively, in 6785 cirrhotic patients treated by hepatic resection between 1988 and 1999.[104] Comparable

results have been reported by other groups worldwide without much difference between Western and Asian studies (Table 1). Survival rates as high as 60% at 5 years may be achieved in Child grade A patients with well-encapsulated tumors of 2 cm in diameter or less. Although less than 10% of patients fit these selection criteria, such results, obtained in patients with good liver function who underwent anatomical resection, could be favorably compared with those of LT.[17,68]

Liver Resection and Liver Transplantation (LT)

LT is obviously the most attractive therapeutic option for HCC because it removes both detectable and undetectable tumor nodules together with the preneoplastic lesions present in the cirrhotic liver. In addition, it simultaneously treats the underlying cirrhosis as well as prevents the development of postoperative or distant complications associated with portal hypertension and liver failure (for details of LT, see Chapter 28).

After the publication of criteria proposed by Mazzaferro *et al.*[11] from the Milan group (i.e. a single nodule less than 5 cm, or two or three nodules each less than 3 cm without vascular invasion) in 1996, several groups published remarkable improved results. Therefore, LT was considered as a first-line option for patients with limited tumor(s).[11,12] However, various series have recently showed a significant decrease of long-term survival in patients who underwent LT for HCC with a high rate of recurrence. It must be noted that the use of (nonspecific) immunosuppressive treatments markedly accelerates the course of recurrence. The recent decline in survival could be partially related to the lengthening of the waiting list.

Tumor management while awaiting transplantation includes several modalities such as percutaneous radiofrequency ablation, TACE, and hepatic resection. The two nonsurgical treatments are widely used, but their impact on survival is unproved. We have demonstrated that surgical resection prior to LT neither increases the surgical risk nor impairs the survival.[14]

The use of laparoscopic or transthoracic approaches for peripheral tumors has contributed to expand on this strategy of minimizing

technical difficulties during the transplant procedure.[105,106] Once the feasibility of this strategy is admitted, several approaches can be applied associating resection and LT. These include the use of resection as a bridge treatment before LT, resection for selection of good candidates based on the specimen analysis, and resection as an initial treatment of HCC indicating LT in the case of recurrence or deterioration of liver function.[14] The longer duration on the waiting list before LT for HCC is a strong argument for antitumoral treatment during the waiting for LT. In patients with good liver function and peripheral tumors, resection can be considered as the most efficient bridge treatment since it removes the tumor completely.

The complete ablation of the specimen allows a precise pathological assessment of unfavorable histological prognostic factors that cannot be established preoperatively, including the degree of differentiation in different areas of the tumor, microvascular invasion, and presence of satellite nodules. Then, the indication of transplantation can be based on these histological factors, with several possibilities including an acceleration of the process of LT in cases with microvascular invasion or a contraindication if a macrovascular invasion is discovered on the specimen.[107]

The concept of resection as the initial treatment for HCC, with salvage transplantation in case of recurrence, is the most attractive approach. After curative resection of HCC with good histological prognosis (i.e. well-differentiated tumor, absence of microvascular invasion and satellite nodules), patients should undergo a close follow-up to detect recurrence and then transplantation if detected. In an era of graft shortage, liver resection is a good first-line treatment option as it is immediately applicable, technically simpler, and not associated with immunosuppression.

After resection of limited HCC, Poon *et al.*[95] observed a 70% 5-year survival rate and a 64% 5-year recurrence rate.[95] The most important result of their study was that in the vast majority of cases, tumor recurrence was limited, fulfilling the Milan criteria; therefore, 80% of patients remained eligible for transplantation at the time of recurrence.[95] Farges *et al.*[102] have demonstrated that in patients who underwent partial resection, LT for recurrent tumor within the Milan criteria had similar

long-term results as LT for primary tumors within the same criteria.[102] However, the analysis of Farges *et al.*'s[102] data, including patients with hepatitis C virus (HCV) infection, was not in accordance with the high rate of limited recurrence described by the Hong Kong group who had hepatitis B virus (HBV) infection.[100] Despite a close follow-up, 60% of Farges *et al.*'s[102] patients with HCV infection who experienced recurrence were no longer eligible for transplantation at the time of recurrence. This high rate of multiple recurrences, including major vascular invasion and extrahepatic dissemination, could be related to the oncogenic process of HCV infection.

This important result has not modified the author's policy of resection in patients with small HCC and good liver function, but after resection patients with HCV infection are listed in the waiting list and are transplanted before recurrence.

Therefore, resection and transplantation can be complementary.

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17

Anterior Approach Using the Hanging Technique

Jacques Belghiti and Barbara Alkofer

Introduction

Conventional techniques for major liver resection usually require forceful retraction and mobilization of the liver to control the hepatic veins in order to reduce the amount of surgical blood loss.[1–4] However, this approach may be difficult in patients with large HCC located in the right liver infiltrating the surrounding structures with limited access to the inferior vena cava (IVC). Besides, complete mobilization of the right liver may induce bleeding from avulsion of the hepatic vein and caval branches, prolonged ischemia of the liver remnant with compression of the left liver, and tumor dissemination.[5,6]

The anterior approach was first described by Ozawa as one of the nonconventional approaches to advanced liver cancer in an attempt to avoid prolonged rotation and displacement of the hepatic lobes, which would cause impairment of the afferent and efferent circulation.[7] The use of the anterior approach for major resection in patients who have a large HCC in the right liver includes a primary hilar control

of the inflow blood vessels without prior mobilization of the right liver and the tumor with parenchymal transection using an ultrasonic dissector until the anterior surface of the IVC is exposed. After transection, all venous tributaries, including the right hepatic vein, are controlled before mobilization of the right liver. Liu *et al.*[5] have shown that the anterior approach should be the preferred technique for major right hepatic resection for large HCC because it results in improved surgical and survival outcomes compared to the conventional approach.[5]

The liver "hanging maneuver" developed by our group is a technique by which a tape is passed between the anterior surface of the IVC and the liver, and suspends the liver during the hepatic parenchymal transection. This technique facilitates major hepatectomy with the anterior approach; allows suspension of the liver with a tape, thus facilitating control of bleeding of the deeper parenchymal plane; and guides the direction of an anatomical parenchymal transection. This technique has been used in both right and left hepatectomies.[8,9]

Theoretical Advantages of the Anterior Approach

In the anterior approach, after hilar control of the vascular inflow and without prior mobilization of the right liver containing the tumor, the parenchymal plane is transected directly from the anterior surface of the liver down to the anterior surface of the IVC. After anterior transection of the parenchyma and control of all venous tributaries including the right hepatic vein, the right liver is mobilized and resected without forceful retraction of the left liver. The potential disadvantages of mobilization of the right liver together with the large tumor using the conventional approach include excessive bleeding caused by avulsion of the hepatic vein and caval branches, compression and prolonged ischemia of the remnant liver from rotation of the hepatoduodenal ligament, iatrogenic tumor rupture, and spillage of cancer cells into the systemic circulation.[5,6]

Suppression of the dissection of a large tumor invading diaphragmatic and posterior structures is the first advantage of the anterior approach because of less blood loss.[5] The second potential advantage of

the anterior approach is that it minimizes hematogenous dissemination of malignant tumor cells during manipulation and compression of the tumor. The anterior approach can be considered as a "nontouch isolation technique", with lower levels of circulating cancer cell markers compared to the conventional approach.[7] In a prospective randomized study comparing the anterior approach (AA) and the conventional approach (CA) to right hepatectomy for HCC, the overall cumulative survival of the AA group was significantly better than that of the CA group, with a better survival outcome among stage II disease patients in the AA group.[5] Therefore, modification of the surgical technique can be associated with improved operative and survival outcomes of patients undergoing liver cancer surgery. The third potential advantage of the anterior approach is to decrease the risk of injury of the future remnant liver (FRL). Indeed, the rotation of the resected liver in the conventional approach may decrease the afferent and efferent circulation of the FRL.[7] Furthermore, during the rotation of the resected liver, the FRL is compressed. It has been shown that liver ischemia is not the only factor responsible for postoperative aminotransferase release; surgical trauma probably contributes considerably to this, as suggested by the eightfold increase in serum aminotransferase levels seen after hepatectomy performed without vascular occlusion.[10] Therefore, the anterior approach could contribute to better preservation of postoperative liver function by avoiding compression and impairment of the circulation of the liver remnant.

The "hanging maneuver" facilitates the anterior approach.[8] Using a tape blindly placed in front of the retrohepatic vena cava, the liver is raised away from the anterior surface of the IVC by a tape. The anteroposterior parenchymal transection is facilitated by an upward traction on the tape (hanging the liver parenchyma anteriorly), allowing the surgeon to follow the direct plane and to facilitate the exposure and hemostasis of the transected posterior parenchyma in front of the IVC. This technique, which can be used in patients with either normal liver or chronic liver disease, is contraindicated in large tumors invading the IVC and in the presence of multiple adhesions between the liver parenchyma and the anterior surface of the retrohepatic IVC.[11] When right liver resection includes the middle hepatic vein (MHV), another

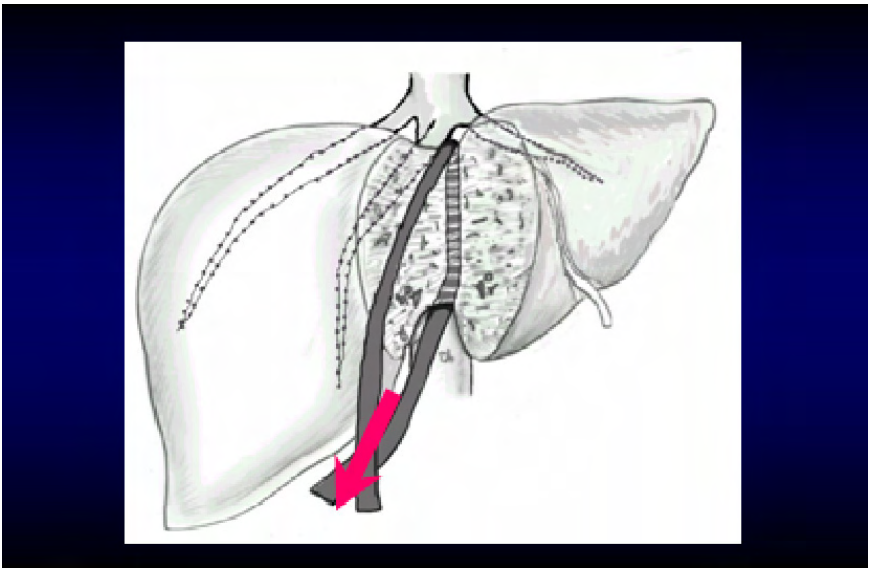

Fig. 1. Hanging technique. The tape is placed on the left side of the MHV.

advantage of this maneuver is to follow the "right" transection plane along the left side of the MHV (Fig. 1).

The Hanging Maneuver: Principles and Technical Procedure

Preoperative decision making to consider the liver hanging maneuver is based on tumor location as assessed by computed tomography (CT). Special attention is given to assess the state of the IVC from the level of the hepatocaval confluence up to the right renal vein. The hanging maneuver is considered to be indicated if tumors do not infiltrate the avascular space located at the 10-to-11–o'clock position of the anterior surface of the retrohepatic IVC (Fig. 2). Direct invasion of tumors to the distal major hepatic veins, diaphragm, retroperitoneum, or tumor in contact with the IVC except the avascular space are not considered as contraindications to the hanging maneuver. Even if initial assessment shows tumor infiltration of the anterior surface of the IVC, tumor regression induced by systemic chemotherapy makes the retrohepatic

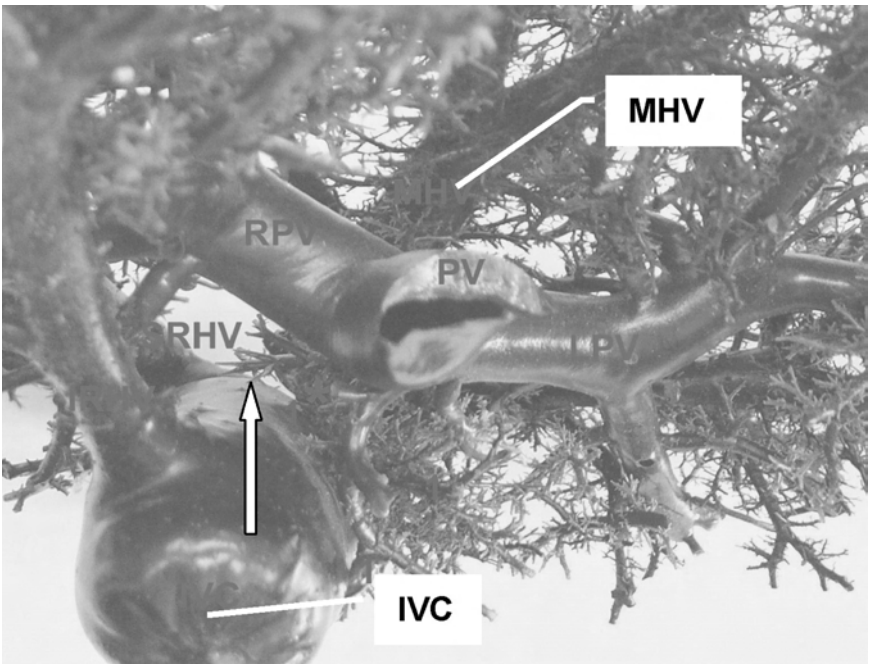

Fig. 2. Avascular space on the anterior surface of the retrohepatic IVC. The arrow shows the avascular space, between the right and middle hepatic veins, where the tape can be safely placed. RHV, right hepatic vein; MHV, middle hepatic vein; IVC, inferior vena cava; PV, portal vein; RPV, right portal vein.

space free of tumors, thus enabling the surgeon to consider the hanging maneuver.[11]

The liver is exposed through an abdominal incision using either a bilateral subcostal or a J-shaped incision. Intraoperative ultrasound (IOUS) is performed with special attention to confirm the absence of tumor infiltration and abnormal short hepatic veins at the 10-to-11–o'clock position of the anterior surface of the retrohepatic IVC. After opening the anterior leaf of the coronary ligament and the anterior part of the right triangular ligament (to expose the anterior and left sides of the right hepatic vein), the space located between the right hepatic vein (RHV) and the MHV is dissected via the punch-burn-cut method and subsequently 3–4 cm downwards with a right-angled dissector and

vascular clamp. For caudal retrohepatic dissection, the caudal edge of the caudate lobe is lifted from the IVC, and small short hepatic veins are divided and ligated up to the level of the inferior RHV. A long, light, curved aortic clamp is inserted behind the caudate lobe just to the left side of the inferior RHV and is passed cranially along the anterior surface of the IVC between the 10 and 11 o'clock positions, identifying the position of the clamp tip assisted by ultrasonography (by successively opening and closing the clamp) towards the previously dissected space between the RHV and the MHV until the clamp tip reaches suprahepatically. Normally, retrohepatic dissection can be performed without encountering any resistance. When adhesion between the IVC and the liver is severe due to previous surgery or inflammation in the caudal part of the retrohepatic IVC, causing resistance to the dissection, the retrohepatic dissection should be interrupted. A 10-mm–wide, soft silicon multitubular drain is seized with the clamp and pulled down through the retrohepatic space. When right hepatectomy includes the MHV, the tape is switched from the right to the left side of the MHV; this allows safer dissection of the MHV near the vena cava confluence. Segment 1 is divided to place the tape near the right portal pedicle. For right hepatectomy, liver hilar dissection is performed to divide the right hepatic artery and portal vein. The plane of parenchymal transection is marked on the Glisson capsule, according to the devascularization line.

Parenchymal transection is performed using either the clamp-crush technique or an ultrasound aspiration dissector with or without intermittent clamping of the hepatic pedicle. The liver is suspended with the tape during the transection. During deeper parenchymal transection, continuous traction is applied on the tape by holding both ends of the tape together. This maneuver helps in reducing venous backflow bleeding, facilitating a bloodless transection. Biliostasis and hemostasis of vessels smaller than 3 mm are performed using bipolar coagulation; larger vessels are ligated with clips or sutures. The right biliary duct is splitted near the Glissonian capsule close to the cut surface of the liver in order to avoid injury of the biliary confluence. At the end of transection, the two hemilivers are completely divided, joined together only by the hepatic veins.

After complete exposure of the IVC, the hepatic veins are cut at the ground level of the vena cava using a vascular clamp. All of the small caval branches are then individually ligated, and the RHV is isolated and divided extrahepatically. When the right liver is completely disconnected from the IVC and therefore isolated, the resected parenchyma is mobilized from the left to the right and is freed from its peritoneal attachments. This is the only step of the procedure when the resected liver is manipulated and compressed.

Results of the Anterior Approach and of the Liver Hanging Maneuver

The beneficial effects of the anterior approach on the operative and survival outcomes of patients who have undergone a right hepatectomy for HCC were established by Liu *et al.*[5] in a prospective randomized controlled study.[5] The patients were randomized to undergo resection of the tumor using the anterior approach technique (AA group, $n = 60$) or the conventional approach technique (CA group, $n = 60$). The overall operative blood loss, morbidity, and duration of hospital stay were comparable in both groups. Major operative blood loss of $\geq$2 L occurred less frequently in the AA group than in the CA group (8.3% vs. 28.3%, respectively; $P = 0.005$). As a result, the blood transfusion requirements and number of patients requiring blood transfusion were significantly lower in the AA group. Hospital mortality occurred in one patient in the AA group and in six patients in the CA group ($P = 0.114$). Median disease-free survival was 15.5 months in the AA group and 13.9 months in the CA group ($P = 0.882$); however, overall survival was significantly better in the AA group (median, >68.1 months) compared to the CA group (median, 22.6 months; $P = 0.006$). The survival benefit appeared more obvious in patients with stage II disease and patients with lymphovascular permeation of the tumor. The AA technique was also found to be associated with significantly lower plasma albumin mRNA levels at various stages of surgery compared with the CA technique.

However, there are some limits to the anterior approach. Some patients with a large tumor compressing a major hepatic vein can develop venous collaterals (Fig. 3). In these patients, parenchymal transection

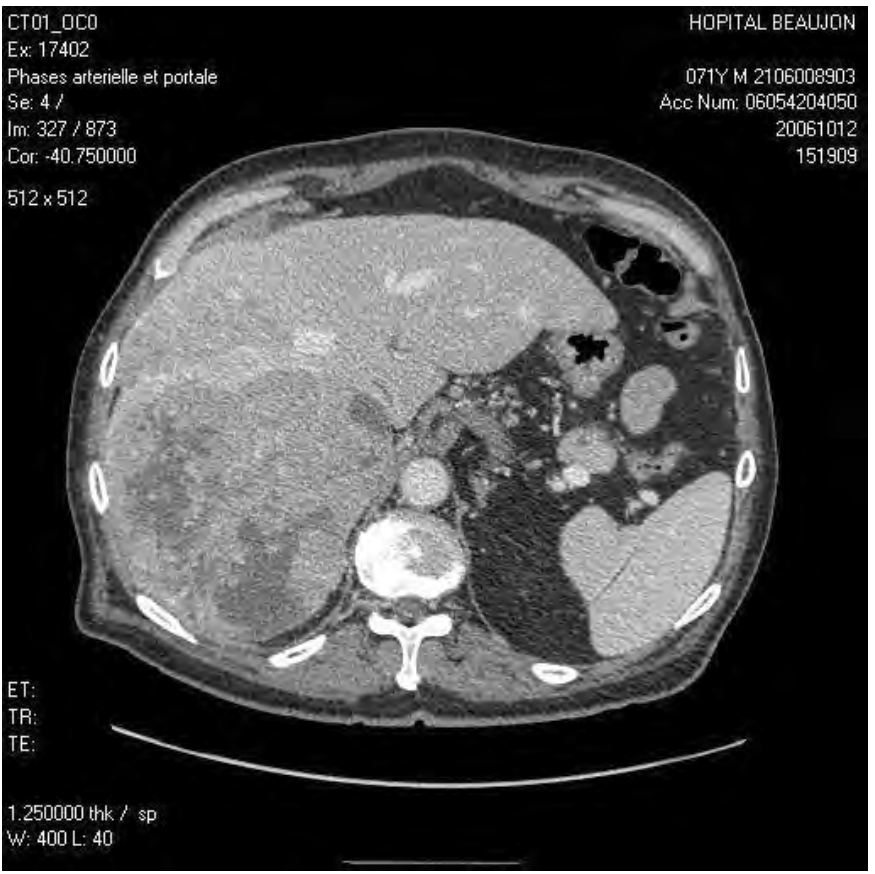

Fig. 3. Large HCC compressing a major hepatic vein with development of venous collaterals in the right liver. In this situation, parenchymal transection can be associated with massive bleeding from venous collaterals, and therefore preliminary mobilization of the liver is recommended.

without previous mobilization of the liver is associated with massive bleeding originating from venous collaterals. In such situations, after inflow clamping, the outflow should be reduced by mobilization of the liver with an upper traction impairing backflow from the IVC through multiple venous channels.

The feasibility and limits of the liver hanging maneuver have been established in a series of 242 patients considered for major hepatectomy

in our center. After the exclusion of 14 (6%) patients who were considered to have a contraindication to this maneuver preoperatively because of tumor infiltration of the anterior surface of the retrohepatic IVC, this maneuver was successful in 201 patients with an overall feasibility of 88%. The feasibility has increased significantly in recent years compared to the initial years (94% in 2003–2005 vs. 76% in 2000–2002, $P < 0.0001$). Bleeding during retrohepatic dissection occurred in 5 (2%) patients; it was minor in 3 (1%) cases due to injury of the hepatic capsule and major in 2 (1%) cases due to injury of the short hepatic vein. In all cases, bleeding stopped spontaneously. The maneuver was abandoned in 27 patients, of which 15 cases were abandoned due to severe adhesions between the liver and the IVC. Univariate analysis showed that adhesions between the IVC and the liver were the only significant negative predictor affecting the feasibility; cirrhosis, large tumor, and preoperative radiological treatments did not influence the feasibility. Thus, we advocate the attempt of this maneuver routinely in patients requiring a major hepatectomy.

Conclusions

The anterior approach for major liver resection for HCC represents a major technical improvement, leading to better intraoperative and postoperative outcomes. The advantages include intraoperative reduction of blood loss, preservation of postoperative liver function, and oncological benefits, ultimately resulting in better survival. According to the results of prospective studies and from our experience, it is possible to state that the anterior approach should be the preferred technique for major right hepatic resection for large HCC. It can be expected that this approach has the same advantages for all major resections in patients with other malignant tumors.

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18

Segment-based Liver Resection

W. Y. Lau and Eric C. H. Lai

Introduction

In 1898, Cantlie[1] first described the main anatomical division of the liver by showing that it was divided not along the plane of the falciform ligament, but rather along the principal plane (Cantlie's line) extending from the gallbladder fossa to the inferior vena cava (IVC). Couinaud[2] refined the functional anatomy of the liver, and demonstrated that the liver is divided into four sectors and eight segments. The eight segments are numbered clockwise in a frontal plane. The right liver consists of segments V to VIII, and is nourished by the right hepatic artery and the right portal vein; while the left liver consists of segments II to IV, and is nourished by the left hepatic artery and the left portal vein. The caudate lobe is segment I, which is nourished by both the right and the left hepatic arteries and portal veins. Each Couinaud segment receives its own tributaries from the portal pedicles (hepatic artery, portal vein, and bile duct) and drains independently into the tributaries of the hepatic veins. Each segment is therefore an independent

functional unit supplied by a single portal triad. Thus, each Couinaud segment can be resected individually or in combination with other liver segments.

Liver resections based on the liver segments are called segment-based liver resections.[3–7] The Brisbane 2000 system of nomenclature of hepatic anatomy and resections was introduced to provide a universal terminology in order to have better communications among surgeons (see Chapter 2).[8,9] This chapter illustrates the concept and the techniques of segment-based liver resection.

Rationale for Segment-based Liver Resection

There are many theoretical advantages of segment-based liver resection.[3–7,10–12] The anatomical boundaries between the individual liver segments are not crossed by large branches of the portal pedicles (hepatic artery, portal vein, and bile duct); therefore, these boundaries are relatively avascular planes that facilitate surgical resection and decrease intraoperative blood loss. Similarly, by avoiding damages to the portal pedicle, segment-based liver resection avoids leaving behind devitalized liver parenchyma in the liver remnant; this avoids the risk of infection and bile duct fistulation. Also, by predetermining the liver segments to be removed and by following the intrahepatic anatomy during parenchymal transection, an adequate resection margin can be guaranteed while at the same time preserving the largest amount of nontumorous liver parenchyma; this is particularly important for patients with cirrhotic livers. Lastly, there is a good oncological rationale for using segment-based liver resection because of liver tumor characteristics. Hepatocellular carcinoma (HCC) usually grows and is confined to one liver segment in the early phase of the disease. Intrahepatic tumor spread originates from tumor invasion of the portal venous branches, giving rise first to satellite metastases within the same liver segment, followed by involvement of the corresponding part of the same sector, and ultimately a complete hemiliver or bilateral spread to the whole liver. Indeed, vascular invasion and intrahepatic metastases are the risk factors that most strongly influence postoperative prognosis. Given that early satellite metastases lie in the same liver segment as the main tumor,

segment-based liver resection should be used to give the best chance of oncological tumor clearance.

In modern liver surgery for HCC, anatomical segment-based liver resection is considered to be a better operation than nonanatomical resection, although there is still a lack of good evidence from randomized studies to support this view. The prognostic benefit of segment-based anatomical resection has been evaluated. The retrospective study by Hasegawa *et al.*[13] showed that anatomical resection for patients ($n = 210$; Child–Pugh class A liver cirrhosis, 83%; Child–Pugh class B liver cirrhosis, 17%) with a single HCC achieved more favorable results than nonanatomical resection. Both the 5-year overall survival and disease-free survival rates in the anatomical resection group ($n = 156$; median tumor size, 35 mm) were significantly better than those in the nonanatomical resection group ($n = 54$; median tumor size, 30 mm) (66% vs. 35% and 34% vs. 16%, respectively). No hospital mortality occurred in both groups. Another retrospective study by Regimbeau *et al.*[14] showed that in selected patients with Child–Pugh class A liver cirrhosis and a small HCC ($\leq$4 cm), anatomical resections achieved better long-term and disease-free survivals than nonanatomical limited resections, without any increase in the postoperative risk. The 5- and 8-year patient survival rates were significantly better in the anatomical resection group compared with those from the nonanatomical resection group (54% vs. 35% and 45% vs. 6%, respectively). The 5- and 8-year disease-free survival rates in the anatomical resection group were also significantly better compared with those from the nonanatomical resection group (45% vs. 26% and 21% vs. 0%, respectively).

Although segment-based anatomical liver resection has been reported to improve the survival rate of patients with HCC, the decision whether to perform anatomical resection or nonanatomical resection in patients with colorectal liver metastases remains unclear. Survival data from some studies were in favor of anatomical resection,[15–17] while survival data in other studies showed no difference or were in favor of nonanatomical resection.[18,19] In a recently published review by Yasui and Shimizu,[20] they analyzed only those studies with more than 50 curative hepatectomies for colorectal liver metastases. The incidence of anatomical resection was >50% among patients in 56 series, while anatomical resection

was performed in <50% of patients in 17 series. Comparison between these two groups revealed a significant difference in the incidence of anatomical resection (72% vs. 34%, respectively), but no difference in terms of morbidity; mortality; 3-, 5-, and 10-year survival rates; or hepatic recurrence rate.

It should be noted that, in contrast to HCC, the underlying liver status in patients with liver metastases is usually noncirrhotic and the mode of spread of the disease is different. Surgical procedures are not selected in a random manner; instead, they are selected based on the size, location, or number of tumors. Small single tumors near the liver surface are usually resected by nonanatomical limited resection, while relatively large tumors or tumors that are deeply located near the hepatic pedicle are resected by anatomical major hepatectomy. Since the prognosis of colorectal liver metastases highly depends on the size and number of metastatic lesions, randomized studies are more appropriate for the evaluation.

Technique of Segment-based Liver Resection

The application of the principles of segment-based resection has been facilitated by the development of liver imaging techniques. In the preoperative investigation, ultrasonography (US) scan, computed tomography (CT) scan, and magnetic resonance imaging (MRI) can relate the location of the tumor to the anatomy of the intrahepatic vessels. However, the task of locating the tumor to the anatomy of the liver is made significantly more difficult when the procedure is performed on a cirrhotic liver because the intrahepatic vessels and ducts can be grossly distorted by the underlying cirrhosis. Another problem is that a small HCC within a cirrhotic liver is frequently not visible and not palpable, and preoperative imaging by US or CT scan may fail to pick up other satellite lesions within the liver.

Intraoperative ultrasound (IOUS) is indispensable in this situation, as it allows visualization of small tumors that usually escape detection during surgical exploration of a cirrhotic liver.[21–23] Our group[24] reported that IOUS decisively altered the preoperatively planned surgical treatment strategy in 25% of patients who underwent laparotomy,

and significantly decreased the rate of positive tumor margin involvement after liver resection compared with patients who received no IOUS (0% vs. 16%).

There are four methods to carry out segment-based liver resection, as described below.

Surface anatomy + IOUS

This method traces the borders of the liver segments on the surface of the liver using surface anatomical landmarks as well as the hepatic and portal vein structures on IOUS.[24–26] In general, the steps of IOUS in segment-based liver resection are as follows: (1) general inspection of the whole liver to detect unexpected lesions not detected preoperatively; (2) a systematic anatomical study to trace the three hepatic veins, the portal bifurcation, and its branches so that the individual Couinaud liver segments can be determined (please see latter part of the text); (3) location of the tumor in the liver segment(s); (4) determination of the liver segment(s) to be resected; and (5) marking of the parenchymal transection line on the surface of the liver and redetermination of the distance from the resection margin to the edge of the tumor.

The three major hepatic veins divide the liver into four sectors. By tracing the sectorial portal venous branch of each liver sector, the branch of the portal vein supplying each individual liver segment can be identified. The division between the right liver and the left liver is along a plane that runs from the gallbladder fossa to the IVC, i.e. the principal plane. Inside this principal plane, the middle hepatic vein is shown on IOUS. The left liver is further divided into the lateral sector and the medial sector along a plane inside which runs the left hepatic vein (left medial sector, segments III and IV; left lateral sector, segment II). On surface anatomy, the medial sector is divided by the falciform ligament into segments III and IV. Segment IV lies between the principal plane and the falciform ligament. The right liver is divided into the right anterior and posterior sectors along a plane inside which runs the right hepatic vein; each of these two sectors consists of two segments (right anterior sector, segments V and VIII; right posterior sector, segments VI and VII). There is no surface anatomical landmark in the right liver to identify the

individual sectors/segments. The caudate lobe (segment I) is the dorsal portion of the liver posteriorly and embraces the retrohepatic IVC; it is mainly recognized by its anatomical landmarks (see Chapters 2 and 21).

After marking the liver segments on the surface of the liver, the liver parenchyma is then transected, and the pedicles of the vessel and the bile ducts of the relevant liver segments are divided at the end of the parenchymal transection. As intraoperative blood loss and transfusion during liver resection are significant prognostic factors for the outcome of liver resection, and clamping of the portal triad (Pringle's maneuver) is associated with less blood loss compared with no clamping, Pringle's maneuver is usually used. Its use is determined by the tumor location, underlying liver disease, patient's cardiovascular status, and most importantly the experience of the surgical and anesthesia teams. It should be noted that, in the use of this method of segment-based liver resection, it is essential for surgeons to have a detailed knowledge of the intrahepatic vascular anatomy and skill in IOUS.

Preliminary control of the vascular pedicles of the segment to be removed

This approach is especially useful in the resection of segments of the right liver.[27,28] The right and left hepatic pedicles are dissected extrahepatically on the undersurface of the liver. Lowering of the liver plate helps to increase the extrahepatic length of these pedicles. By dissecting and tracing the right pedicle distally, the right anterior sectorial pedicle (segments V and VIII) and the right posterior sectorial pedicle (segments VI and VII) are found. Similarly, by dissecting and tracing the left pedicle distally, the segment IV pedicle as well as the segment II and III pedicles are found. Further dissection distally exposes the pedicles inside the liver (segmental pedicles to the liver segments require liver parenchymal transection). Occlusion of the relevant pedicle by a bulldog clamp results in a change in color of the liver segment. The arterial and portal pedicles are ligated and divided at the end of the parenchymal resection. This technique requires more tissue dissection and a longer operating time than the other techniques, and is technically more difficult in patients with cirrhosis and portal hypertension.

Ultrasound-guided puncture of portal vein branch and injection of dye

The portal branch supplying the liver segment to be resected is punctured under ultrasound guidance.[21–23] A few mL of methylene blue or Congo red is then infused into the portal branch. The dye stains the liver segment corresponding to the limits of the liver transection plane. Transection is then carried out. This technique requires great expertise in interventional US, and for this reason has not gained wide acceptance (see Chapter 20).

Selective portal venous occlusion using a balloon catheter through a branch of the superior mesenteric vein

This technique is carried out during open surgery using a bilateral subcostal incision with an upward midline extension.[29] The liver is completely mobilized by division of the liver ligaments. A 6 French balloon catheter is inserted into the portal vein via a branch of the superior mesenteric vein. The catheter is guided to the corresponding branch of the portal vein (either the right or the left) where the HCC is situated, with the surgeon's hand in the porta hepatis. Once the tip of the catheter is in the intrahepatic portal venous system, further advancement of the catheter into the sectorial and segmental portal venous branches is done by rotating and advancing the catheter using the trial-and-error method. Guidance of the catheter tip into the desired portal venous branch is assisted with ultrasound and the surgeon's hand in the porta hepatis.

When the balloon catheter is in the right position, the balloon is inflated with 3 mL of normal saline to occlude the venous branch. A few milliliters of methylene blue is injected through the catheter to delineate the liver segment to be resected. The line of demarcation is marked on the liver surface with a diathermy device. The procedure is repeated if more than one liver segment needs to be delineated. The time required to get the catheter in the right position is around 10 min. The hepatic parenchyma is then transected along the line of demarcation. After hemostasis on the raw liver surface, the balloon catheter is deflated.

The branch of the superior mesenteric vein is ligated after the catheter is removed.

Nonanatomical Liver Resection

Nonanatomical resection is a more suitable operation than segment-based liver resection in two situations: first, when the tumor is situated at the border of several segments; and second, when the tumor is small and is situated peripherally at the edge of the liver. Under such a situation, a wedge excision made in the shape of an arch or box is a simpler operation than a segment-based liver resection. Wedge excision should not be done in a V-shape because of the higher chance of the resection margin being involved by the tumor on histological study.

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19

Intrahepatic Glissonian Approach

Bernard Launois and Khoon Hean Tay

Introduction

By analogy to the lung, the two divisions of the liver are best called the right liver and the left liver. Thus, "right hepatectomy" and "left hepatectomy" are semantically appropriate terms for the removal of those parts of the liver. Eight anatomic segments — which are numbered in turn from the caudate lobe in a spiral, like the arrondissements of Paris — compose the two livers; any one of these segments can be removed individually (by segmentectomy). The right lateral, right medial, and left medial sectors are agglomerations of segments and can be removed by sectorectomy.[1,2] This segmental anatomy of the liver — which has led to such a rapid evolution of resectional surgery — is based on the intrahepatic distribution of the portal trinity, the principal components of which are the portal vein, the hepatic artery, and the bile duct (and their divisions).

Glisson described the connective tissue capsule surrounding the liver tissue — which bears his name — in 1645, although Valoeus had already

described connective tissue surrounding the structures in the hilum of the liver in 1640. Glisson's capsule condenses around the hepatic trinity structures as they enter the liver substance; and each bile duct, hepatic artery, and portal vein unit is surrounded by a fibrous sheath called the Glissonian or Valoean sheath. Any portal pedicle entering the parenchyma takes a sheath, which accompanies the pedicle up to the sinusoids. All variations in the branching of the sectorial and segmental pedicles are inside the Glissonian sheath, which contains the exact elements supplying the parenchyma entered by this sheath; at this level, no error is possible (if, for instance, a pedicle is duplicated, two sheaths enter the parenchyma).

Suprahilar control of the portal trinity of the resected liver substance is an important step of the procedure, as it can delineate the precise frontiers of the resection.

Different Approaches to the Glissonian Sheaths (Fig. 1)

Intrafascial or hilar (extrahepatic) approach

This approach was first used in liver surgery by Lortat-Jacob and Robert[3] for the first extended right hepatectomy. Vascular and biliary structures of the portal trinity are extrahepatically dissected in the hilum (Fig. 2). This dissection is difficult and time-consuming, as the operator must recognize variations and errors in identification of the branches as much as is possible. Nevertheless, this technique has been taken to its extreme, mainly by Japanese authors who continue the dissection of the portal pedicle inside the Glissonian sheaths until the segmental branches are reached within the liver.

Within each sheath, the portal vein is surrounded by loose areolar tissue, making dissection of it relatively easy. The condensation of fibrous tissue around the bile duct and hepatic artery is tougher, and dissection of these structures is therefore more difficult within the sheaths. There are many variations, however, that make dissection of individual structures within the liver difficult and even hazardous.

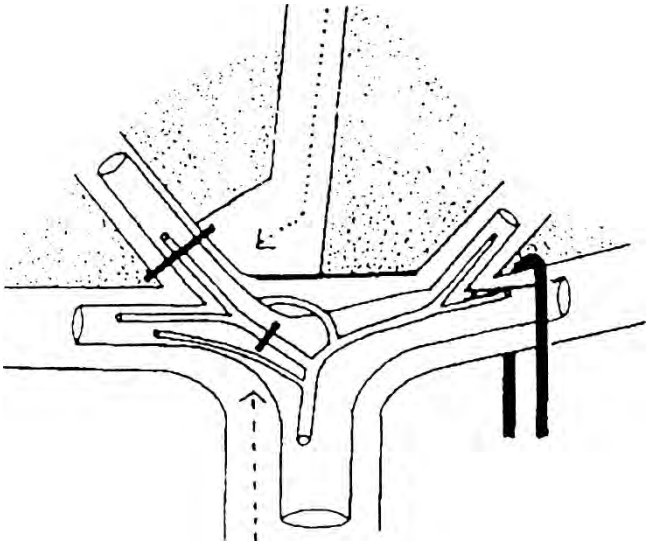

Fig. 1. The three approaches of intrahepatic Glissonian pedicles: intrafascial (within the hilum), extrafascial (outside the sheath), and transfissural.

Extrafascial approach[1,4–10]

In this approach, the whole sheath of a pedicle is dissected directly. This isolates the portal elements of the supplied territory exactly, and so avoids any possible error. In the extrafascial approach alone, a whole pedicle is rarely dissected directly[1,4–7]: the left medial pedicle when the umbilical fissure is open (without the intervening liver parenchymal bridge), often the whole left pedicle, and occasionally the right lateral pedicle when visible in a Rouviere's fissure. However, Takasaki developed this procedure for the right liver in 1986,[6] and published this technique in the English-language literature in 1990.[7] He recognized that Couinaud developed this extrafascial approach, but only for left hepatectomy[4–7]:

> The first branches of the Glissonian sheaths are located outside the liver. This portion is joined to the hepatic parenchyma by thin connective tissue only. Therefore, it is quite easy to detach

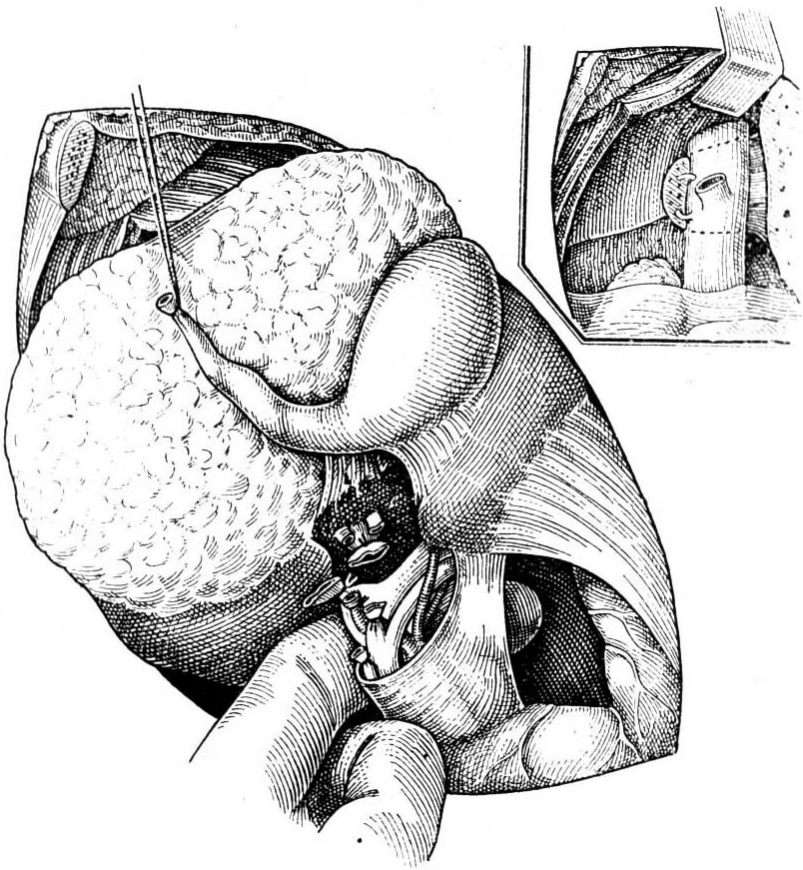

Fig. 2. Intrafascial (extrahepatic) approach.[3]

the connective tissue from the liver tissue without lacerating the hepatic parenchyma and tape it after blunt dissection. For the right and middle sectors, the Glissonian sheath is ligated and cut at this portion as one bundle. The root of each secondary branch, as well as those of the first branches can be easily taped in the same manner. The root of the branches of the right lateral and medial sectors can be isolated with ease. There are holes about one cm in diameter at the right edge of the hepatic hilus. Through these holes, the branches of Glissonian sheaths in the right lateral and medial sectors are seen to enter the liver parenchyma.[6,7]

The same year, in 1990, Galperin and Karagiulan[8] used small incisions on the inferior surface of the liver, tunneling into the liver parenchyma, until the sheath was found.

In the extrafascial approach, combined with detachment of the hilar plate,[9] the peritoneum and the connective tissue are incised at the junction between the quadrate lobe and the hilum. Dissection close to the plate separates it from the parenchyma without hemorrhage. This approach was used by Lazorthes *et al.*[10] for suprahilar control of the right main sheath and right medial sheath.

Transfissural (or intrahepatic) approach

This approach comprises the anterior intrahepatic approach[1,4,11–13] and the posterior intrahepatic approach,[14,25] which was recently described.

Principles of the anterior intrahepatic approach

These principles were first elaborated by Couinaud[1] and were developed by Tung.[11] Essential points in this approach that differ from the traditional approach are as follows:

1. The extrahepatic pedicle structures (portal vein, hepatic artery, bile duct) are not dissected separately. A finger or blunt instrument is passed through the epiploic foramen and through the lesser omentum; and the hepatic pedicle is thus encompassed, a tape is passed, and the structures are clamped *en masse*. Clamping is for periods of 15–20 min, with a period of unclamping for 10 min before further clamping.
2. The hepatic veins are not dissected extrahepatically, but are sought posteriorly within the liver towards the completion of a resection.
3. Dissection usually begins with an incision along one of the scissurae of the liver. Thus, for right or left hepatectomy, the incision is along the line of the main fissure before the hepatic pedicles or veins are isolated. The main fissure of the liver has no external markings, and so the lines of dissection are usually only estimates of where the fissure lies. The hepatic pedicle structures are then isolated as the final stage in the operation.

The aim is always to dissect out the Glissonian sheath at as early a point in time as possible. With large right-sided tumors, it is often necessary to incise the main scissura with the advantage of not mobilizing the liver, which means dissecting an appreciable amount of anteriorly placed liver substance, in order to find the sheath to the right side of the liver (Fig. 3). But with smaller and left-sided tumors, the appropriate sheath can usually be dissected early in the operation. In fact, for a right hepatectomy, complete mobilization of the liver before parenchymal dissection is considered a basic maneuver for a safe procedure.

When a huge tumor invades the diaphragm, this mobilization may be difficult. Lai *et al.*[12] emphasized the role of the anterior approach with parenchymal transection from the anterior surface down to the inferior vena cava (IVC). The absence of liver rotation has many advantages. It may avoid tumor dissemination and requires no compression of the remnant liver. Because it may be difficult to control bleeding in the deeper parenchymal plane, Belghiti *et al.*[13] proposed a new procedure of "hanging the liver" after lifting it with a tape passed between the anterior surface of the IVC and the liver parenchyma.

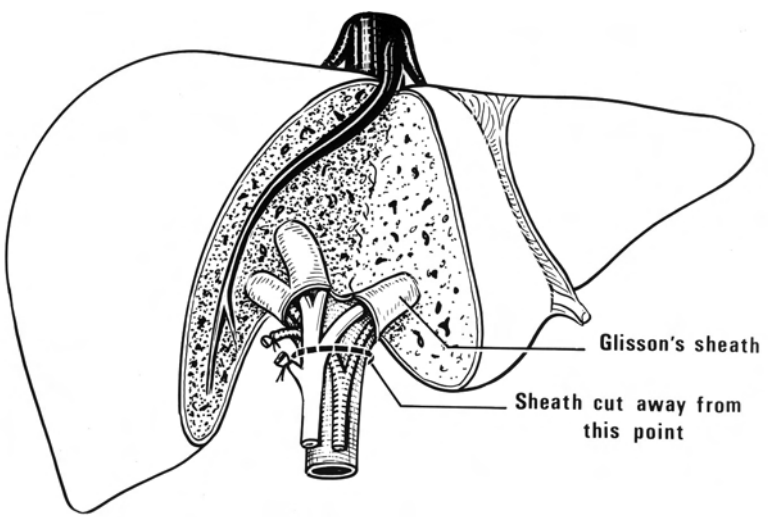

Fig. 3. Anterior transfissural approach.[1,11,12] With permission from *Surg Gynecol Obstet.*

Posterior intrahepatic approach (through the dorsal fissure)[14,15]

It is possible to gain certain advantages of the intrafascial (extrahepatic) and anterior (intrahepatic) approaches without their attendant disadvantages, and essentially without any mobilization of the liver. This combines the intrahepatic approach to the Glissonian sheaths with the precision attendant upon early division of the hepatic pedicle extrahepatically in providing a precise delineation of the line of resection for both hepatectomy and segmentectomy procedures. This approach is made via the dorsal fissure, i.e. between segments 4 and 1 as well as between segment 8 and the new segment 9, as described by Couinaud (Fig. 4).[4] This dorsal fissure is an oblique plane, which is located from the posterior edge of the hepatic hilum to the confluence of hepatic veins to the IVC. (Fig. 5).[16]

Approach to the confluence, the right main pedicle, and the right medial pedicle

It is important to first ligate the lowermost retrohepatic veins draining from the caudate process and lower part of the liver to the vena cava. Failure to do this may tear these veins, resulting in hemorrhage during the placement of a finger or a dissector about the right portal

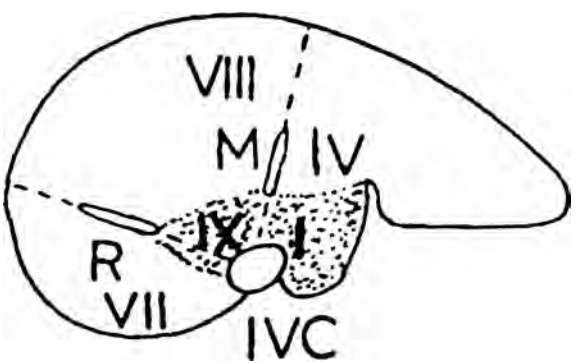

Fig. 4. Dorsal fissure between segments 4 and 1, and between segments 8 and 9.[4] M, middle hepatic vein; R, right hepatic vein.

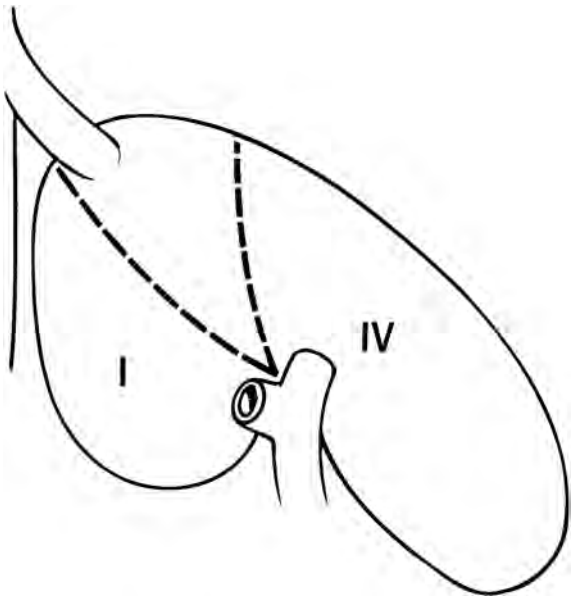

Fig. 5. The dorsal fissure is orientated from the posterior edge of the hepatic hilum to the confluence of the hepatic veins.

pedicle. This preliminary move is essential before utilizing the posterior Glissonian approach.[17]

The caudate process immediately behind the hilum is divided at the junction of the hilum with the liver substance. The incision is approximately 30 mm in length. A second incision is then made (Fig. 6) in front of the hilum and parallel to the first incision, extending from the gallbladder bed on the right to the umbilical fissure on the left. The incision is deepened and the liver parenchyma is pushed upwards and away from the hilum in front in order to expose the Glissonian sheath of the confluence of the hepatic pedicle structures. This dissection in front of the hilum corresponds to the procedure that Couinaud[1] as well as Hepp and Couinard[9] described as detachment of the hilar plate. An index finger is now passed into the incision behind the hilum and the undersurface of the sheath is kept above the finger (Fig. 7), which is insinuated between the sheath anteriorly and the caudate process posteriorly until the superior part of the previously dissected

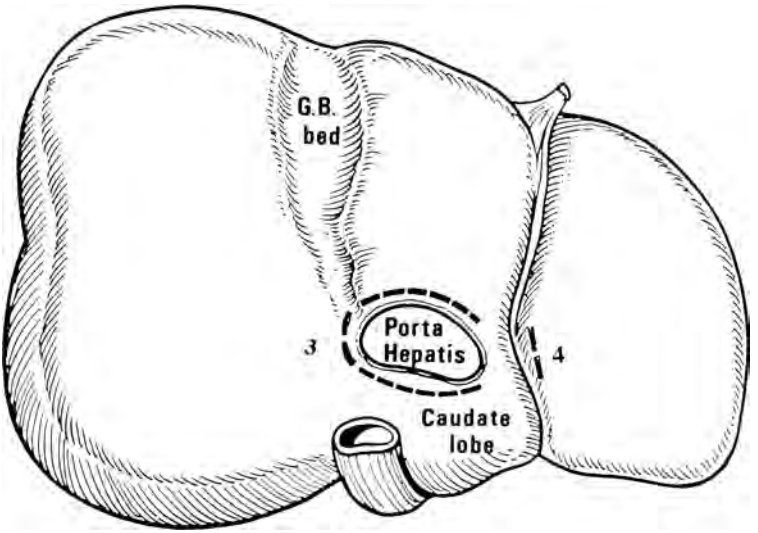

Fig. 6. Incisional lines to allow Glissonian sheaths to be isolated. With permission from *Surg Gynecol Obstet.*

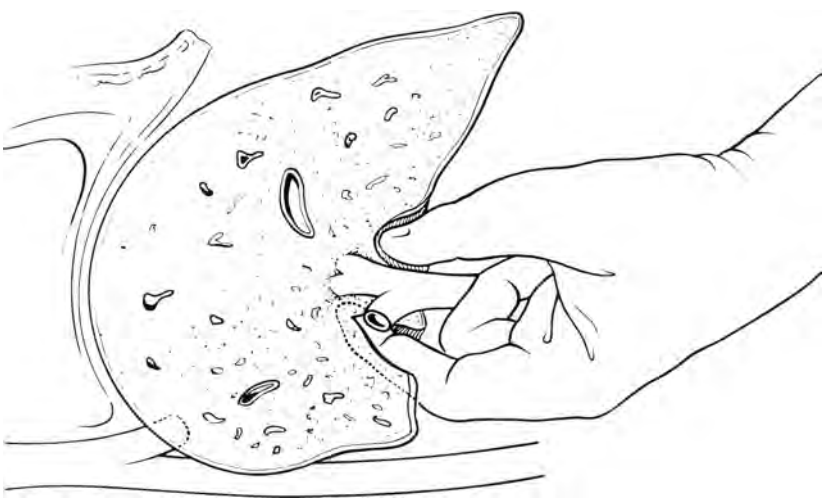

Fig. 7. Illustration of the digital isolation of the Glissonian confluence. With permission from *Surg Gynecol Obstet.*

sheath is reached. The surgeon's index finger and thumb of one hand are now placed in the liver substance, with the index finger in the caudate process incision and the thumb in front of the hilar plate (Fig. 7). A large curved clamp is then used to pass a tape around this region of the confluence. Traction on the tape tends to exteriorize both the right and left main sheaths (Fig. 8). By further dissection distally, tapes can be passed around whichever sheath is required for further dissection.

The identity of the sheaths dissected may be known from a knowledge of the intrahepatic anatomy; but variations are so common that confirmation should always be sought by clamping each sheath with a vascular clamp, with the main hepatic pedicle unclamped (Fig. 8). Color changes in the liver substance then identify the region of the liver that the sheath subserves. A sheath to segment 6 is often found first just behind the posterior edge of the gallbladder bed. The sheath to the right medial sector is deeper and often appears (Fig. 9) to be the continuation of the main sheath. This sheath can usually be exposed relatively easily through this approach.

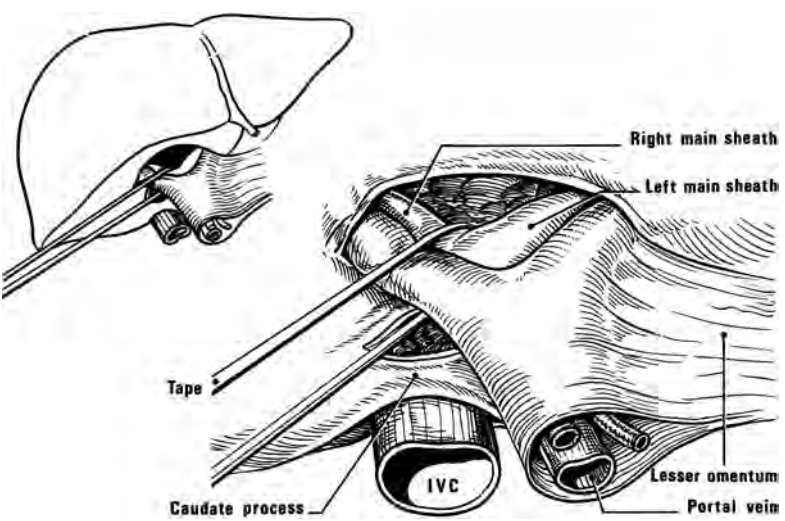

Fig. 8. Traction on the tape to exteriorize the right and left main sheaths. With permission from *Surg Gynecol Obstet*.

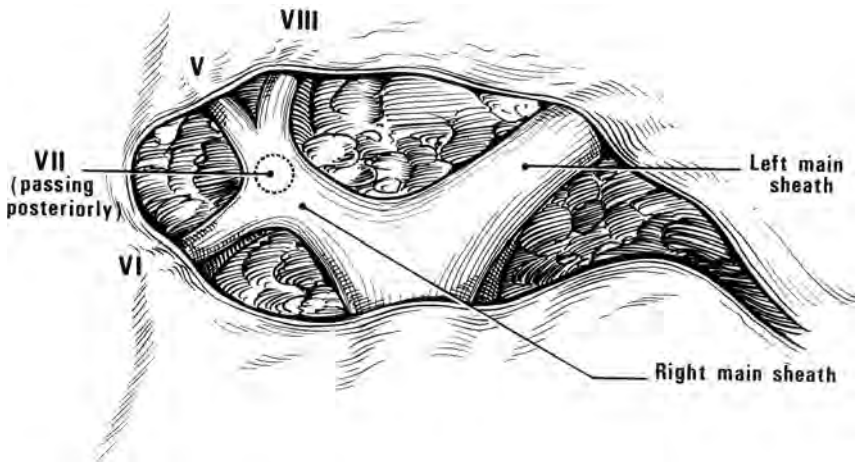

Fig. 9. Anatomy of the pedicles. The anterior sectorial pedicles to segments 5 and 8 pass upwards. The posterior sectorial pedicles to segments 6 and 7 run posterolaterally. With permission from *Surg Gynecol Obstet.*

Approach to the right lateral pedicle

Further dissection is required to obtain the sheaths to branches for segments 5 and 8. The sheath to the right lateral sector is the most deeply placed of the right sheaths. Dissection is facilitated by dissection in the gallbladder bed with the use of a semicircular incision that vertically joins the anterior incision in front of the hilum and the posterior incision behind the hilum. Laterally, the liver parenchyma is pushed away. The tape placed around the Glissonian confluence is held downwards and forwards. The surgeon's right index finger is now passed upwards and inwards along the undersurface of the right main sheath. A sheath that dives backwards is found, and the forefinger lies on its medial surface. The sheath between the surgeon's thumb and forefinger is the right lateral sheath (Fig. 10).[15]

Hepatectomies

For hepatectomies, color changes in the liver substance identify sectors and fissures. In right hepatectomies, once the medial and right lateral

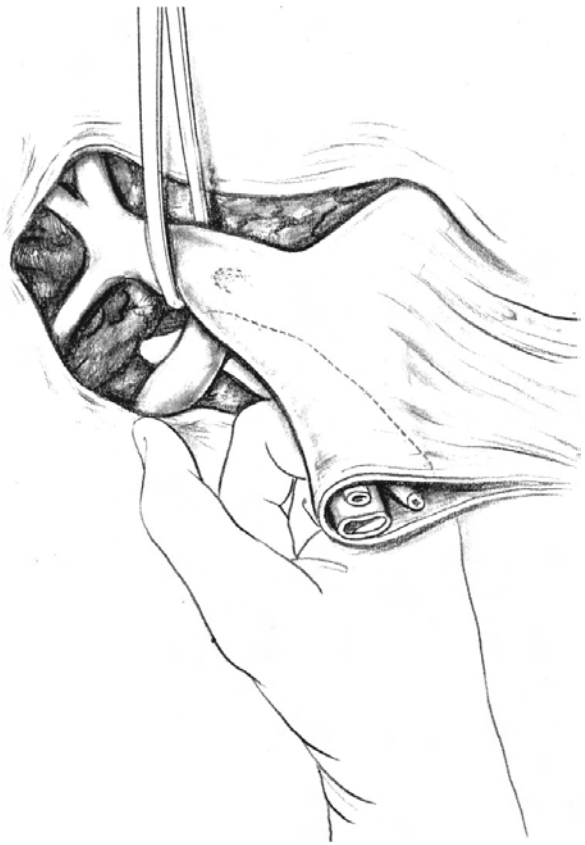

Fig. 10. The method of dissecting out the sheath to the right lateral (posterior) sector of the liver. It is difficult to render this life-like and, in reality, the posterior-dissected sheath — shown with the surgeon's index finger behind it — is much deeper than shown in the diagram. In the case represented, the sheath to segment 6 has come off seemingly separate from the posterior sheath, which is therefore the sheath to segment 7.[15]

sheaths have been exposed and trial clamping demonstrates the demarcation line along the main fissure, both Glissonian sheaths are divided with a vascular stapler (TA or Endo GIA). (Fig. 11).[15,17,18] The division of both Glissonian pedicles is safer than the division of right main Glissonian pedicles, with no risk of the left hepatic bile duct being inadvertently damaged resulting in subsequent stricture.

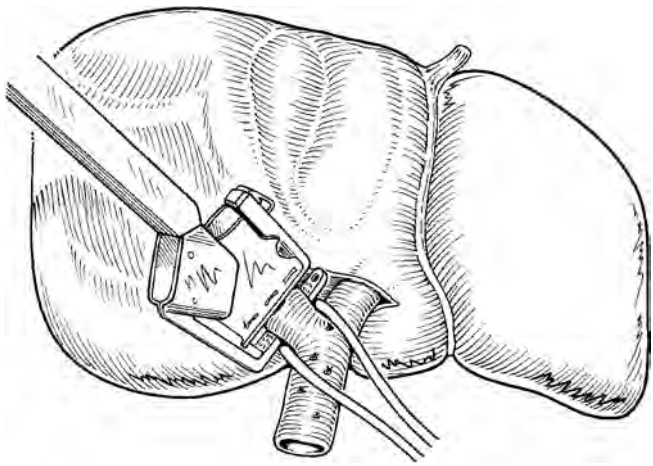

Fig. 11. The right medial pedicle is controlled by a vascular stapler, and is subsequently divided or maybe controlled and divided with the Endo GIA vascular stapler.[17]

In a right extended hepatectomy, the first step is to utilize the posterior approach for clamping and dividing the right medial and lateral pedicles. This posterior approach also has the important objective of protecting the left hepatic pedicle by taking down the main hepatic duct from the undersurface of segment 4. The second step is to open the umbilical fissure and to divide veins and arteries from the left portal trinity to segments 4a and 4b.

In a left extended hepatectomy, the left hepatic Glissonian sheath is controlled and divided, usually extrahepatically. The difficulty here is the identification of the transection line of liver parenchyma. Moreover, the right lateral fissure can be very variable; it can terminate at the main fissure, to the right edge of the liver, or between these two limits. This fissure can be accurately defined by clamping the medial Glissonian sheath to the right liver (or alternatively, the right lateral sheath when the right medial pedicle is inaccessible), utilizing the posterior approach with the opening of the dorsal fissure.[14,15] The right lateral sector bile duct (the only remaining bile duct) is extremely vulnerable to injury during an extended left hepatectomy (Fig. 12). If the operator ligates the sheath to the medial sector *en masse*, it is important to do this as distally as possible in order to avoid damaging the lateral sector bile

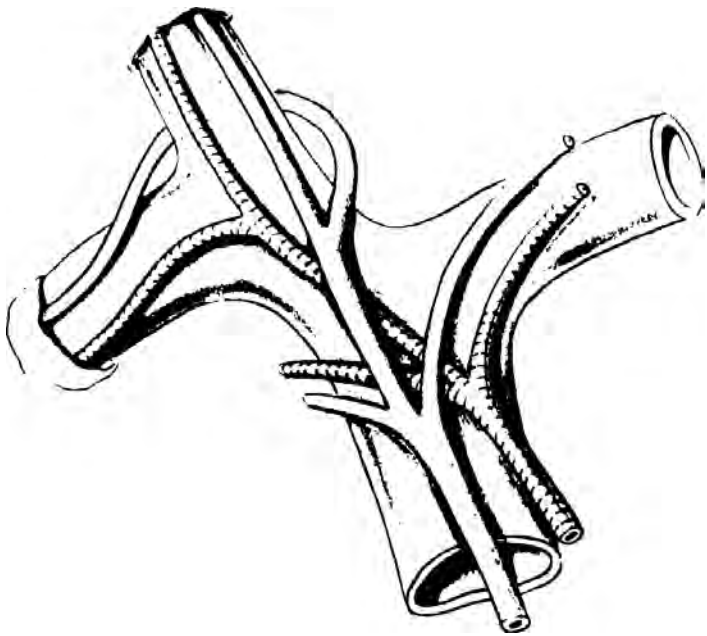

Fig. 12. The risk of stricture of the right lateral bile duct by clamping and stapling the right medial pedicle.

duct. The safest technique is to ligate the sheaths to segments 5 and 8 individually.[14,15,19]

The advantages of using the vascular stapler are that it allows for easy handling and secure suturing, taking all of the structures of the portal trinity *en bloc*, but at the same time including the strong structure of the Glissonian sheath — hence, a concomitant lower risk of biliary fistula.

Sectorectomies and Segmentectomies

If it is easy to recognize the limits of right lateral and right medial sectors, it is more difficult to know the limit between segments 6 and 7 as well as between segments 5 and 8. The clamping of the first sheath to segment 6 in the hilum permits recognition of its upper boundary with segment 7. The limit between segments 5 and 8 is recognized by elective clamping or ligation of each pedicle of segment 5, often after opening the main

fissure. For elective segmentectomy 8, the right index finger should be passed upwards and forwards in the dorsal fissure above the sheaths to segment 5 in order to permit an anterior incision of liver parenchyma in front of Glissonian sheaths to segment 8. When the confluence of the main sheaths is mobilized as described, access to the left main sheath is gained. This approach proves useful to the left sheath mainly when there is a huge tumor of the left liver. However, for access to the left main sheath, it is usually better to undertake the posterior approach from the left; thus, the lesser omentum is divided and the posterior incision is behind the ligamentum venosum on the caudate lobe. Finally, a circular incision around the hilum exposes all of the Glissonian sheaths. This circular incision realizes a complete "superficialization" of the Glissonian sheaths.

Indications and Discussion

The indications for the posterior approach of the hilum are technical and oncological. The extrahepatic approach to liver resection is time-consuming and does not easily lend itself to carrying out resections of single or double segments of the right side of the liver. Furthermore, there are many anatomical variations which may be encountered that increase the difficulty of the procedure and introduce the danger of damaging essential structures. An intrahepatic approach from the anterior surface of the liver requires considerable division of liver parenchyma before the intrahepatic pedicle is reached; and whilst this is of no consequence if a hepatectomy is to be carried out, it may be unnecessary for segmental resections, particularly on the right side of the liver. Neither of these approaches allows early delineation of the segments of the liver, leading some surgeons to suggest ultrasound and staining techniques in order to define the segments.

The approach described here allows the surgeon to dissect and clamp the required sheath early in the operation and to define the boundaries of the segment(s) to be removed. This is particularly helpful when removal of one or more individual segments from the right side of the liver is planned. Another advantage relates to clamping of blood supply to the liver. If the right lateral sector of the liver or one of its segments (segment

6 or 7) is to be removed, only the right main sheath need be clamped, allowing the clamp on the main hepatic pedicle to be removed. The main technical indications[15] are left and right hepatectomies in which the Glissonian sheaths are clamped, stapled, and divided before opening the liver parenchyma. It is particularly useful in left hepatectomy extended to segments 5 and 8, in which the section of the liver parenchyma follows the right lateral fissure containing the right superior hepatic vein. In fact, this right lateral fissure is very variable, finishing sometimes in the right edge of the liver and sometimes in the main fissure. Here, the posterior approach is useful, as mentioned earlier in this chapter, to define the right medial anterior sheath for two reasons. First, the clamping of this sheath allows delineation of the line of incision in the liver substance. Second, the sheath which is to be retained and the right main sheath are dissected early, minimizing the risk of damage to them during the procedure.

However, the main interest of the posterior approach of the hilum is to give access to the pedicles of the segments of the right liver: pedicles of segments 5, 6, and 8. With the identification of the Glissonian pedicles at the beginning of the procedure, there is no blind dissection of the liver parenchyma. Right medial and lateral sectorectomies as well as segmentectomies 5, 6, and 7 are particularly easy. The limits of segment 8 can be similarly defined before dividing liver parenchyma. The posterior intrahepatic approach is also an excellent method of preparing for resection of the caudate lobe, when dissecting the confluence from segment 1 and when opening the dorsal fissure.

The main oncological indications for the posterior approach are Klatskin tumor, primary liver cancer, and liver metastases. In primary liver cancer without cirrhosis, the use of the posterior approach fulfills two objectives: initial ligation of the vascular pedicle (avoiding the dissemination of neoplastic cells) and a large clear margin. A third objective of saving liver parenchyma is achieved in cirrhotic liver, but the liver parenchyma is difficult to dissect. If the caudate process is enlarged in a cirrhotic patient, it may prove to be difficult to make the incision behind the hilum of the liver; therefore, this approach is not suitable in such cases.

In cases of bilateral and several hepatocarcinomas, the posterior approach facilitates hemisegmentectomies, unisegmentectomies, or bisegmentectomies in both livers *à la carte*. The only oncological contraindication to the posterior approach is the involvement of the Glissonian confluence. In such cases, it is preferable to use the intra-Glissonian extrahepatic approach with elective division of the portal vein, hepatic artery, and biliary duct. A clear margin of more than 1 cm can be obtained. Even in liver transplantation, this approach makes possible a precise undertaking of split liver with the dissection *in situ* of the Glissonian sheaths through selective clamping of the sheath and precise delineation of the fissure.

We believe that the use of the perihilar posterior intrahepatic approach to the hepatic sheaths of the right liver segments has been a considerable advance in our management of neoplastic liver disease. It allows oncologically sound but minimally resective surgery to be performed safely, with excellent short- and medium-term results.[20] The Glissonian approach should be part of the armamentarium of all hepatic surgeons.

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20

Ultrasonically Guided Segmentectomy and Subsegmentectomy

Taku Aoki, Norihiro Kokudo and Masatoshi Makuuchi

Introduction

Radical treatments for small hepatocellular carcinoma (HCC) include liver transplantation and liver resection. In this era of severe graft shortage, liver resection remains a valid therapeutic option for patients with good hepatic functional reserve.[1]

HCC cells have a high propensity to invade the portal venous system.[2,3] HCC cells infiltrate the portal vein, where they can then grow into a portal venous tumor thrombus and/or spread via the portal blood flow, resulting in the formation of intrahepatic metastases. If these cells form a macroscopic tumor thrombus, the thrombus itself becomes a new source of metastatic cancer cells (Fig. 1).[2] In fact, vascular invasion and intrahepatic metastasis are the strongest prognostic factors among various clinicopathological features after surgery for HCC.[4–13] Therefore, surgery for HCC should involve, in theory, resection of the tumor-bearing portal venous branches and the corresponding liver parenchyma. On the other hand, HCC frequently arises in cirrhotic

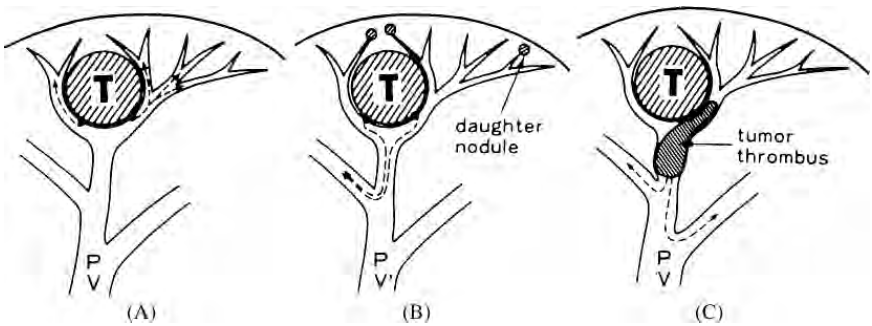

Fig. 1. Schema for intrahepatic extension and invasion of hepatocellular carcinoma (HCC). (A) A HCC tumor invades the portal venous branches, and tumor cells are carried to the distal part of the liver by the portal venous flow. (B) These cells grow into microscopic tumor thrombi and then into intrahepatic metastases. (C) Tumor thrombi are a source of wider tumor spread. PV, portal venous branch; T, tumor (reproduced from Ref. 3, with permission).

livers; such patients are often affected by compromised liver functional reserve and have a high risk of postoperative morbidity because of their poor liver functions.[14,15] Thus, surgeons should aim to spare as much functional hepatic parenchyma as possible.

Ultrasonically guided subsegmentectomy (Makuuchi's procedure) is a method for performing minor liver resections that can be classified as an anatomic hepatectomy. This procedure was developed to overcome the dilemma between the benefits and risks of surgical procedures.[2] The use of intraoperative ultrasound (IOUS) enables surgeons to resect portal areas of one segment or smaller.[15–17]

Indications

The indications for hepatectomy are decided mainly by two factors: the spread of HCC and liver function. Based on the clinical experiences of the National Cancer Center Hospital in Tokyo, Japan, patients are selected and the resection area is decided using the criteria shown in (Fig. 2).[18] Briefly, patients without ascites and with a normal bilirubin level (less than 1.0 mg/dL) are considered good candidates for various surgical procedures other than limited resection, and the area of the liver

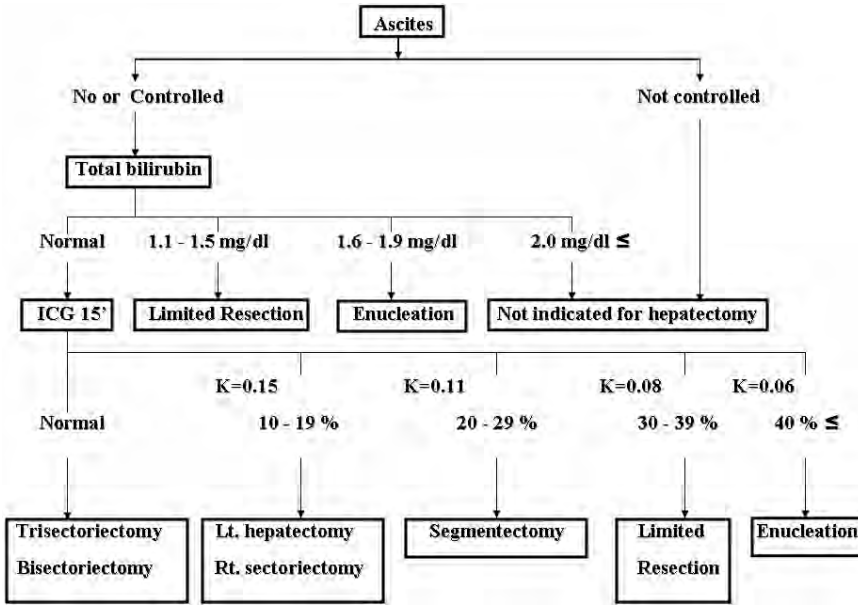

Fig. 2. Decision tree for selecting operative procedures in patients with HCC and liver cirrhosis (reproduced from Ref. 18, with permission).

that can be safely resected is determined according to the indocyanine green retention rate at 15 minutes (ICG-R15). When the ICG-R15 is more than 20%, a sectoriectomy — which results in the removal of approximately one third of the liver parenchyma — is not indicated, but a segmentectomy remains feasible. Such a resection is roughly equivalent to the removal of one sixth of the liver parenchyma. If the ICG-R15 is 30% or more, an anatomic resection — even a subsegmentectomy — is not considered to be indicated, and the tumor is resected using a limited resection or enucleation. When the extent of the HCC in the liver is limited to a resectable area defined according to the above-described criteria, hepatectomy is considered to be indicated even if multiple tumors are present.

Using these criteria, we have performed more than 900 hepatectomies in patients with HCC, resulting in only two postoperative deaths during the last 12 years at the Tokyo University Hospital.[19] The two deaths were attributed to postoperative acute pancreatitis in one patient

and the rapid growth of lung metastases in another patient with a hepatic venous tumor thrombus.

Operative Procedure

The operative procedure for an ultrasonically guided segmentectomy/subsegmentectomy is roughly composed of three steps: (1) identification of the tumor-bearing segment/subsegment by IOUS-guided dye injection into the portal venous branches feeding the domain, (2) recognition of the correct ligation point on the portal venous branch, and (3) resection of the liver parenchyma under blood inflow occlusion (Fig. 3).[2]

In most cases, the portal area of one segment or smaller cannot be identified by ligation of the extrahepatic feeding artery and the portal venous branch for the area, except for segments in the left hemiliver

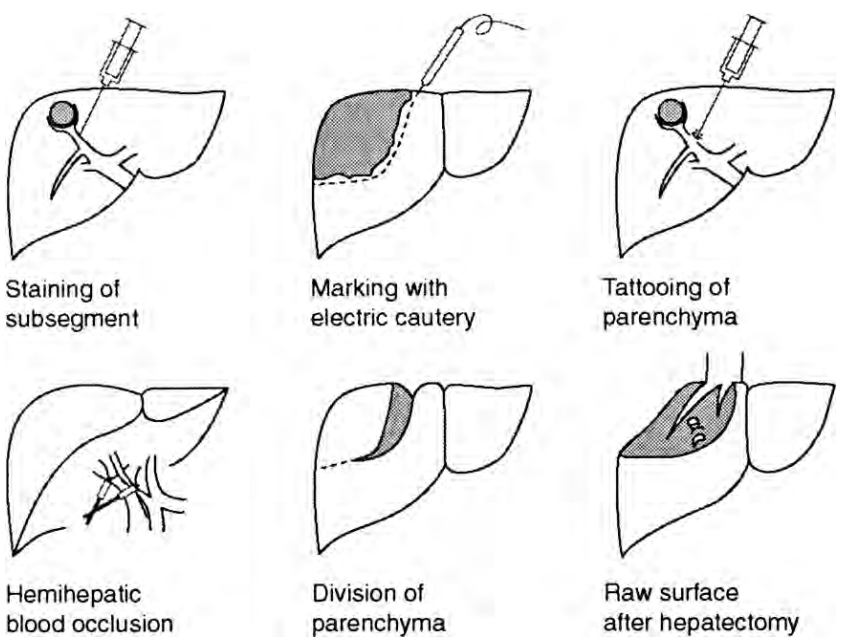

Fig. 3. Operative procedure for a segmentectomy/subsegmentectomy (reproduced from Ref. 3, with permission).

(segment 2 to segment 4) that can be identified by discoloration after ligation of the relevant portal venous and arterial branches in the umbilical fossa. Therefore, segmentectomy/subsegmentectomy requires precise identification of the tumor-oriented intrahepatic vascular anatomy. Before performing such a surgery, the surgeon should have information on the approximate intrahepatic vascular anatomy provided by preoperative ultrasound (US) and computed tomography (CT) images. This information facilitates surgeons' understanding of the anatomical layout during IOUS scanning in the individual patient.

Identification of tumor-bearing segment/subsegment

After entering the abdominal cavity, the round and falciform ligaments are divided and the liver is mobilized. Pulling the round ligament, the liver surface is then widely exposed, and the entire liver is explored using IOUS to trace the portal venous branches and the hepatic veins as well as to confirm the location of the HCC-bearing segment and portal venous branches that feed the corresponding area. To identify possible nodules that were not detected preoperatively, the liver surface is carefully scanned. Then, IOUS-guided staining is performed to identify the segmental domain to be resected, and the border of this domain is marked on the liver's surface by electrocautery.

During the staining procedure, the tip of the needle and the dye injected into the portal venous branch are clearly recognized as hyperechoic moving echoes (Fig. 4). To prevent the dye from regurgitating into other portal venous branches that should be preserved, the puncture point of the portal venous branch must be about 1 cm distal to the predetermined ligation point. Also, the speed of the dye injection should be adjusted by observing the movement of the injected dye in the portal venous branch under IOUS so that it is restricted to the segment of the portal venous branch to be resected. When the portal area containing the tumor is fed by two or more portal venous branches, the deeper or dorsal branch should be punctured first; otherwise, small air bubbles may enter the ventral branch, disturbing the sound penetration and obscuring the dorsal branch. If the portal area is not clearly stained after the IOUS-guided dye injection has been correctly performed, arterioportal

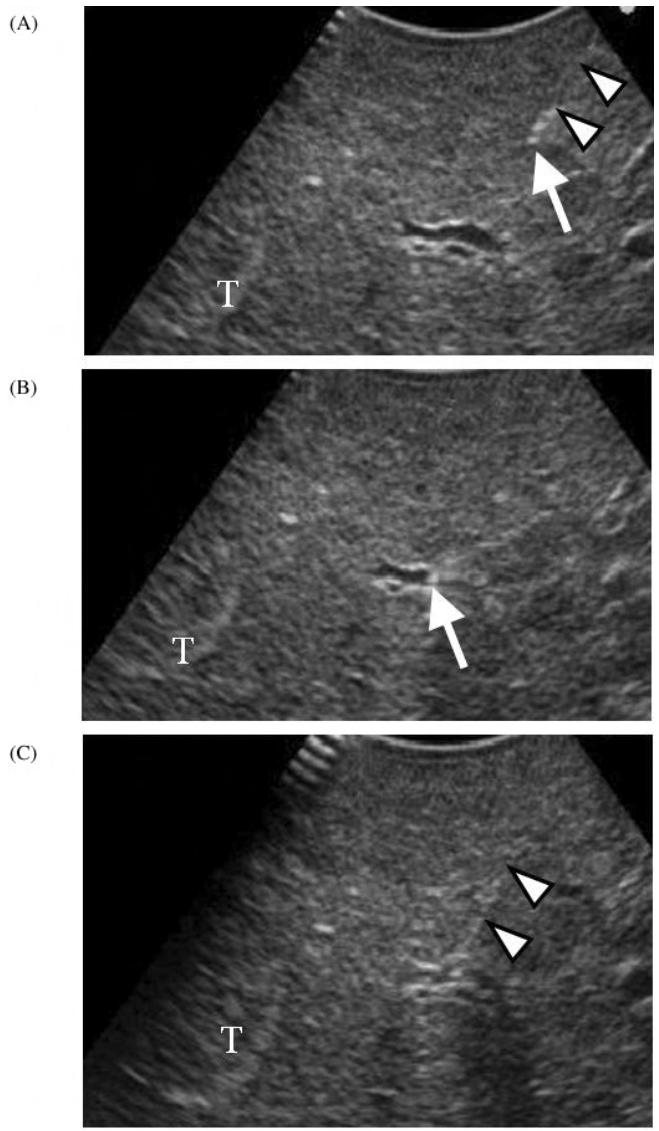

Fig. 4. Dye injection technique under IOUS visualization for segmentectomy. (A) A 22-G needle is inserted under IOUS guidance (arrowheads show the puncture line). The tip of the needle is visualized as a strong echo (white arrow). (B) A portal venous branch for segment 8 is punctured. The tip of the needle is visualized as a strong echo in the portal vein (white arrow). (C) The dye is injected. The dye is visualized as a moving hyperechoic echo with a posterior shadow. The white arrowheads show the needle's shifting position. T, tumor.

shunting or a portal venous tumor thrombus may be present. Moreover, liver cirrhosis itself can cause arterioportal shunts. Therefore, the hepatic artery should be routinely clamped at the hepatic hilum. Alternatively, the arterial branch running parallel to the portal venous branch can be punctured and the dye injected (arterial approach), but this method is difficult and not always applicable because of vascular thinness.

As another alternative, the counterstaining identification technique, in which the neighboring portal units are sequentially stained, is used to define the segment to be resected as the unstained area.[20] This technique is feasible in cases with a portal venous tumor thrombus or with preoperative portal venous embolization. The technique is particularly useful when many small portal venous branches are present, like in segment 5. Figure 5 shows an example of the counterstaining identification technique used to identify segment 6 by counterstaining segment 7 and the right paramedian sector.

Recognition of the correct ligation point on the portal branch

If the surgeon is accustomed to IOUS and understands the intrahepatic anatomical layout, the relationship between the dissection plane and the portal branch can be easily used to confirm the ligation site on the portal branch. However, the precise identification of the ligation point on the portal venous branch is occasionally difficult, especially in cases where a considerable amount of bleeding occurs during the division of the liver parenchyma. Therefore, under IOUS guidance, blue dye is injected into the parenchyma just in front of the vessels to be ligated prior to dissection (a procedure known as "tattooing of the liver parenchyma").[2] This tattooed spot can be clearly identified during parenchymal dissection. When the surgeon is not sure whether the Glissonian sheath exposed on the dissection plane corresponds to the presumed ligation site of the segmental portal branch, the "hooking technique" can also be applied.[21]

Briefly, the exposed Glissonian sheath is skeletonized and encircled with a 2-0 thread, which appears as an echogenic spot with a posterior shadow on IOUS. Then, the thread hooking the exposed vessel is gently pulled upwards under IOUS control. As a result of this hooking, the portal branch is stretched and the traction point can be clearly visualized

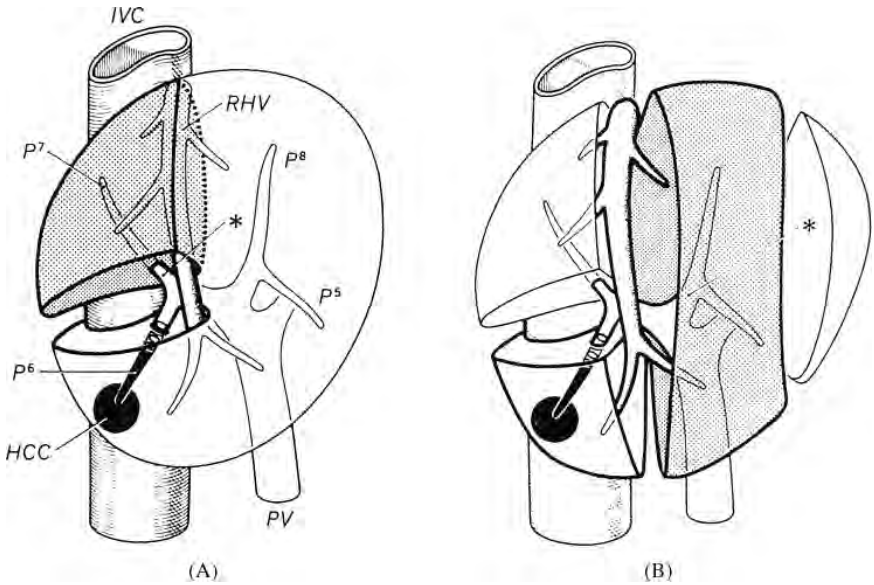

Fig. 5. Counterstaining identification technique. A case of hepatocellular carcinoma (HCC) in segment 6 is treated using arterial and portal venous embolization by placing a steel coil at the root of P^6 prior to surgery. (A) The portal venous branch of segment 7 is punctured and the dye is injected, staining segment 7. (B) The right paramedian sector is then stained to visualize segment 6 as an unstained area, accurately identifying the segment 6 domain. IVC, inferior vena cava; PV, portal vein; RHV, right hepatic vein. Each asterisk indicates a puncture point (reproduced from Ref. 20, with permission from Elsevier).

using IOUS. If this target site is correct, the portal branch is ligated and divided (Fig. 6).

Resection of the liver parenchyma under intermittent blood inflow occlusion

Under intermittent hemihepatic vascular occlusion[22] or the Pringle maneuver,[23] the hepatic parenchyma is divided along the external landmark (visualized by dye injection) using the clamp-crushing method. The anatomical relationship between the resection plane and the relevant portal branch to be resected is occasionally confirmed by IOUS

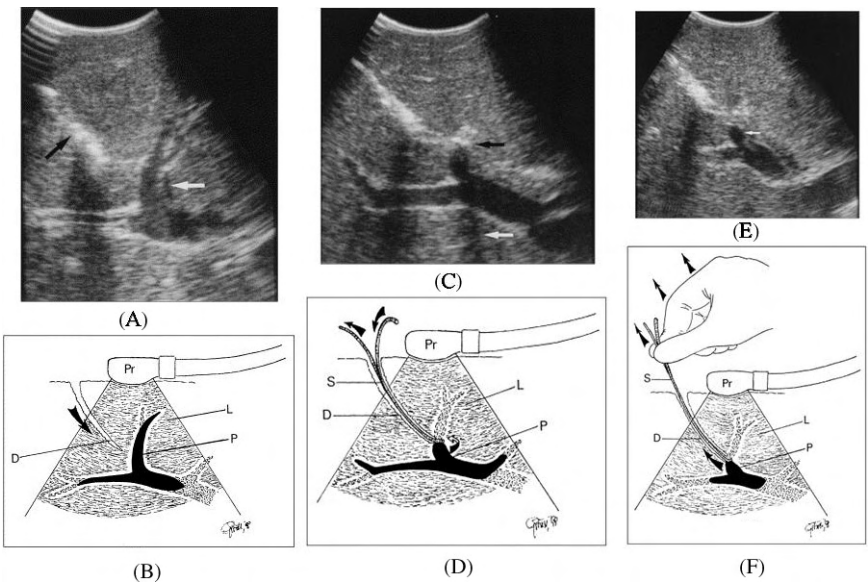

Fig. 6. (A) Visualization by IOUS of the portal branch to be ligated (white arrow), which is approached along the dissection line (black arrow). (B) Schema of (A). The arrow indicates the route of the dissection (D). (C) The exposed portal branch is encircled with a stitch (the high echoic spot is indicated by the black arrow), the acoustic shadow of which is visible (white arrow). (D) Schema of (C). The arrows indicate the route of the stitch (S) encircling the portal branch (P). (E) The hooked portal branch is then stretched (the arrow indicates the direction of traction) to confirm that the ligation point is correct. (F) Schema of (E). The arrows indicate the direction of the traction applied on the stitch (S), which is encircling the portal branch (P). L, liver; Pr, ultrasound probe; D, dissection line (reproduced from Ref. 21, with permission).

to ensure a correct transection plane. The plane appears as a glittering line on IOUS. If a glittering line is not evident, the placement of gauze on the transection plane can help to strengthen the glittering; alternatively, insertion of the surgeon's index finger between the planes can also be done to visualize the plane on IOUS. Upon completion of the segmentectomy, the major hepatic venous trunks running along the intersegmental planes are exposed on the raw surface.

Intermittent blood inflow occlusion should be routinely used to minimize blood loss during transection. Generally, 15 minutes of occlusion alternating with 5 minutes of perfusion under total afferent vascular

occlusion (Pringle maneuver)[23] as well as 30 minutes of occlusion alternating with 5 minutes of perfusion in hemihepatic or selective vascular occlusion are performed.[22] The major bleeding sites are the hepatic veins, especially near their confluence at the inferior vena cava (IVC), where sizable tributaries commonly originate. When bleeding occurs from this point, the proximal portions of the right and middle hepatic veins must be compressed by the surgeon's left hand to control the bleeding. To make this digital compression effective, the confluence of the hepatic veins into the vena cava should be dissected such that the surgeon's left index finger can be insinuated between the middle and right hepatic veins in front of the IVC and also behind the right hepatic vein.

Anatomic resection of segment 8

As a representative example of this operation, the total resection of segment 8 is described below. The abdominal cavity is entered through a J-shaped incision. The diaphragm is incised, and the thoracic cavity is opened at the nineth intercostal space. The intercostal muscles are divided to the midpoint between the vertebra and the posterior axillary line, and the xiphoid process is removed. The falciform ligament is divided and a cholecystectomy is performed. The common bile duct, hepatic arteries, and portal veins are dissected and taped.

Segment 8 usually has two major segmental branches (P^8 ventral and P^8 dorsal); therefore, staining must be performed twice to identify the whole domain. The stained area on the liver surface is marked by electrocautery (Fig. 7A). The Pringle maneuver is performed; and the hepatic parenchyma is then divided, starting at about 1 cm to the left of the Rex line and continuing until approximately the distal two thirds of the right side wall of the main middle hepatic vein have been exposed. The parenchyma is then divided between segments 5 and 8; the division is continued along a line slightly caudal to the border between these segments. Deep in the parenchyma, the pedicle of the P^8 ventral area is ligated and divided. Parenchymal dissection must always be performed after this pedicle has been identified using IOUS. Usually, the distance between this pedicle and the middle hepatic vein is only 1–2 cm.

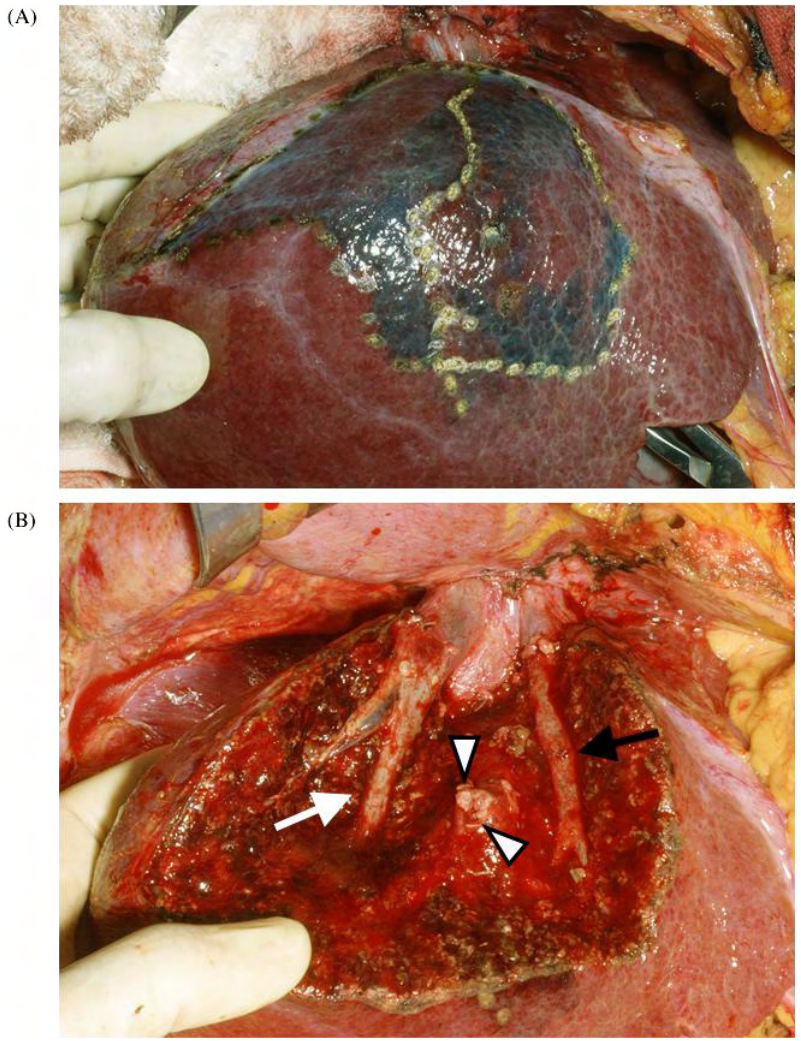

Fig. 7. Anatomic resection of segment 8. (A) After the portal branches to segment 8 are punctured and the dye is injected, the liver surface corresponding to this segment is clearly stained. (B) Completion of the resection. The trunks of the middle hepatic vein (black arrow) and right hepatic vein (white arrow), as well as the stumps of P^8 ventral and dorsal (white arrowheads), are visible on the raw surface.

After continuing the parenchymal division along the cranial side of the right paramedian portal pedicle, P^8 dorsal is identified just dorsal to the ligation point of P^8 ventral and is ligated and divided. After the division of P^8 dorsal, the parenchymal division is performed again along with the middle hepatic vein. The proximal one third of the middle hepatic vein is thus fully exposed. A few thick tributaries remain near the confluence with the vena cava; these tributaries must be carefully ligated and divided. At this point, the right wall of the middle hepatic vein is completely exposed as far as the IVC. The next step is the exposure of the right hepatic vein, which in most cases is situated about 2–3 cm dorsolateral to the P^8 dorsal branch. The parenchymal division is continued to the distal portion of the right hepatic vein under IOUS guidance. Further division exposes this vein from its caudal to cranial aspect. The final division is directed toward the premarked line on the cranial surface of the liver. The complete resection of segment 8 reveals the trunks of the middle and right hepatic veins as well as the stumps of the P^8 ventral and dorsal branches on the raw surface. The cranial part of the retrohepatic vena cava is also visible (Fig. 7B).

A subsegmentectomy of the dorsal or ventral portions of segment 8 can also be performed by resecting the P^8 dorsal or P^8 ventral areas. In such subsegmentectomies, the branch of the right or middle hepatic vein is exposed on the raw surface. If the lateral portal branch of segment 8 is present, the area fed by this branch must be stained to ensure the removal of all of segment 8.

Other types of segmentectomies

Other types of segmentectomies can be performed in a manner similar to the above-described segment 8 resection. When segment 7 is removed, the dorsal wall of the right hepatic vein trunk and the stump of the portal pedicle are visible (Fig. 8). When the combined resection of segments 7 and 8 is performed, the right hepatic vein is dissected at its confluence; thus, the drainage vessels for segment 6 should be secured. When the tributary of the short hepatic vein draining segment 6 (inferior right hepatic vein) is thick, a combined resection of the right hepatic vein

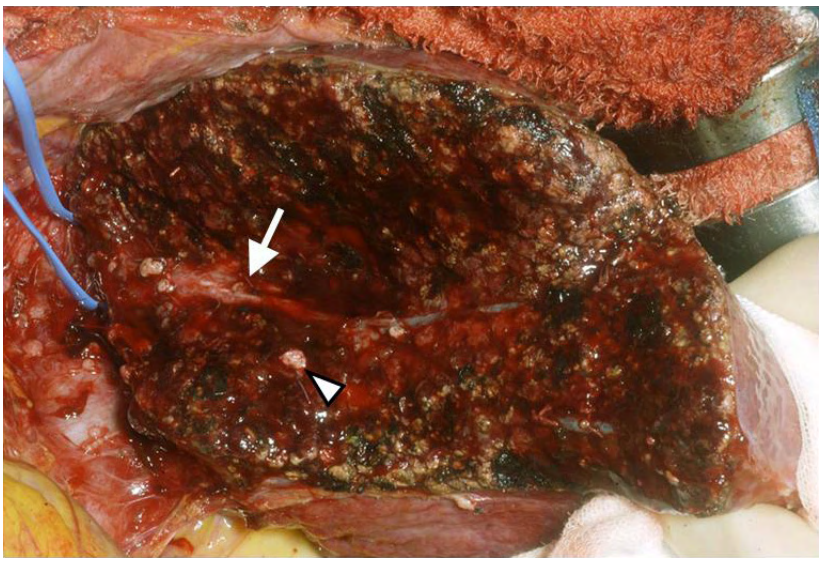

Fig. 8. Anatomic resection of segment 7. The trunk of the right hepatic vein (white arrow) and the stumps of P^7 (white arrowhead) are visible on the raw surface. The root of the right hepatic vein is encircled.

can be conducted without venous reconstruction; otherwise, the right hepatic vein must be reconstructed using an autologous vein graft or a cryopreserved cadaveric vein graft. The main hepatic veins are not exposed after the resections of segment 5 or 6. For the resection of segment 5, the counterstaining technique is useful because several portal branches feed this segment.

Prognostic Impact of Segmentectomy/Subsegmentectomy

To date, five retrospective reports have confirmed the prognostic benefits of anatomic resections.[7,13,24–26] A randomized controlled trial is now in progress in Japan (ID: C000000086; http://center.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi). Four of the previous five reports documented a better overall survival after anatomic resection compared with nonanatomic limited resections,[7,24–26] and four reported a better

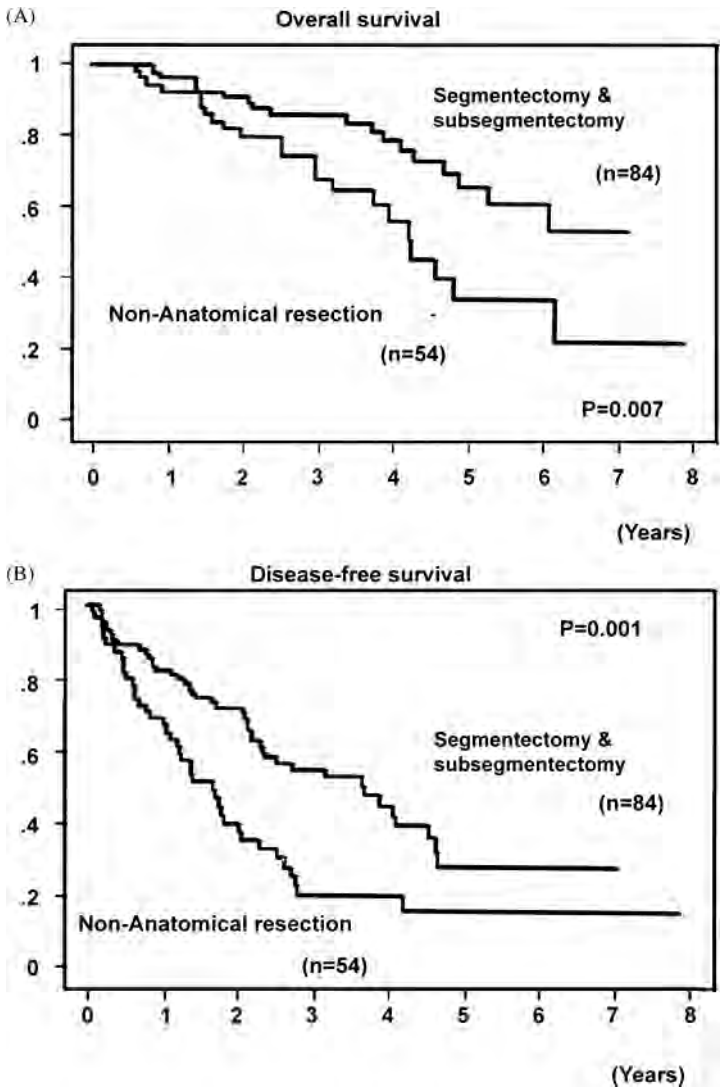

Fig. 9. Overall (A) and disease-free (B) survival curves after segmentectomy and subsegmentectomy and after nonanatomic resection for single HCC. Reprinted from Hasegawa K, Kokudo N, Imamura H, *et al.*, Prognostic impact of anatomic resection for hepatocellular carcinoma, *Ann Surg* **242**(2):252–9, 2005, with permission.

disease-free survival after anatomic resection.[13,24–26] In the latest report, Hasegawa *et al.*[26] reported that the overall survival and disease-free survival rates after segmentectomy/subsegmentectomy were significantly better than those after nonanatomic resection (Fig. 9). In addition, anatomic resection was identified as an independent factor for a favorable patient prognosis using multivariate analysis.

Acknowledgments

We thank Dr Hiroshi Imamura and Dr Kiyoshi Hasegawa for preparing the manuscript.

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21

Isolated Caudate Lobe Resection (Resection of Couinaud Segment 1)

Shu-You Peng

Introduction

Recent advances in liver surgery have made hepatic resection much safer. However, hepatic resection for a tumor located around the hepatic hilum or near the inferior vena cava (IVC) remains technically difficult, even when the tumor is small. The caudate lobe is situated behind the major lobes of the liver, and between the hepatic hilar structures and the IVC. Isolated resection of the caudate lobe is still a challenge to the surgeon.

Compared to the other liver segments, the caudate lobe has a small volume, but it is frequently involved by both primary[1,2] and secondary[3] liver tumors. Hepatocellular carcinoma (HCC) arising from the caudate lobe is not rare.[1,2] In addition, cholangiocarcinoma at the confluence of the hepatic ducts frequently involves the caudate bile ducts and may extend to the caudate lobe. Combined resection of the caudate lobe has become a common operation for curative resection in patients with hilar cholangiocarcinoma.[3]

With the steady improvement in diagnostic modalities, an increasing number of hepatic malignancies originating in the caudate lobe can be detected while at a resectable stage. When resection of the caudate lobe is required for tumor clearance, the operation may be an isolated caudate lobe resection or a caudate lobe resection combined with a major hepatectomy. Caudate lobectomy is thus classified into isolated and combined resection; it is also classified into complete and partial resection. Thus, caudate lobectomy can be classified into four types: isolated complete resection, combined complete resection, isolated partial resection, and combined partial resection.

For patients with fair-to-excellent liver functions, most surgeons prefer to carry out complete caudate lobectomy combined with another hepatic resection because this operation is technically less demanding. However, a hepatic malignancy arising in the caudate lobe of a cirrhotic liver presents surgeons with some difficulty in choosing the best therapeutic strategy. A cirrhotic hepatectomy (even a limited resection) sometimes ends up in patient death because of the fatal loss of functional hepatic parenchyma. Under this situation, an isolated caudate lobe resection, despite its technical difficulty and perioperative risks, may be the best choice of treatment because the operation achieves complete removal of the tumor while at the same time preserves the maximum amount of nontumorous hepatic parenchyma.

Recently, there has been an increasing number of reports on caudate lobe resection in the medical literature. Most of these reports are case reports or small series of cases. Furthermore, most series contain few cases of complete caudate lobectomies or isolated resection of the caudate lobe; isolated complete resection of the caudate lobe is even less reported in the medical literature. Several procedures for resecting the caudate lobe carcinoma have been described.[4–7] The difficulty of the surgical procedure in caudate lobectomy has resulted in a mortality rate of 5.3%–14%.[8]

Anatomy

The caudate lobe is the dorsal portion of the liver lying posteriorly and embracing the retrohepatic IVC in a semicircumferential fashion. The

caudate lobe lies between the major vascular structures — the IVC posteriorly, the portal triads inferiorly, and the hepatic venous confluence superiorly (Fig. 1).[9]

In the Chinese medical literature, the porta hepatis denotes not only the hepatic hilum in the general sense, but also two other locations: the confluence of the major hepatic veins (HVs) (the right, middle, and left HVs), and the segment of the retrohepatic IVC with a series of short HVs draining directly into the liver (F. Z. Qiu, personal communication, 1957). These three different locations are named the first, second, and third portae hepatis, respectively. In other words, the first porta hepatis denotes the hilum in

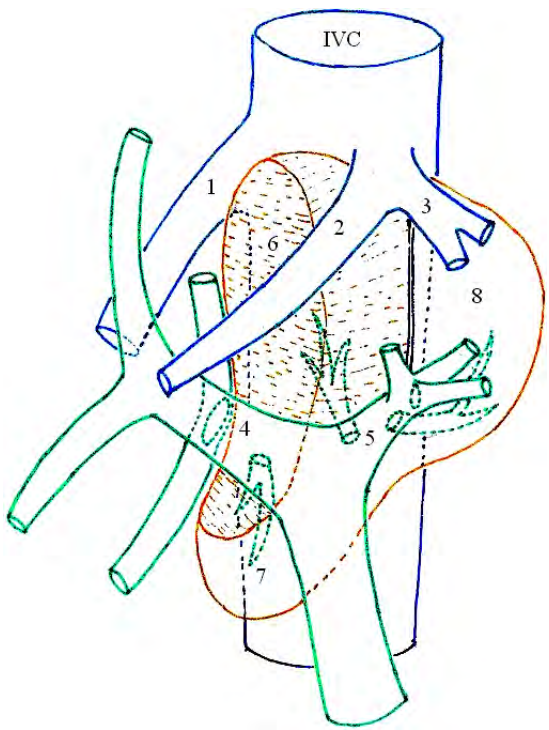

Fig. 1. Schematic illustration showing the subsegments of the caudate lobe and the surrounding structures. 1, right hepatic vein; 2, middle hepatic vein; 3, left hepatic vein; 4, right portal pedicle; 5, left portal pedicle; 6, paracaval portion; 7, caudate process; and 8, Spiegel lobe.

the general sense, the second porta hepatis denotes the confluence of the major hepatic veins to the IVC, and the third porta hepatis denotes the segment of the retrohepatic IVC with a series of short hepatic veins (SHVs). The caudate lobe is thus surrounded by the three portae hepatis, which consist of important and potentially dangerous structures in the operations of caudate lobe resection. In view of the unique anatomical location, caudate lobe resection, especially isolated caudate lobectomy, has been considered as technically challenging.

Kumon[10] considered the caudate lobe to consist of three parts: (1) the Spiegel lobe, which is located behind the lesser omentum and extends to the left of the retrohepatic IVC; (2) the paracaval portion in front of the retrohepatic IVC, just to the right of the Spiegel lobe, that is closely attached to the right and middle hepatic veins; and (3) the caudate process, a small projection between the IVC and the adjacent portal vein anteriorly, just to the right of the paracaval portion (Fig. 1). We adopt Couinaud's classification, in which the caudate lobe is subdivided into a left part (segment 1) and a right part (segment 9) using the middle hepatic vein (MHV) as the landmark.[11] Segment 9 may further be divided into two subsegments. The caudate process is only a tongue-like projection that attaches the caudate lobe to the right liver (Fig. 1). The border between the caudate process and the right liver is quite clear: it is at the site where the tongue-like portion meets the thick right liver. The ligamentum venosum lies in front of the caudate lobe and enters the IVC (Fig. 1); it has been used as a conventional index of the median border between segment 1 and segment 9.

The caudate lobe is supplied by blood vessels and is drained by biliary tributaries from both the right and left portal triads, usually two on the left side and one on the right side (Fig. 1); hereafter, they are called the caudate portal triad (CPT). The right portion of the caudate lobe, including the caudate process, predominantly receives portal venous blood from the right portal vein or from the bifurcation of the main portal vein; while the left portion of the caudate lobe receives portal venous blood from the left portal vein. Similarly, the arterial supply and biliary drainage of the right portion is most commonly associated with the right posterior sectorial pedicle, and the left portion with the left

pedicle. The hepatic venous drainage of the caudate lobe is unique. It is the only hepatic segment that drains directly into the IVC through a series of SHVs. However, there may be some small veins draining into the right and/or middle hepatic veins when the caudate lobe tumor is large in size.

Surgical Approaches to Caudate Lobectomy

Isolated caudate lobectomy is a technical challenge because of the unique anatomical location — the caudate lobe is surrounded by the first, second, and third portae hepatis, all of which consist of important and potentially dangerous structures. The surgical approach to caudate lobectomy is still not well standardized. The choice of approach is essential to the choice of operation. Approaches are mostly dependent on the size and location of the lesion as well as the severity of cirrhosis.

In the medical literature,[4–7,12–17] four approaches have been used for the various types of caudate lobectomy: (1) left-sided approach, suitable for small tumors situated in the Spiegel lobe or when the caudate lobe is to be resected together with the left liver; (2) right-sided approach, suitable for a tumor located in the caudate process or when the caudate lobe is resected together with the right liver, i.e. right hepatectomy with caudate lobe resection; (3) bilateral approach, a combination of the left-sided and right-sided approaches — the caudate lobe may be approached mainly from the right or left side, although dissection from both sides is necessary in most cases; and (4) anterior transhepatic approach, suitable only for cases when the tumor is closely in contact with the major HVs or when the tumor is huge and especially when it is also in close contact with the IVC, thus preventing the liver from being turned from one side to the other side. This operation is most suitable for patients in whom as much noncancerous liver parenchyma should be preserved as possible due to cirrhosis of the liver. In this approach, the liver is split through the midplane into two halves, thus fully exposing the caudate lobe as well as the first and third portae hepatis.

Among the various types of caudate lobectomy, isolated complete resection of the caudate lobe is technically the most difficult operation.

Some of the isolated caudate lobectomies can be performed through the left-sided and/or right-sided approach(es) when the tumor is small. When the tumor is large or when major HVs are compressed by the tumor, the abovementioned approaches may not be appropriate due to the possibility of lacerating the major HVs. Under such circumstances, the best choice for isolated complete caudate lobectomy is the anterior transhepatic approach.

The anterior transhepatic approach for an isolated caudate lobectomy was first described by Yamamoto *et al.*[18] in 1992 for a patient with cirrhosis and with a 3 cm × 3 cm HCC in the paracaval portion of the caudate lobe. This approach provides a safe approach for isolated complete caudate lobectomy.[18] The separation of the hepatic parenchyma overlying the caudate lobe exposes the major HVs and the hilar plate to be under direct vision, thus facilitating the control of venous bleeding and the division of the ascending paracaval portal branches from the hilar plate. However, the anterior transhepatic approach for isolated caudate lobectomy is usually associated with a significant amount of bleeding. Asahara *et al.*[4] reported that the minimum operative time and blood loss were 355 min and 1100 mL, respectively.

Isolated Resection of the Caudate Lobe by the Bilateral Approach

Indications

Some isolated caudate lobectomies can be performed through a left-sided approach.[7] Asahara *et al.*[4,7] suggested that it is even possible to perform an isolated caudate lobectomy utilizing only the left-sided approach if the tumor size is less than 3 cm. However, for most isolated caudate lobectomies, a combined left and right approach is employed. Generally, the bilateral approach for an isolated caudate lobectomy is only suitable for small lesions of the caudate lobe, especially when the lesions are in the Spiegel lobe or in the caudate process. When the tumor size exceeds 4 cm, resection of the tumor becomes difficult even by a bilateral approach, as the tumor is often incarcerated between the IVC, the portal veins, and the HVs.[4,7]

Surgical procedures

Several skin incisions have been used for an isolated caudate lobectomy in the medical literature. These include a reversed L-shaped incision,[1] a Mercedes incision,[4,7] and an inverted T-shaped incision.[16] Regardless of the incision used, excellent exposure is of vital importance for caudate lobectomy. After entering the abdomen, the whole abdominal cavity needs to be explored thoroughly to rule out intra-abdominal metastasis.

Mobilization of the liver

The ligamentum teres needs to be ligated and transected near to the umbilicus. The falciform ligament is divided up to the front of the suprahepatic IVC, and the roots of the major HVs are dissected anteriorly and exposed. The fossa between the upper margin of the liver, the right hepatic vein (RHV), and the MHV is dissected to expose the anterior surface of the IVC. Next, the incision is directed to the right, dividing the right coronary ligament, the right triangular ligament, and the hepatorenal ligament. The right liver is then turned medially and upward to expose the bare area behind the right liver. The right adrenal gland is detached from the liver. The posterior surface of the right liver is cranially dissected until the right side of the suprahepatic IVC and the retrohepatic IVC are completely exposed.

Taping the IVC

The retroperitoneum overlying the infrahepatic IVC is opened on the right side 1–2 cm above the right renal vein. The surgeon's forefinger can then pass behind the infrahepatic IVC, and a tape is guided to encircle the infrahepatic IVC.

Dissection is now directed to the left liver. After the left coronary ligament and left triangular ligament are divided, the left liver is turned to the right. The peritoneal reflection between the Spiegel lobe and the IVC is incised cranially from below up to the left side of the suprahepatic IVC. The suprahepatic IVC is then bluntly dissected with a finger posteriorly toward the right until a tunnel is created, and the IVC is taped.

Taping the common trunk of the MHV and LHV

Isolation of the superior edge of the Spiegel lobe can be achieved by exposing the junction of the left hepatic vein (LHV) and the IVC. If the left phrenic vein drains directly into the LHV, it should be ligated and divided. A blunt dissector is then inserted superiorly from above in the previously dissected fossa between the RHV and MHV, and carefully dissects free the IVC anteriorly and the MHV posteriorly. The common trunk of the MHV and LHV is then encircled with a tape.

Taping the RHV

Dissection is now directed to the right liver again. The right liver is turned to the left. The right side of the suprahepatic IVC and the retrohepatic IVC have already been well exposed. The SHVs draining posteriorly from the posterior surface of segment I into the IVC are carefully dissected and divided, proceeding cranially to the confluence of the RHV and IVC (Figs. 2 and 3). At this level, the hepatocaval ligament needs to be carefully divided and ligated, since it may contain a large vessel. The confluence of the RHV and the IVC is well exposed from the right side after division of the hepatocaval ligament. A blunt dissector is gently passed along the anterior surface of the retrohepatic IVC to the left side of the RHV in order to meet the previously dissected fossa between the RHV and MHV. The RHV is then encircled with a tape.

Detachment from the surrounding structures

To be resected, the caudate lobe has to be detached from its four boundaries; namely, the first, second, and third portae hepatis and the neighboring liver.

Detachment from the IVC and the third porta hepatis

The right liver is well mobilized as mentioned above, and the posteriorly draining SHVs along the entire retrohepatic IVC are divided.

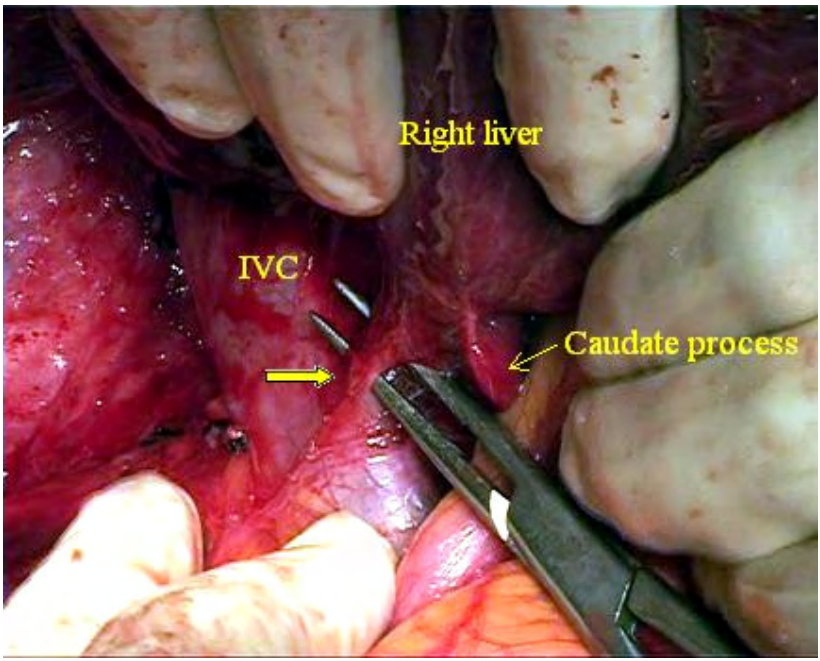

Fig. 2. The SHV (arrow) on the right side of the IVC, drained posteriorly from the posterior surface of segment I into the IVC, is carefully dissected and divided.

The dissection proceeds along the anterior surface of the retrohepatic IVC, allowing identification and dissection of the SHVs. The remaining SHVs on the left lateral side of the IVC can be easily isolated via a left-sided approach. The left liver is turned to the right once more. The left lateral margin of the Spiegel lobe is freed by dividing the fibrous attachments to the IVC and the diaphragm (Fig. 4). The remaining SHVs are exposed and can be easily ligated from the left side (Fig. 5). The caudate lobe is now completely separated from the IVC and totally detached from the third porta hepatis.

Detachment from the hilum and the first porta hepatis

It is advisable to transect the caudate process before the portal triad to the caudate process is isolated and divided. The branches to the caudate lobe

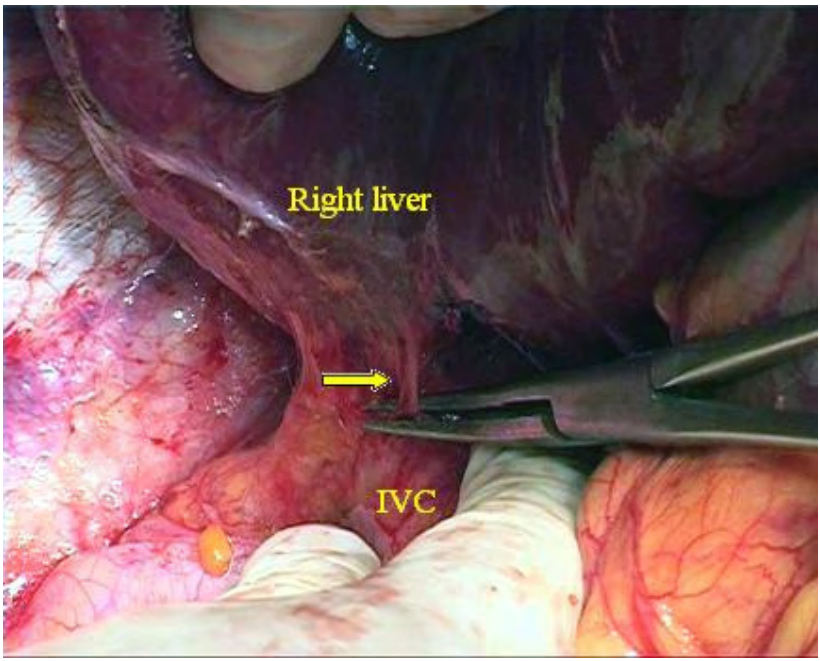

Fig. 3. Another SHV (arrow) on the right side of the IVC, drained posteriorly from the posterior surface of segment I into the IVC, is carefully dissected and divided.

from the left portal vein and the left hepatic artery (i.e. the CPTs) are then dissected and divided one by one close to the base of the umbilical fissure (Fig. 6).

Detachment from the neighboring liver, hepatic veins, and second porta hepatis

There are no well-defined landmarks between the paracaval portion and the right posterior sector. Asahara *et al.*[4,7] punctured the portal venous branch of the posterior segment under ultrasonic guidance to inject indocyanine green (ICG), and stained the posterior liver segment to delineate the right border of the caudate lobe.

The author finds it useful to use two points as landmarks: the tip of the caudate lobe, which is located at the angle between the LHV and

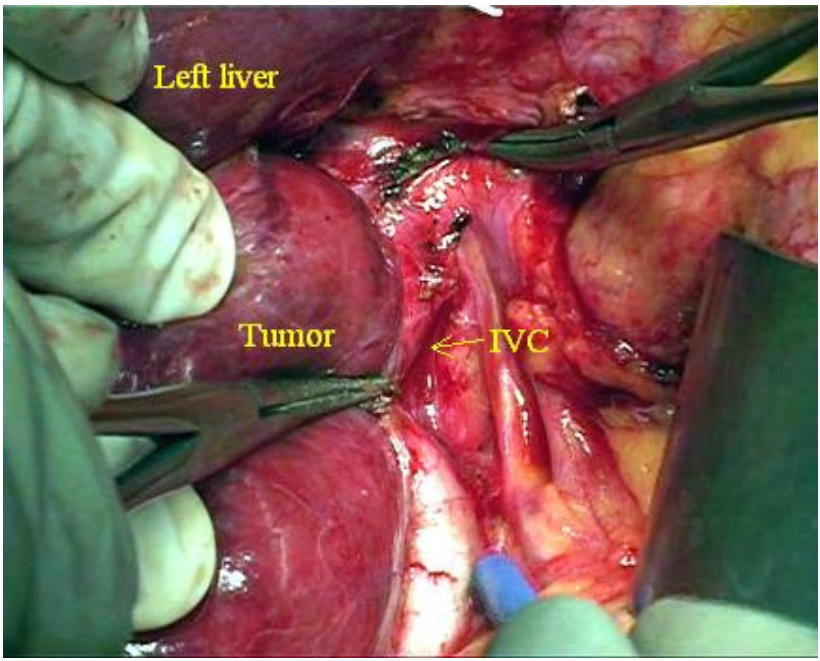

Fig. 4. The left lateral margin of the Spiegel lobe is freed by dividing the fibrous attachment posteriorly to the IVC and diaphragm.

IVC (Fig. 7); and the point where the caudate process meets the right liver. An imaginary line joining these two points can be considered as the caudate boundary for liver transection. Transection can start from either end. It is easier to start from the top of the caudate lobe when the tumor is situated at the inferior part of the caudate lobe; conversely, it is easier to start inferiorly at the caudate process when the tumor is at a more superior location. Sometimes, the transection can start from both ends to facilitate the transection.

During transection of the liver parenchyma, meticulous care should be paid not to injure the major HVs. Bleeding from these veins is very difficult to control, as visibility is very poor. Injury to the major HVs is a big risk at this stage. If the liver parenchyma needs to be transected very close to the root of the major HVs and if these veins become inadvertently lacerated, bleeding can be controlled through temporarily

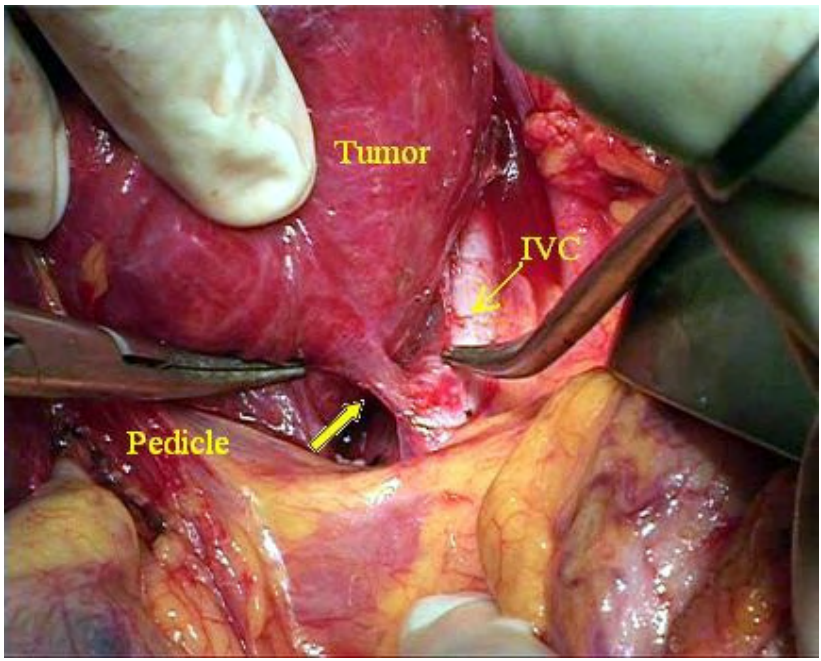

Fig. 5. Exposure and dissection of the SHVs from the left side (arrow shows the SHV between the IVC and the Spiegel lobe).

excluding the HVs by pulling onto the tapes which have been previously positioned. Hemostasis can be achieved by suturing with 5-0 prolene.

The liver parenchyma can be transected by the "curettage and aspiration" technique using Peng's multifunctional operative dissector (PMOD) under intermittent inflow occlusion at the hepatoduodenal ligament (Pringle's maneuver). The occlusion time is 10 min with 2 min of reperfusion. The cycle of occlusion and reperfusion can be repeated. Total vascular exclusion is infrequently used, except when the tumor involves the IVC or the major HVs. PMOD is a special instrument that was designed by Professor Peng and colleagues.[6] It has the functions of dissection, coagulation, and aspiration, which can be used separately or synchronously to keep the surgical field clear and clean. The advantage of PMOD is that it can dissect clean all of the vessels and ductal

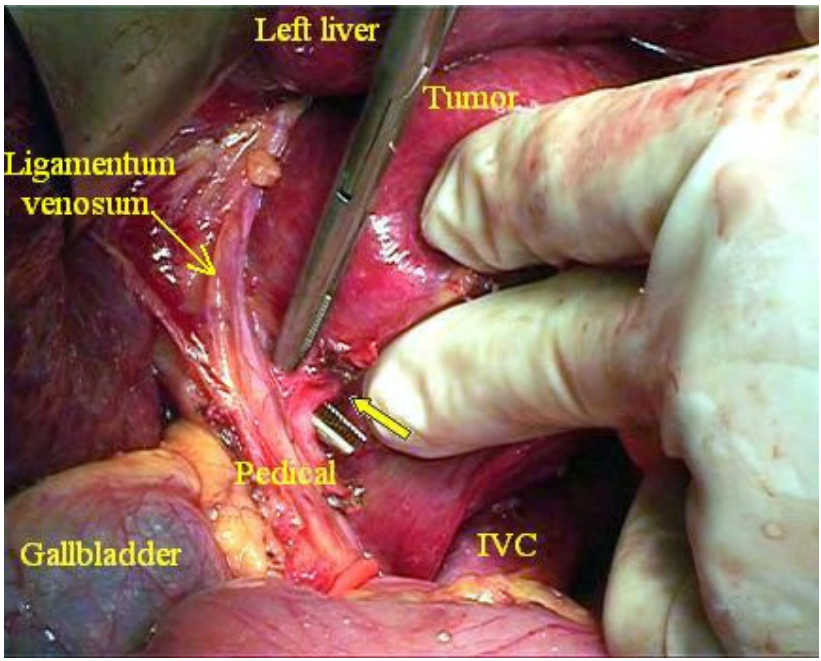

Fig. 6. The caudate portal triad (arrow) is dissected and divided close to the base of the umbilical fissure.

systems so that the intrahepatic ductal structures can be identified, isolated, and treated individually. The use of PMOD saves operative time and enhances the safety of the operation. If the tumor is closely attached to the major HV(s), it is advisable to use the anterior transhepatic approach.

Isolated Resection of the Caudate Lobe by the Anterior Approach

Indications

When a caudate lobe tumor is larger than 4 cm, especially when the tumor is located in the paracaval portion or is in close contact with the major HVs (Fig. 8), the anterior transhepatic approach for isolated caudate lobectomy is indicated. This approach provides a better

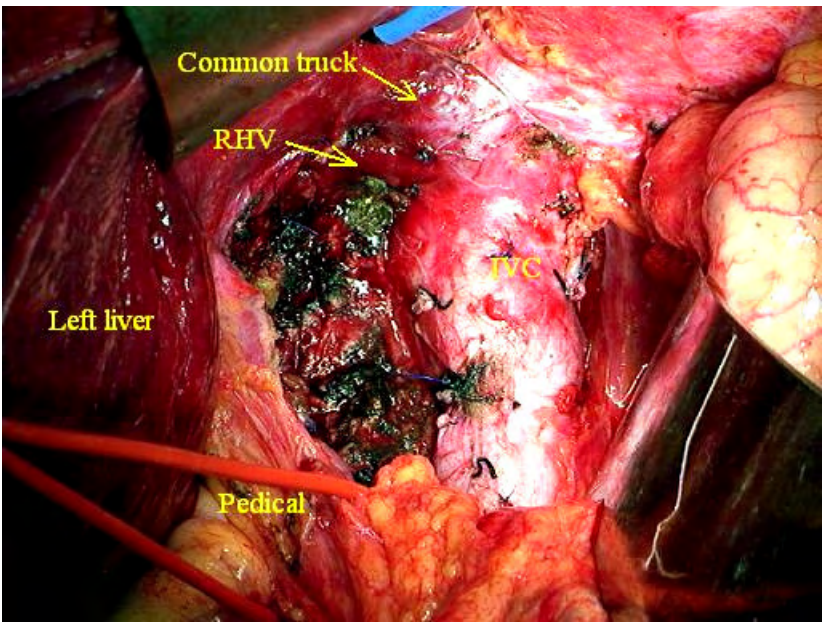

Fig. 7. The caudate lobe has been completely resected and removed. The well-exposed angle between the HVs and the IVC is the location of the tip of the caudate lobe.

operative field than the dorsal approach by opening up the midplane of the liver widely so as to expose the major HVs and the hilar plate to direct vision, thus facilitating dissection of the tumor from the major vessels, especially when there are numerous small communicating vessels between them.

Surgical procedure

The initial steps of the operation are similar to those of isolated caudate lobectomy by the bilateral approach, as described previously. The falciform ligament is divided up to the front of the suprahepatic IVC. The dissection is then directed to the right and the left, dividing the coronary ligament, triangular ligaments, and hepatorenal ligament. The right adrenal gland is detached from the liver, and the hepatogastric ligament is completely divided. The SHVs are dissected and divided

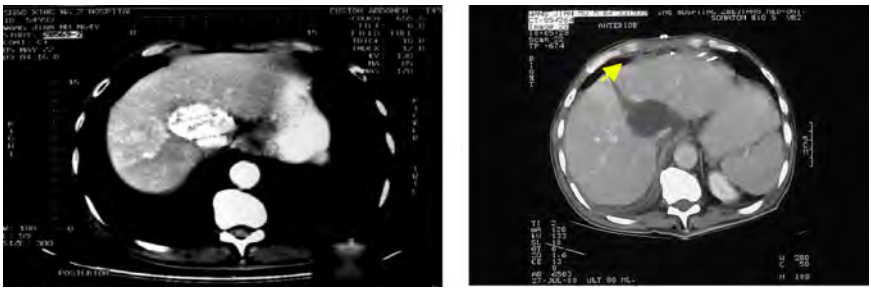

Fig. 8. Left: preoperative computed tomography (CT) scan showing the tumor in the caudate lobe. Right: postoperative CT scan showing the liver transection plane (arrow).

in a caudal-to-cranial direction from both the right and the left sides (Fig. 9). When the caudate lobe is completely separated from the retrohepatic IVC, the suprahepatic IVC, infrahepatic IVC, major HVs, and hepatoduodenal ligament are encircled by tapes for temporary hepatic vascular exclusion, in case of need.

The liver is split through the midplane. The plane of liver transection starts from the point between the roots of the RHV and the MHV to the fossa of the gallbladder, which should have just been removed. The transection is continued up to the plane 1 cm from the caudate tumor, as shown on intraoperative ultrasound (IOUS). The transection then goes along a plane 0.5 cm from the tumor surface. The tumor capsule should be kept intact, and the major HV should be pushed away by PMOD. When the transection reaches the hilar plate at the hilum, the CPTs are isolated and divided (Fig. 10).

Up to this point, the tumor has been detached from the third and first portae hepatis, i.e. from the IVC and the liver pedicles. All minute vessels to the tumor are meticulously ligated and divided until the tumor is completely detached from the HVs (Fig. 11). At this stage, the caudate lobe can be easily detached from the neighboring liver. After resection of the tumor, the MHV should be clearly seen on the cut surface of the left liver with the RHV on the right side. During parenchymal transection, we usually use Pringle's maneuver with intermittent inflow blood occlusion. When a major HV is damaged and needs to be repaired,

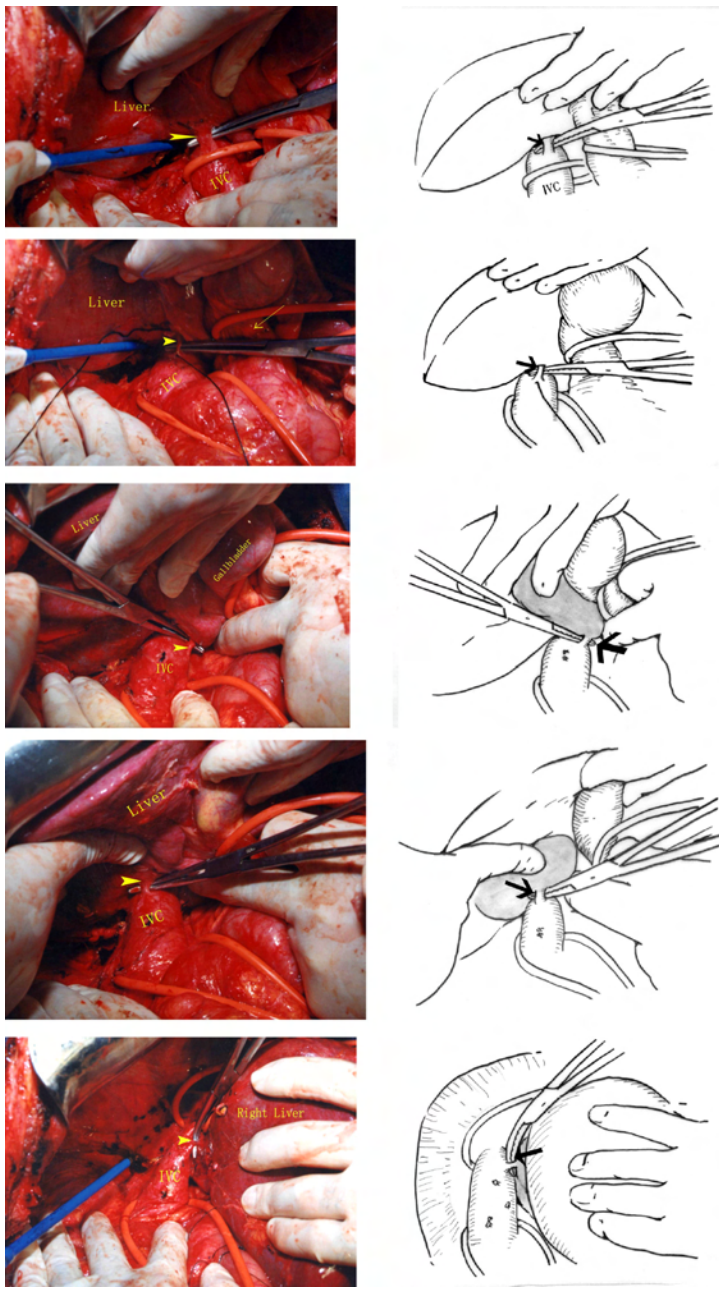

Fig. 9. Five short HVs are ligated from a caudal-to-cranial direction (arrowheads).

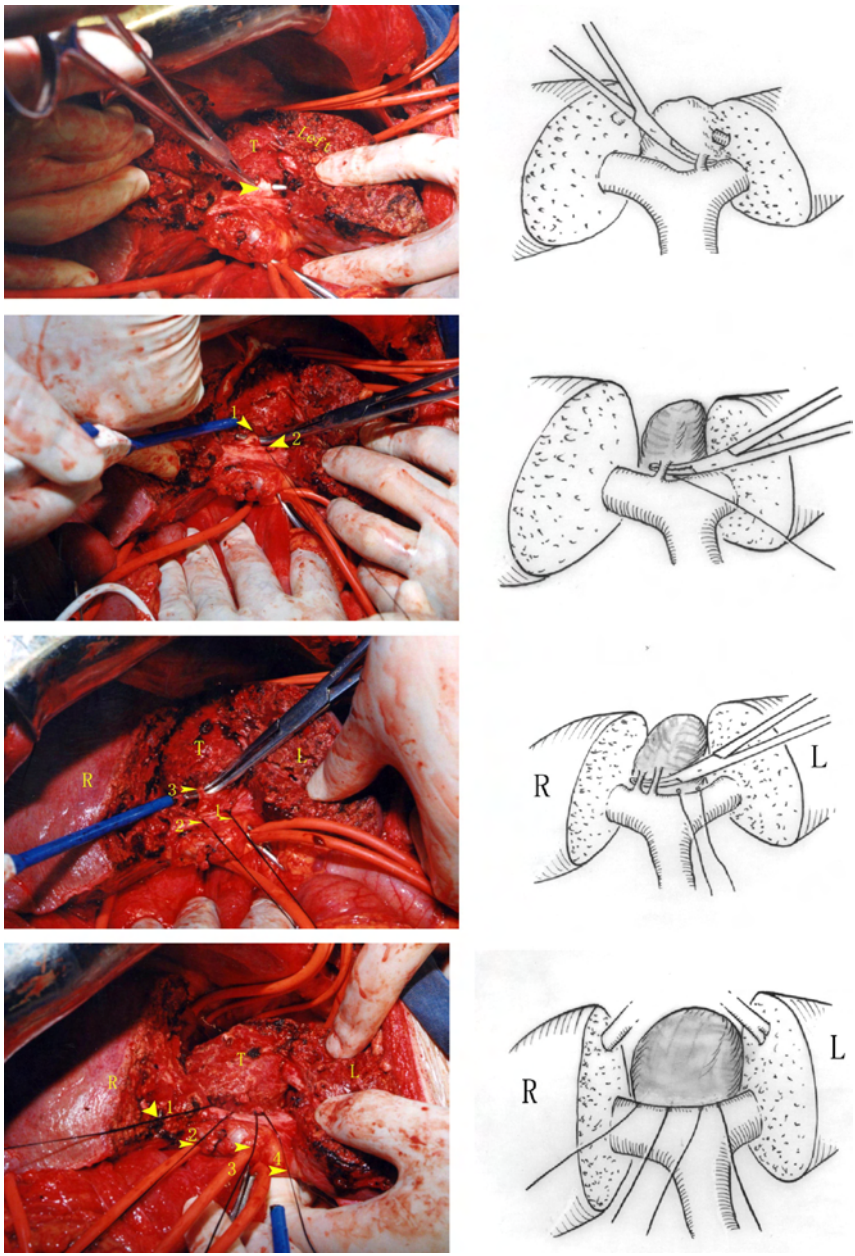

Fig. 10. Four groups of portal triads to the caudate lobe (arrowheads) are divided, and the tumor is detached from the hilum.

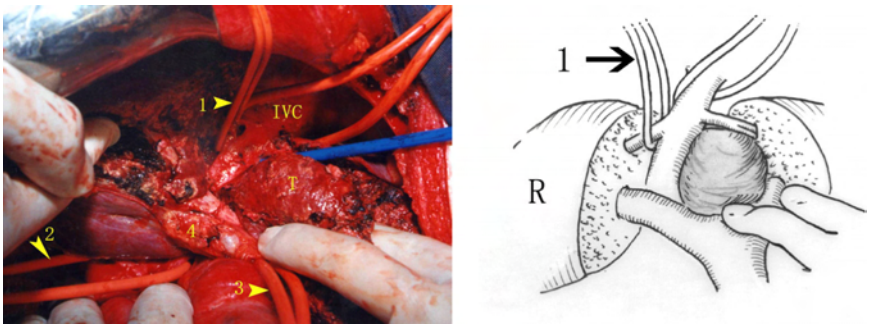

Fig. 11. The tumor is still attached to the MHV. 1, tape across the RHV; 2, tape across the IVC; 3, tape across the pedicle; 4, bifurcation of the pedicle; T, tumor.

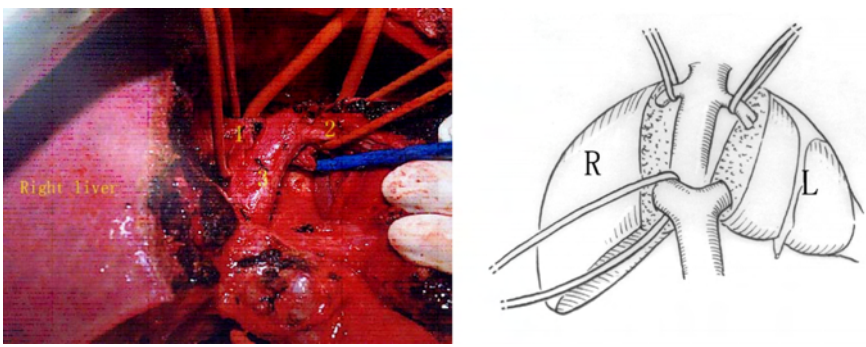

Fig. 12. After removal of the caudate lobe, the three portae hepatis — the hilum, the confluence of the major HVs, and the retrohepatic IVC — can be clearly seen. 1, RHV; 2, common trunk of the MHV and LHV; 3, IVC.

vessel occlusion using the tapes at the roots of the major HVs is of great help to reduce blood loss. After removal of the caudate lobe, the three portae hepatis — the hilum, the confluence of the major HVs, and the retrohepatic IVC — can be clearly seen (Fig. 12).

Any bleeding points and bile leaks on the raw liver surface are carefully controlled. The split left and right livers are sutured together to prevent internal herniation (Fig. 13). A drain should be placed to the right side of the retrohepatic IVC. The abdomen is closed to complete the operation.

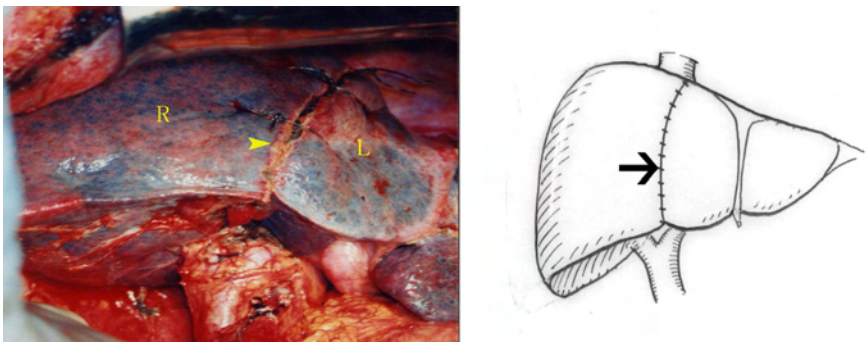

Fig. 13. The tumor is completely resected, and the two halves of the liver are sutured together. R, right liver; L, left liver; arrowhead, interlobar plane.

Special Procedures for Special Conditions

Retrograde caudate lobectomy

The technical approach of conventional caudate lobectomy as described by Lerut *et al.*,[19] Colonna *et al.*,[20] and Nagasue *et al.*[21] emphasizes the importance of dividing the vascular attachments from the caudate lobe to the IVC as a first step, followed by hepatic parenchymal transection. All of the SHVs originating in the caudate lobe are divided and ligated at the initial stage of the operation. However, if the caudate lobe tumor is closely adherent to or has infiltrated the IVC or if it is too large in size to be turned from one side to the other, such a tumor is not suitable for conventional caudate lobectomy, as the SHVs cannot be dissected under these circumstances. A new technique of retrograde caudate lobectomy can be used instead. In this operation, the division and ligation of the SHVs are carried out at the final stage instead of at the initial stage of the operation. The author has designed and used this procedure successfully in nine patients.

The surgical procedure includes three steps:

1. Mobilization of the whole liver

A reversed L-shaped skin incision is made from the base of the xiphoid to the tip of the 12th right rib. The perihepatic ligaments — including the round, falciform, coronary, hepatorenal, and triangular

ligaments — are dissected and divided to completely mobilize the liver. The hepatoduodenal ligament is looped for inflow blood control. Both the suprahepatic and infrahepatic IVCs are also looped for temporary occlusion if required.[5]

2. Detachment of the caudate lobe from the liver

The choice of approach is essential to the success of caudate lobectomy. The approach chosen should depend on the size and location of the lesion, the severity of cirrhosis, and the general condition of the patient. For retrograde caudate lobectomy, the combined approach or the anterior transhepatic approach may be used.

In the combined approach, the operation starts from the healthy side of the caudate lobe. For example, if the tumor is located mainly in the Spiegel lobe and the paracaval portion, a right-sided approach is used first. The liver is turned to the left to expose the right side of the IVC. The right adrenal gland is detached from the liver. The dissection is then carried out on the left side. The liver is turned to the right to expose the tumor and the left side of the IVC. The retroperitonium covering the IVC is incised along the border of the caudate lobe from the inferior to the superior pole of the caudate lobe, which can be lifted up a little bit from the IVC. The right side of the upper pole of the caudate lobe serves as a landmark to join the other landmark on the right side of the caudate process in order to form an imaginary line of parenchymal transection. The caudate hilum is then dissected. There are two to five branches of the caudate portal triad entering the caudate lobe from the left and right liver pedicles (Fig. 14). These branches are sequentially isolated and divided one at a time from left to right until the caudate lobe is completely detached from the liver pedicle. The liver parenchyma is then transected to separate the caudate lobe from the other parts of the liver. Transection is carried out from the point where the caudate process meets segment VI toward the upper pole of the caudate lobe, as mentioned above. Anteriorly, the transection plane is just behind the major HVs. A thin layer of liver parenchyma is left for protection of the HVs. How thin the liver parenchyma should be left depends on the size of the tumor; in general, the transection plane should be 1.0–1.5 cm from the tumor.

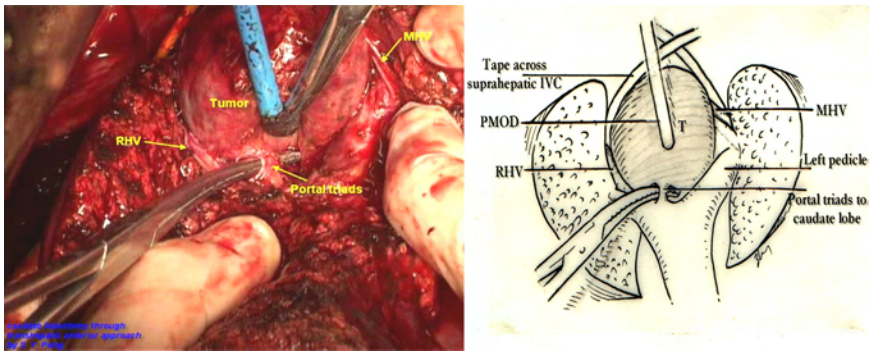

Fig. 14. Branches of the caudate portal triad entering the caudate lobe from the right liver pedicle.

If the tumor is very close to the HVs, using the combined approach is difficult and risky; as an alternative, the anterior transhepatic approach should be used. The midplane of the liver is split along the Cantlie line down to 1 cm from the tumor.[6] The HVs are exposed under direct vision, and meticulous dissection and ligature can be undertaken to tie off the branches from the HVs to the tumor. Upon completion of the liver parenchymal transection, the tumor is attached only to the IVC.

3. Detachment of the caudate lobe from the IVC

As the only attachment is to the IVC, the caudate lobe containing the tumor can be grasped with the hand for a safe dissection from the IVC. Both the distal and proximal parts of the caudate lobe can be dissected without interrupting the blood flow to the liver. Finally, the SHVs are dissected and divided, and the tumor is completely resected (Figs. 15 and 16). Occasionally, part of the IVC can be resected together with the tumor, and the IVC can be repaired with 4-0 prolene or reconstructed with an artificial graft.

Dissection of the SHVs through a thickened caudate margin

For dissection of SHVs using the left-sided approach, it is important that the peritoneal reflection between the Spiegel lobe and the IVC

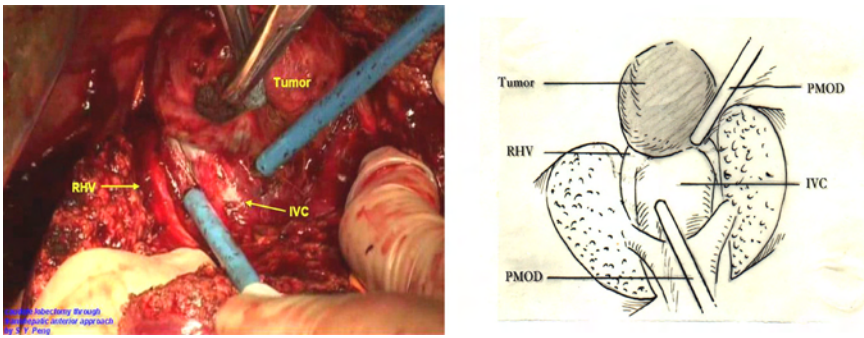

Fig. 15. The SHVs are dissected and divided until the tumor is detached from the IVC.

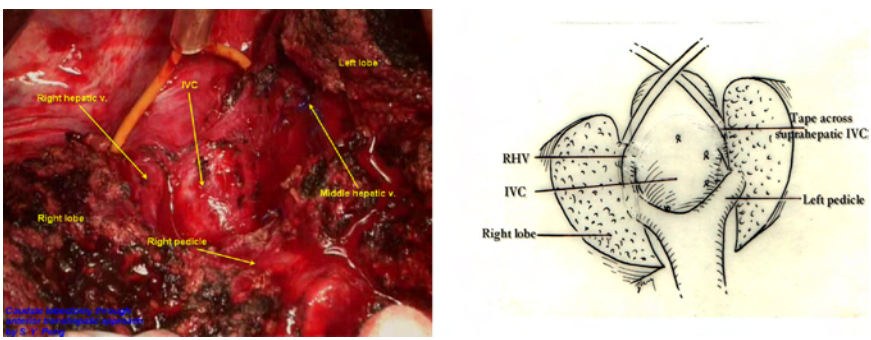

Fig. 16. The tumor is completely removed.

is incised from a caudal-to-cranial direction up to the left side of the suprahepatic IVC.

It is important to note that there is still a thin layer of fibrous tissue underneath the peritoneum that should also be incised before the caudate lobe can be lifted up for dissection of the SHVs. This ligamentous band from the posterior edge of the Spiegel lobe often passes posteriorly behind the IVC and attaches to segment VII. In some patients, this band is replaced by a bridge of hepatic parenchyma, and the caudate lobe may thus completely encircle the IVC to reach segment VII of the liver on the right side. This anomalous anatomy of the caudate lobe may

make a left-sided approach to the SHVs difficult or even impossible. The author has successfully carried out five such caudate lobe resections. The key to success is to start incising the liver tissue at the lowermost margin of the caudate lobe on the left side of the IVC, before raising the flap of the liver from the IVC. The dissection is then carried out cranially. Using PMOD, the SHVs between the flap of the liver and the IVC can be isolated and divided.

Tips and Tricks for a Safe Caudate Lobe Resection

Adequate abdominal incision

The abdominal incision for caudate lobe resection should be big enough to give an adequate exposure of the whole liver. The reverted L incision and a pair of self-retaining retractors can be used to achieve an excellent exposure.

Taping of major veins

As a precautionary measure, the suprahepatic and infrahepatic IVCs should be taped. The RHV as well as the common trunk of the MHV and the LHV should also be taped, if possible.

IVC control with fingers

The alveolar tissues behind the IVC are dissected to create a retrocaval space, through which the fingers can be inserted. Once bleeding occurs during dissection of the SHVs, the bleeding can be easily and promptly controlled by pressing the IVC against the caudate lobe at the distal and proximal sites to the bleeding point.

Application of the liver hanging maneuver

The liver hanging maneuver has been widely used since it was first described by Belghiti *et al.*[22] For caudate lobe resection, not only can it help in the dissection of SHVs by lifting the liver anteriorly to expose

the SHVs, but it is also useful in patients who require liver transection through the midplane for the anterior transhepatic approach.

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22

Laparoscopic Liver Resection

Rong Liu

Introduction

Since the 1990s, laparoscopic surgery has been widely applied in various kinds of diseases. However, laparoscopic procedures for solid organs are still unpopular due to the difficulty in hemostasis or insufficient exposure of the operative field. Hepatic resection is a procedure that does not need any reconstruction, and is therefore suitable for a laparoscopic approach. Improved technology (ancillary equipment and instrumentation) has led to the introduction of the laparoscopic approach for hepatic resection of both benign and malignant tumors.[1–3]

In 1992, Gagner *et al.*[4] reported the first complex laparoscopic liver resection for a 6-cm focal nodular hyperplasia, using an ultrasonic dissector, monopolar cautery, and clip appliers. In 1995, Ferzli *et al.*[5] reported the excision of an 8–9-cm segment IV hepatic adenoma, using an ultrasonic dissector and endoscopic vascular staplers. The first successful laparoscopic anatomical hepatectomy was reported in 1996 by

Azagra *et al.*,[6] who performed a left lateral sectionectomy (segments II and III) in a patient with a benign adenoma.

Technological advances in recent years are beginning to make the routine use of laparoscopic liver resection a clinical possibility. These advances include refinements in laparoscopic ultrasound, refined stapling techniques for the liver, and the development of coagulating parenchymal dissection tools. Obstacles to routine laparoscopic surgery on the liver are mainly related to difficulty in retraction with current instrumentation, difficulty in assessing safe margins of resection without the use of tactile sense, difficulty in safe parenchymal dissection laparoscopically, and the potentially catastrophic consequences of injuring major adjacent structures.

Laparoscopic hepatectomy avoids many disadvantages of a standard hepatectomy and is beneficial for patients' quality of life. However, the laparoscopic procedure requires expertise in open liver surgery and advanced laparoscopic surgery. Moreover, it is essential that the indications, based on preoperative liver function and on the location and size of tumors, are strictly adhered to.

Up to now, both anatomical and nonanatomical laparoscopic hepatic resections have been practiced. However, laparoscopic hepatectomy will not entirely supplant open hepatectomy. Nevertheless, the laparoscopic approach should be considered the treatment of choice in selected patients.

Indications (See Table 1)

Currently, the laparoscopy approach is employed mainly for minor hepatic resections, wedge resections, segmentectomy, and bisegmentectomy. However, patients who require anatomical resection, such as those requiring right hepatectomy, would most likely be poor candidates for laparoscopic liver surgery.

The localization of lesions is of crucial importance in laparoscopic liver resection. Small, focal, and localized tumors on the anterolateral segments (segments II–VI, according to Couinaud) are typically considered suitable for laparoscopic resection because the periphery of the

Table 1. Indications for laparoscopic hepatectomy.

Preoperative liver function
Child class A or B
Tumor factors
(1) Size: < 4 cm (pedunculated type, < 6 cm)
(2) Location: lower or lateral segments
(3) Type: solid and nodular types (pedunculated type is best)

liver is devoid of large venous structures and bleeding can be easily controlled with clamps or cautery. Nodular tumors smaller than 4 cm or pedunculated tumors smaller than 6 cm are proper candidates.[7,8] For tumors located in the upper segments, thoracoscopic hepatectomy may be feasible.[9] However, it would be difficult to obtain a tumor-free resection margin for the inferior border of the tumor. Moreover, if accidental bleeding were to be encountered, meticulous bleeding control would be required but technically difficult to achieve. Thus, thoracoscopic hepatectomy is acceptable only for pedunculated tumors.

In cirrhotic patients with coexisting compromised hepatic function, laparoscopic liver resection has been performed with good results.[10–12] The authors of these studies concluded that preserving the abdominal wall vascular collaterals in the laparoscopic approach reduced postoperative hepatic decompensation in patients with portal hypertension.[13] However, patients with an indocyanine green 15-minute clearance retention rate (ICG-R15) of more than 20%,[14] prothrombin activity less than 75%,[15] serum albumin level below 3.5 g/dL, and total bilirubin more than 1.5 mg/dL are not good candidates for major hepatic resection.[16] Cirrhosis is considered a limiting factor for a massive liver resection, and extensive surgery may be hazardous in such patients.[17]

Laparoscopic treatment of malignant lesions is still a matter of debate. Although laparoscopic liver resection has been successfully applied in cirrhotic patients with primary liver tumors,[13] the same oncologic principles should be applied as in open surgery: radical resection, and achievement of at least a 1-cm tumor-free surgical margin.[18] Enucleation of a metastatic lesion with a 2-cm margin is sufficient, and this can

be performed laparoscopically. Comparative studies with open surgery have shown a shorter hospital stay with the laparoscopic approach, with similar morbidity, mortality, and long-term results.[19,20] However, a multicenter study reported discouraging results, with a surgical margin of <1 cm in 30% of resected HCCs and 20% of resected metastases; moreover, positive surgical margins were found in 6.7% of patients.[21]

Benign lesions are generally referred for laparoscopic surgical resection because of symptoms or uncertain diagnosis. Hemangiomas and focal nodular hyperplasia are rarely submitted to surgical resection, and few cases have been reported in the literature.[19,22–25]

Patient and Instrument Positioning

Patient positioning and trocar placement

An individual patient's position and trocar placement are decided based upon the location of the tumor. Laparoscopic hepatectomies are generally performed with a four- or five-trocar technique.

The patient is positioned on the operating table in a supine position, and the surgeon stands on the right side of the patient. A 10-mm trocar and 30° laparoscope, which provides a wide-angle view of the operative field, are placed below the umbilicus. After pneumoperitoneum is created by infusion of carbon dioxide, more trocars are inserted at the epigastrium and the bilateral subcostal lines for dissection.

When hepatic resection is performed on the anterior-inferior segment (Sg V) or the posterior-inferior segment (Sg VI), the patient is placed on a left-sided semidecubitus position. After pneumoperitoneum is created, three more trocars are inserted at the right subcostal line, the anterior clavicular line, and the epigastrium. For resection of the superior or posterior segment of the right liver, a lateral approach is considered to be more convenient.

Instrumentation

Improved instruments have greatly improved the safety of laparoscopic hepatectomy. The critical determinant for safe laparoscopic hepatectomy is thorough familiarity with the relevant laparoscopic instruments and equipment.

Laparoscopic flexible ultrasonography[26] is not only useful, but indispensable, for seeing clearly the boundaries of the tumor and the exact anatomic location of the vessels, mainly the hepatic veins. It frequently allows accomplishing anatomical resections that are otherwise not possible. If nonanatomical resection is performed, intraoperative ultrasonographic guidance allows safer surgery. Precise localization of hepatic vessels with color Doppler expands the indications of laparoscopic surgical resection.

Ultrasonic dissectors, microwave coagulators, and argon beam coagulators have been recognized for their efficacy in liver surgery. Compared to the crushing techniques for parenchymal division, the use of the ultrasonic dissector is beneficial because it allows for division of liver parenchyma with less hemorrhage. Ultrasonic dissection allows complete clearance of the liver parenchyma all around the pedicles for a length of several millimeters, allowing safe ligatures. For the approach to the hepatic veins, ultrasonic dissection allows precise dissection without traction, minimizing the risk of tearing the fragile wall of the hepatic veins and the collaterals. An ultrasonic scalpel and the Cavitron ultrasonic surgical aspirator (CUSA) are usually used to transect the parenchyma. The ultrasonic scalpel works by means of a vibrating blade or scissors, and can be used for tissue dissection, coagulation, and preparation. It can effectively seal small vessels and bile ducts with minimal fogging of the camera lens, and seldom sticks to the liver parenchyma as conventional electrocautery does. The most important advantages when compared with electrocautery are limited heat generation, lack of smoke production, and lack of current flowing through the adjacent tissues. CUSA allows selective fragmentation and aspiration of collagen-sparse tissues such as the liver parenchyma. Blood vessels and bile ducts are preserved.

A microwave coagulator is used along the resection line to prevent bleeding from the surrounding hepatic parenchyma. A combination of microwave coagulation and ultrasonic dissection minimizes intraoperative blood loss. The jet cutter is a promising new instrument in liver surgery that uses a high-pressure water stream for safe dissection of hepatic tissues.

The argon beam coagulator is useful for hepatic resections, primarily for superficial hemostasis. However, the plume of the argon flows into

the peritoneal cavity; and in the presence of CO_2 pneumoperitoneum, it can increase intra-abdominal pressure and might cause hemodynamic instability. For this reason, the use of argon beam coagulation is not recommended in laparoscopic liver resections.[27,28]

Endoscopic disposable clip appliers and vascular staplers contribute to the reduction of major intraoperative bleeding during laparoscopic hepatectomy. Because of their safety, rapidity, and ease of application, these stapling devices are efficient for controlling and dividing the major hepatic veins. Titanium endoclips or endostaplers are used to close the main vascular branches and bile ducts. Small vascular or biliary radicles are divided with bipolar coagulation or between endoclips. Moderate-sized hepatic veins and bile ducts in Glisson's sheath are clamped with a clip. The application of tissue glue on the resection surface further improves hemostasis and prevents bile leak.

Gasless laparoscopy is an alternative to the use of CO_2 pneumoperitoneum, and uses an abdominal wall lift device. It provides a tent-shaped operative field rather than the more spacious dome-shaped field provided by a pneumoperitoneum. In effect, intra-abdominal organs are closer to the laterally situated port sites, increasing the risk of injury and limiting work area. However, gasless laparoscopy avoids the rapid changes in intra-abdominal pressure that are associated with a greater risk of gas embolism. Maintaining intra-abdominal pressure equal to that of the ambient environment may minimize this risk, especially if the hepatic vein is lacerated intraoperatively. Unfortunately, the exposure with the gasless approach is somewhat unsatisfactory.

Procedures

Limited resection

Recent data suggest that wedge resection is adequate for a solitary and small malignant tumor, a benign tumor, or a metastasis in the liver.

Resection begins with the scoring of Glisson's capsule by electrocautery. Progressive dissection more deeply into the hepatic parenchyma is then carried out with a combination of the Kelly fracture technique, electocautery, and an ultrasonic dissector. As larger vessels are encountered, clips should be applied. Maintaining a bloodless field is

critical and can only be accomplished by constant irrigation of the dissection area. When bile leak is of concern, cholecystectomy is added and cholangiography via the cystic duct stump is performed. If the site of bile leakage is evident, it should be closed with a suture. In the case of possible bile leakage, decompression of the bile duct with a tube placed via the cystic duct is helpful.

Laparoscopic left lateral sectionectomy

Left lateral sectionectomy is probably the easiest anatomical hepatectomy, as the left lateral section is easy to mobilize and small enough to be removed. Its vascularization is standard and simple, and the raw surface after hepatectomy is small. Left lateral sectionectomy can be performed laparoscopically to treat liver tumors for which enucleation may be an incomplete and inadequate treatment. Large lesions in the lateral section of the left liver may be optimally treated by classical sectionectomy, whereas the enucleation procedure may actually be dangerous.

Laparoscopic left lateral sectionectomy can be performed following the same rules as in open hepatic surgery. Mobilization of the section, ultrasound examination of the parenchyma, Pringle maneuver, and selective control of segmental pedicles and the left hepatic vein can be similarly performed.

The first step in the procedure is to gain control of the porta hepatis. Early control of the porta hepatis allows the Pringle maneuver to be applied quickly at any time during the procedure. The porta hepatis is reached by opening the lesser omentum. The porta is encircled, and an umbilical tape is passed around it to be later used as a tourniquet. The falciform ligament is divided until the inferior vena cava (IVC) and root of the left hepatic vein are reached. The left hepatic vein is then dissected and ligated. If there is no hepatic vein outside the liver, then dissection is not laparoscopically feasible. The procedure should be completed with open laparotomy. Glisson's capsule is incised by electrocautery along the left side of the falciform ligament. Although the hepatic parenchyma can be dissected by the classical Kelly fracture technique, the use of an ultrasonic dissector is preferable for more precise destruction of the hepatic parenchyma and better identification of the pedicles.

The pedicles encountered first are the pedicles of segment III, and the small vessels can be cut with laparoscopic coagulating scissors. Pedicles 1 mm or larger should be double-clipped and transected. Pedicles of segment II become evident as the dissection progresses. The last structure encountered during the procedure is the left hepatic vein inside the liver that has been ligated earlier. A laparoscopic linear cutting stapler with white vascular staples is then used to staple and divide the left hepatic vein. The remaining attachment of the lateral section may now be dissected and the resection completed. The sectionectomy specimen should be placed into a retrieval bag for extraction. Because of its size, morselization is sometimes needed for withdrawal. The raw surface of the liver is then carefully inspected for hemostasis and biliostasis. Cholangiography, or the administration of dye via the cystic duct, is useful at this stage of the operation to detect significant bile leakage.

Laparoscopic left hepatectomy

As a strategy for laparoscopic liver dissection, a hemihepatic inflow control technique has been reported. As a left hepatic inflow control technique, *en masse* occlusion of the left Glisson's sheath at the bifurcation is performed. A long tape can be confidently passed through the bifurcation. This technique can be used exactly the same way as in open surgery. Needless to say, this technique can prevent the right liver from ischemic damage. After full exposure of Glisson's sheath, the left pedicle is divided with an Endo GIA stapler. A pitfall of this technique is division of the vessels and bile ducts to the caudate lobe. The flexible laparoscope enables visualization of the back of the pedicle to the left liver in order to visualize and protect the vessels and bile ducts to the caudate lobe before the application of the Endo GIA stapler.

Right hepatectomy

Classical right hepatectomy should not be attempted laparoscopically at present. For right hepatectomy, the operative time is long, a skin incision of at least 10 cm is required to remove the large amount of liver tissue, and the conversion rate to standard open hepatectomy is high.

As the overriding principle of laparoscopic surgery is to achieve minimal invasiveness with optimal safety, laparoscopic right hepatectomy is too invasive to provide the usual and expected benefits of laparoscopic surgery, unless more advanced technology is acquired.

Hand-assisted technique

The two major complications of liver resection are bleeding and air embolism. A hand-assisted method has been recently introduced for laparoscopic surgery. With the introduction of the "laparoscopic hand", finger fracture and blunt dissection are possible. The method also provides immediate hemostasis and prevents air embolism in case the hepatic vein is severed. This technique can help in resolving the difficulties and pitfalls of laparoscopic liver resection and in making this surgery safe.[29]

The greatest potential benefit of laparoscopic liver resection is minimalization of the size of the incision as well as minimization of heat loss and evaporation during surgery. A 7.5-cm hand-port incision should lead to a more rapid recovery than a 35-cm subcostal incision, and should result in a decreased chance for leakage of ascites in chronic liver disease. Although major resections are feasible with current instruments, the best candidates for laparoscopic hepatectomy are those requiring the removal of two or fewer segments of the liver because tissues of this size are readily removable through an incision the size of a hand port.

Results

From July 2002 to September 2006, a total of 123 cases (83 males and 39 females) with a mean age of 48.2 years (range, 27–69 years) underwent total laparoscopic liver resection in the author's department.[30] Surgical procedures included 65 anatomical hepatectomies and 58 local resections. The pathology included 52 malignant and 71 benign diseases. The operative time was 201.5 min $\pm$ 100.5 min (range, 105–280 min). The median intraoperative blood loss was 210 mL (range, 50–500 mL). The postoperative hospital stay was 4.5 days $\pm$ 1.5 days (range, 3–14 days). The largest size of the resection was 18 cm $\times$ 16 cm $\times$ 12 cm.

Biliary fistula occurred in two patients postoperatively and resolved spontaneously after 5 days. Our experience is comparable to those reported by others with a mean hospital stay duration of 3.5–7.7 days, a mean intraoperative blood loss of 300–315 mL, an average operative time of 198–214 min, an overall morbidity of 5%–20%, an overall conversion rate of 5%–7%, and an overall mortality of 0%–0.5%.[31–34]

In comparative studies with open liver surgery, mortality and morbidity were lower in laparoscopic surgery. Postoperative complications frequently seen in open hepatectomy, such as subphrenic fluid collection, hemorrhage, or liver decompensation, were uncommon in laparoscopic hepatectomy.[1–3] The operative time was similar or slightly longer, blood loss was similar or lower, and mean hospital stay was shorter for the laparoscopy group. Hemostasis is a major concern in liver surgery, and the use of ultrasonic scalpels (used more commonly during laparoscopic resection) helps to reduce blood loss. However, failure to control bleeding during laparoscopic surgery is still the most important reason for conversion to open surgery.

Complications

The most common perioperative complications are bleeding and bile leakage. Despite the recent improvements in sealing parenchymal vessels, intraoperative hemorrhage remains the most common life-threatening complication, which may lead to conversion to open surgery, postoperative complications, and the need for massive blood transfusion. Almost 80% of procedures are converted to open surgery because of bleeding. Careful selection of patients and meticulous operative techniques reduce this postoperative complication. Other common reasons for conversion are associated with liver malignancies, including insufficient tumor excision and positive margins.

Laparoscopic liver resection carries an increased risk of gas embolism when compared with an open approach.[35] Gas embolus is a life-threatening complication in the presence of pneumoperitoneum, but it is very rare and is not reported as a major problem in large series of laparoscopic liver resection. The risk of venous gas embolism can be reduced by locating the left hepatic vein using an intraoperative ultrasound (IOUS),

by creating a positive-pressure pulmonary insufflation when approaching the liver vessels, and by reducing intra-abdominal pressure with less pneumoperitoneum or by using gasless laparoscopy.

Clinical and experimental studies have shown that CO_2 pneumoperitoneum is associated with impaired portal blood flow, hemodynamic instability, increased systemic arterial pressure, and decreased central venous pressure and cardiac outflow.[36] These hemodynamic changes are usually reversible. Other less frequent complications, such as intestinal or organ damage, are usually the results of technical error.

The Role of Laparoscopic Liver Resection

The controversies of laparoscopic liver resection mainly surround (1) the practicability, (2) the safety, and (3) the adequacy of resection in dealing with malignant diseases. There is no doubt that the laparoscopic approach, as compared with open surgery, has its own limitations. Problems include difficult exposure and retraction, loss of tactile sense, demanding suturing skills, risks of massive bleeding and air embolism, and difficult laparoscopic surgery due to the presence of dense adhesions related to previous procedures. Tumor dissemination and inadequate margins are also potential disadvantages of the laparoscopic approach. Moreover, its feasibility is frequently limited to patients who require wedge resections of superficial tumors. Fortunately, most of these problems of laparoscopic liver resection are overcome with improvements in technique and modifications of instruments. The use of the hand port not only facilitates adequate exposure of the pathology, but also assists in mobilizing the liver from its attaching ligaments to the diaphragm.

Many comparative studies favor laparoscopic over open surgery for several reasons: a reduced postoperative analgesic requirement, shorter time to oral intake, shortened hospital stay, decreased postoperative pain, reduced peritoneal adhesions, improved cosmetic results, shorter convalescence, and faster return to normal activities. These advantages are often exemplified in patients undergoing cyst or benign tumor resections. Due to improvements in laparoscopic instruments and operative techniques, intraoperative blood loss is lower compared with open hepatectomy. This is an especially important advantage in cirrhotic

patients in whom intraoperative blood loss is a major factor for postoperative death. Reduced fluid infusion and decreased loss of protein and electrolytes make the laparoscopic approach more suitable in patients with severe liver cirrhosis, in whom open hepatectomy might result in more postoperative complications.

However, the role of laparoscopy in the resection of liver malignancies remains controversial. Patients should be carefully selected. Only small malignant tumors located in the left lateral section or in the anterior segments of the right liver are suitable for laparoscopic resection; otherwise, the complication rate might be too high, especially in patients with hepatocellular carcinoma (HCC) in cirrhotic liver. A tumor-free surgical margin is difficult to obtain. The late outcome needs to be evaluated in further studies.

The problems of tumor cell seeding and port-site metastases have been emphasized in many reports. Until now, there are only reports on small series of patients who underwent laparoscopic resection of HCC or liver metastases. These studies did not provide data on the long-term outcomes of the patients. The controversies regarding tumor cell seeding and port-site metastases in laparoscopic liver resection of malignancies persist. Nevertheless, the short-term outcome is comparable to that of conventional surgery, with the additional benefits of the minimally invasive therapy.

Conclusions

In conclusion, laparoscopic hepatic resection is technically feasible and safe in properly selected patients. Small tumors located in the left lateral section are most suitable for the laparoscopic approach. Complicated liver resection can feasibly be performed, provided that patient selection is appropriate and that surgeons with expertise and the appropriate instruments are available. Complication and conversion rates are acceptable. The laparoscopic approach to malignant lesions is controversial, and results should be confirmed with further prospective studies. In highly selected patients, with appropriate techniques and instruments, laparoscopic liver surgery for malignancy appears to be feasible and safe in experienced hands.

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Techniques of Vascular Control and Protective Strategies for Parenchymal Transection

Markus K. Müller, Henrik Petrowsky and Pierre-Alain Clavien

Introduction

Liver resection has been increasingly performed for hepatocellular carcinoma (HCC) with preserved liver function (Child–Pugh class A) over the last two decades due to improvements in surgical techniques and perioperative management.[1,2] Despite the evolution of liver surgery, there is growing evidence that excessive blood loss and the need for blood transfusions are predictors of poor outcome for both noncirrhotic[3,4] and cirrhotic liver parenchyma patients.[5] Furthermore, the use of perioperative blood transfusions is associated with a poor long-term survival[3,6] mainly through an immune response dysfunction.[7]

Although it is undisputed that certain liver resections can be performed without vascular control, the majority of hepatobiliary surgeons use routine or selective techniques of vascular control to minimize blood loss during parenchymal transection.[8] The goal to avoid blood loss and blood transfusions can be achieved by different vascular clamping techniques, which have to be selected individually based on the

tumor location, the complexity of liver resection, the underlying liver disease, and the patient's cardiovascular comorbidities. Inflow occlusion by clamping the portal triad (Pringle maneuver) has been used since the beginning of the last century,[9] and became the most favored technique during the 1980s.[10] On the other hand, the drawback of each clamping technique is that clamping causes a certain degree of hepatocellular damage due to ischemia/reperfusion injury.[11] Therefore, protective strategies such as ischemic preconditioning and intermittent clamping have been developed to improve the tolerability against prolonged ischemia during vascular clamping.[12–14]

The purpose of this chapter is to describe the different techniques of vascular control for liver transection as well as their benefits and shortcomings. Furthermore, ischemic preconditioning and intermittent clamping are discussed as protective strategies against the negative effects of vascular clamping.

Inflow Occlusion of the Portal Triad (Pringle Maneuver)

The technique of inflow occlusion through clamping of the portal triad was first described by the British surgeon James Hogarth Pringle (1863–1941) in 1908 for reducing hemorrhage in liver trauma.[9] This technique became popular in liver surgery during the 1980s,[15] and is currently the most used technique for vascular control in elective liver surgery and liver trauma.[8] Inflow occlusion is especially effective in preventing blood loss when associated with low central venous pressure (CVP), which reduces backflow bleeding from the hepatic veins.[16–18]

Technique

The site for portal triad clamping is at the hepatoduodenal ligament between the first part of the duodenum and the hilum of the liver. The first step of the Pringle maneuver is to free adhesions to the gallbladder and to open the lesser omentum at the level of the pars flaccida. This can be challenging and time-consuming in patients with adhesions from previous abdominal surgery. This procedure has to be performed carefully to avoid any damage to anatomical structures.

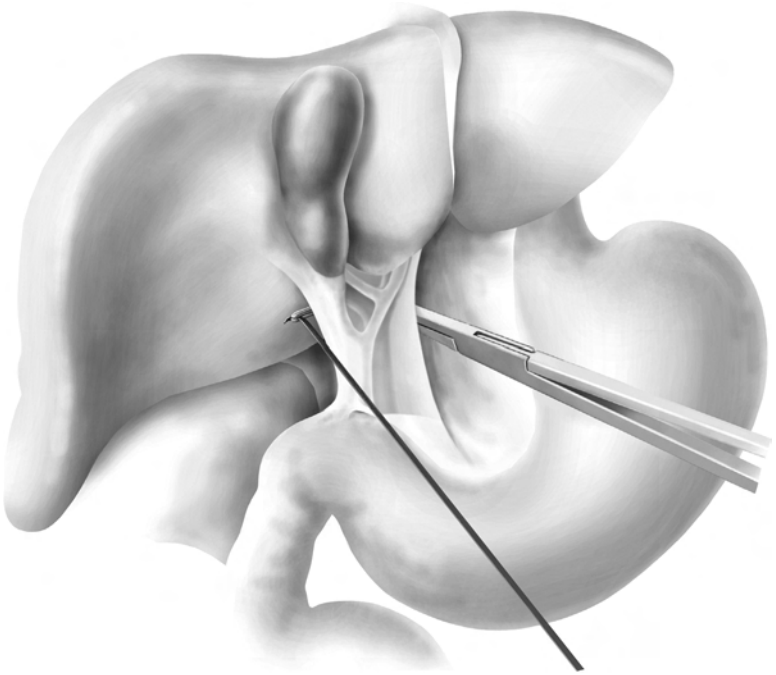

Fig. 1. Pringle maneuver with a tourniquet technique. A tape is passed through Winslow's foramen encircling the hepatoduodenal ligament.

A tape is passed behind the hepatoduodenal ligament through Winslow's foramen (Fig. 1). The tape is then passed through a rubber tube, which serves as a tourniquet. The rubber tube is pushed down and fixed with a clamp (Fig. 2). The Pringle maneuver is sufficient when no pulse is palpable in the hepatic artery distal to the tourniquet. In some patients with thick hepatoduodenal ligaments, an additional tourniquet is used to stop blood inflow. Attention has to be given to arterial variations like the presence of an aberrant left hepatic artery originating from the left gastric artery. This aberrant artery also has to be occluded, usually by bulldog clamps, to prevent bleeding during parenchymal transection.

Instead of tourniquets, soft vascular clamps can be used to achieve inflow occlusion (Fig. 3). In contrast to the tourniquet technique, the occlusion by clamps has a higher risk of vascular and biliary damage if

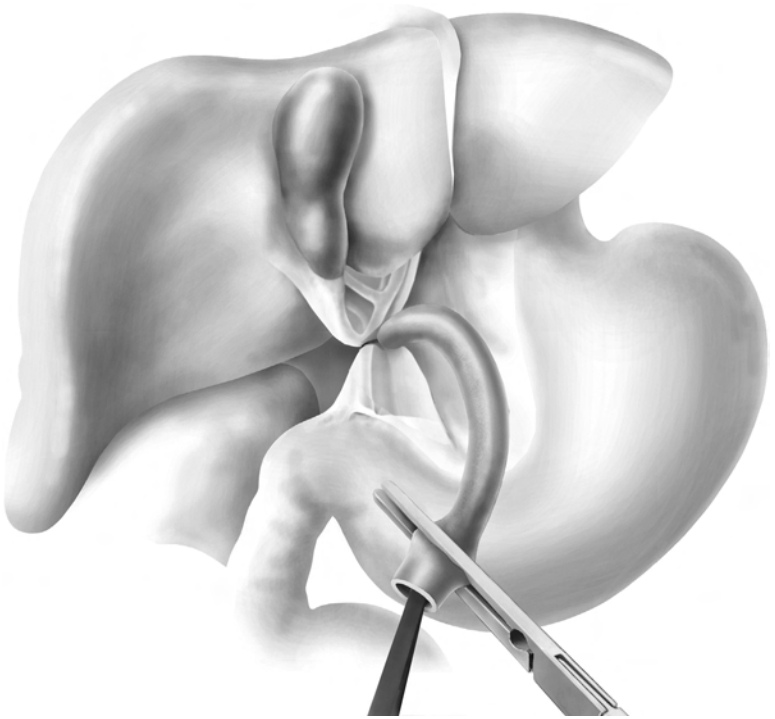

Fig. 2. Pringle maneuver with a tourniquet technique. The tape is passed through a rubber tube, which is pushed down and fixed with a clamp.

not used carefully. Another advantage of using a tourniquet is its higher flexibility, which facilitates visibility in the operative field. Alternatively, inflow occlusion can be achieved by clamping only the vascular structures and sparing the bile duct. This method results in the same effect as portal triad clamping, but requires particular care to prevent bile duct injuries.[13,19]

The evolution of laparoscopic surgery during the last decade has also resulted in an increase in indications for laparoscopic liver resection/ablation.[20] As for open procedures, inflow occlusion is also a very efficient technique to prevent bleeding during laparoscopic transection in cirrhotic and noncirrhotic patients. Several reports have demonstrated the feasibility and efficiency of inflow occlusion in the setting

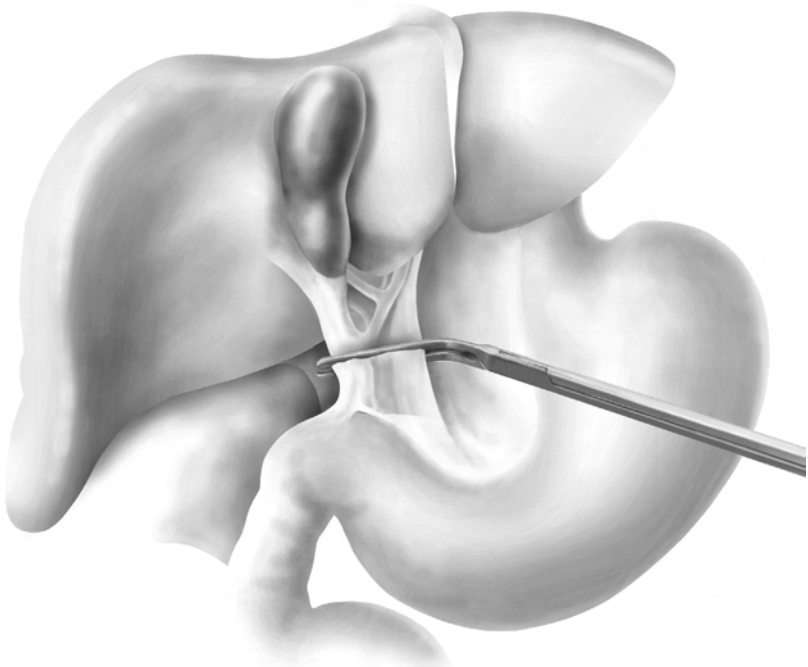

Fig. 3. Pringle maneuver with a vascular clamp. Alternatively, inflow occlusion of the portal triad can also be achieved with a vascular clamp.

of laparoscopic resection for HCC.[21,22] The laparoscopic technique is analogous to the technique of the open approach.

Indications

Vascular inflow occlusion is applied to reduce blood loss during parenchymal transection for minor and major liver resections[23] in the absence of major hepatic vein or vena cava involvement. Although several modern resection devices (ultrasonic dissector, hydrojet, dissecting sealer) claim to enable parenchymal transection without the Pringle maneuver, inflow occlusion has to be applied in about one third of the cases during transection with these so-called "bloodless" devices.[24] Since cirrhotic livers are more vulnerable to ischemia than livers with normal parenchyma, the Pringle maneuver has to be applied with shorter

Table 1. Maximum safe duration of inflow occlusion for different protective strategies.

Strategy	Normal Liver	Cirrhotic Liver
Continuous inflow occlusion (Pringle maneuver)	60 min (c,e)	30 min (c,e)
Intermittent portal triad clamping	>120 min (c,e)	60 min (c,e)
Ischemic preconditioning with Pringle maneuver	75 min (e)	?
Continuous inflow occlusion under hypothermia	90 min (c)	60 min (c)

c, clinical evidence; e, experimental evidence.

occlusion periods in cirrhotic patients and should not exceed 30 min (Table 1).[25,26]

Selective Vascular Inflow Occlusion

Selective vascular clamping refers to the clamping of only those portal and arterial branches which supply the part of the liver that is planned to be removed. This technique was first described as hemihepatic vascular occlusion by Makuuchi *et al.*[13] in 1987. The advantages of this technique are no ischemic insult to the remnant liver, prevention of splanchnic congestion, and better hemodynamic tolerability. On the other hand, the disadvantage is persistent bleeding from the nonclamped hemiliver.

Technique

Selective vascular clamping is applied only to those arterial and portal branches which supply the hepatic region that is to be removed. Selective vascular clamping can be performed at the segmental or hemihepatic level. Dissection of the vascular branches is achieved at the suprahilar level for segmental resections and at the hilar level for hemihepatectomies.

For right hemihepatic vascular clamping, the portal vein is accessed through the right posterolateral route. This approach is

facilitated by cholecystectomy, which is a mandatory part of right hemihepatectomy. During the dissection, the right hepatic artery is identified and encircled. When the portal bifurcation is identified, a small retractor is inserted to lift up the bile duct and to free the right portal vein which can be encircled. For left hemihepatic vascular clamping, the portal vein is usually accessed from the left side of the hepatoduodenal ligament. The right and left hepatic arteries are identified and encircled. The left or right portal branch and hepatic artery are occluded by bulldog clamps or ligatures.

Indications

As the Pringle maneuver or selective vascular inflow occlusion is applied to reduce blood loss during parenchymal transection for minor and major liver resections, they are often used in combination. For the technique of selective vascular inflow occlusion to be used properly, tumors have to be restricted usually to one hemiliver and should not invade into the hemihepatic plane. Selective vascular inflow occlusion is preferred in patients with chronic liver disease with a poor hepatic reserve to avoid any ischemic insult to the remnant liver.[19,27,28]

Total Vascular Exclusion

Total vascular exclusion involves control of the suprahepatic and infrahepatic vena cava as well as portal triad clamping, resulting in total inflow and outflow occlusion (Fig. 4). This technique completely isolates the liver from the blood circulation, and avoids inflow and backflow bleeding during parenchymal transection. On the other hand, interruption of the retrograde blood flow from the hepatic veins enhances ischemia/reperfusion injury when compared to inflow occlusion alone.[29] Total vascular exclusion prevents potential air embolisms due to injuries to hepatic veins.

In contrast to the Pringle maneuver where a low central venous pressure (CVP) (< 5 mm Hg) is recommended, total vascular exclusion requires a higher CVP (12–15 mm Hg) to maintain the cardiac preload in order to tolerate the total clamping.[30] However, 10%–14%

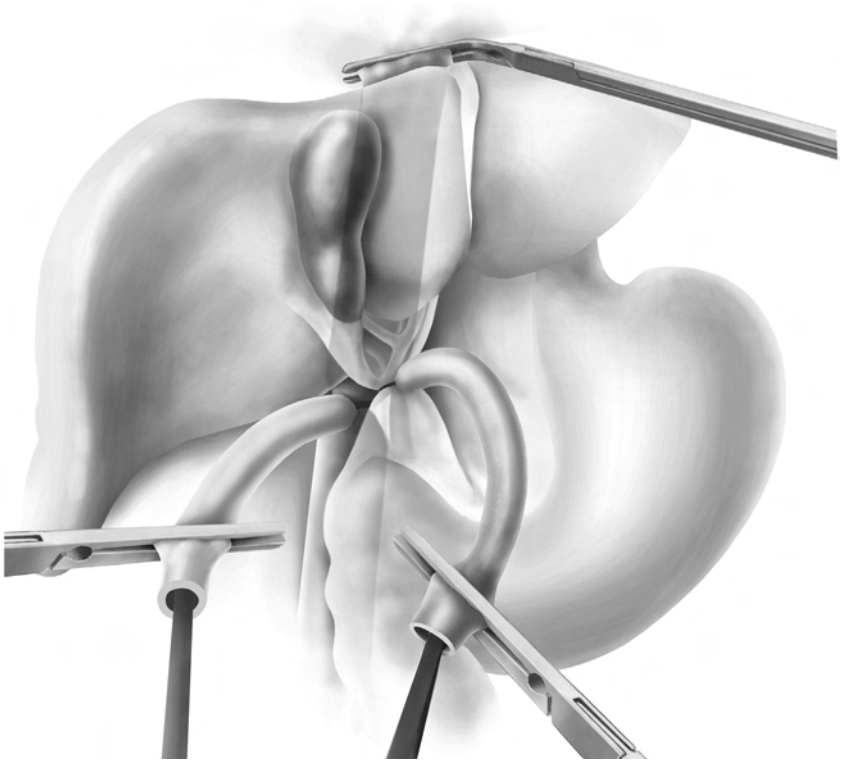

Fig. 4. Total vascular exclusion. First, the infrahepatic vena cava and the portal triad are occluded. If this trial of dual occlusion is tolerated, the suprahepatic vena cava is then closed with a vascular clamp.

of patients do not tolerate this clamping procedure despite adequate volume load before clamping.[31,32] The tolerability of total vascular exclusion closely relates to the experience of the anesthesiology team. A venovenous bypass can be used to prevent side-effects such as mesenteric congestion and cardiovascular instability (Fig. 5).

Technique

The first step is the same as in the preparation of a Pringle maneuver, as described above. Then, the falciform, coronary ligament, and both triangular ligaments are divided and the entire liver is mobilized. The right

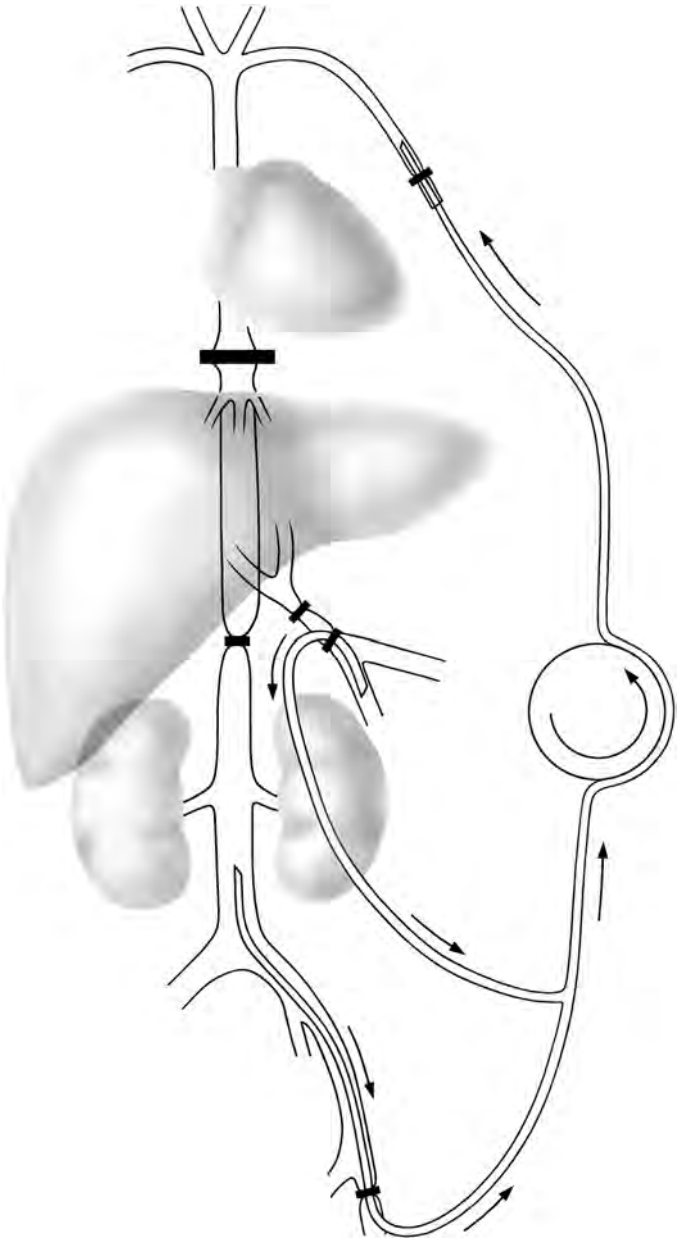

Fig. 5. A venovenous bypass in combination with total vascular exclusion can be used to prevent side-effects including mesenteric congestion and cardiovascular instability.

hemiliver is detached from its posterior retroperitoneal surface. Then, the suprahepatic and infrahepatic vena cava are mobilized and encircled. Ligation of the right adrenal vein is helpful and facilitates clamping or occlusion of the infrahepatic vena cava.

For vascular exclusion, the infrahepatic vena cava is occluded first using the tourniquet technique or a soft vascular clamp. Then, the tourniquet or vascular clamp around the hepatoduodenal ligament is closed (Pringle maneuver). This trial of dual clamping should be performed for a few minutes to detect hemodynamic instability. If this is not well tolerated despite adequate volume load, total vascular exclusion should not be performed; for these patients, a venovenous bypass should be considered (Fig. 5). If the trial of dual clamping is well tolerated, then the suprahepatic vena cava is closed using a large curved vascular clamp, which is passed around the vena cava from the left side (Fig. 4). After the hepatic transection is completed, the clamps/tourniquets are sequentially released in reverse order.

Indications

Total vascular exclusion is mainly indicated for the resection of central tumors involving the hepatic veins and/or vena cava. Furthermore, this technique can be life-saving in the operative management of severe liver trauma with torn major hepatic veins.

Complications of Vascular Clamping

Prolonged ischemia during vascular clamping is associated with a high degree of ischemia/reperfusion injury and hepatocellular damage.[12,33] Livers with underlying chronic disease have an especially higher vulnerability against ischemia than livers with normal parenchyma.[34] Therefore, prolonged clamping can result in deterioration of the liver function and, in the worst-case scenario, liver failure.[5,25,35,36]

Long periods of vascular inflow occlusion may also result in congestion of the alimentary tract, with negative effects on intestinal blood perfusion and postoperative bowel function.[37] Splenic ruptures have also been reported as a result of inflow occlusion–induced congestion.[38]

However, these complications are rare since there are usually sufficient portosystemic collaterals that enable adequate decompression of the splanchnic region. In splenic rupture, the Pringle maneuver is released and conservative management of the rupture should be attempted; if this fails, splenectomy has to be performed.

Another potential complication of vascular clamping is damage to the vascular structures. This might require complex vascular repair with an increased risk of thrombosis. If clamping of the portal triad (Pringle maneuver) results in severe damage to the common bile duct, external biliary drainage or bilioenteric anastomosis has to be performed; this might increase the risk of postoperative complications. Such complications are, however, exceptional.

Total vascular exclusion can result in cardiovascular instability, which is often corrected with fluid load. The drawbacks of overfluid correction are postoperative tissue edema, pleural effusions, and intra-abdominal fluid collections, all of which contribute to increased postoperative morbidity. Total vascular exclusion may also have deleterious effects on postoperative kidney function,[32] particularly in the presence of a preexisting, compromised renal function, resulting in renal failure.

Protective Strategies Against Prolonged Ischemia During Vascular Clamping

Inflow occlusion (Pringle maneuver) and total vascular exclusion minimize blood loss during liver resection and the need for perioperative blood transfusions. Furthermore, these procedures facilitate parenchymal transection by providing a better visual field of the transection plane. While liver resections with clamping periods below 30 min are usually well tolerated, prolonged periods of continuous inflow occlusion may cause severe ischemia/reperfusion injury in the remnant liver.[33] Injured and diseased livers are more vulnerable to ischemia than healthy livers (Table 1). Prolonged ischemia can have deleterious effects on postoperative liver function, liver regeneration, and survival.[33,39]

There are two principles that can be applied to avoid the negative effects of clamping and ischemia. First, the application of the clamping period can be reduced or avoided through the use of the so-called

"bloodless" transection devices such as the ultrasonic dissector, hydrojet, or dissecting sealer. These modern devices claim to enable safe parenchymal transections without the use of vascular control techniques. This topic will be discussed further in the next chapter. The second principle is the use of protective strategies that increase hepatic tolerability to inflow occlusion. The protection can be achieved through the use of pharmacological or surgical strategies.[11] While pharmacological strategies have been evaluated mostly in experimental models, surgical protective strategies have been adopted in clinical practice and have proven at the highest level of evidence to be effective in liver surgery. In this chapter, only surgical strategies such as intermittent portal triad clamping, ischemic preconditioning, and topical cooling are discussed.

Intermittent portal triad clamping

Intermittent portal triad clamping is the technique of alternating portal triad clamping with short intervals of unclamping and portal reperfusion (Fig. 6); the total time duration of the hepatic parenchymal transection thus determines the number of occlusion/reperfusion cycles. The first clinical attempt of this protective strategy during liver surgery was performed in the 1980s by Makuuchi *et al.*,[13] who applied a 30-min inflow occlusion followed by a 5-min reperfusion. Since then, various experimental studies have found that intermittent clamping is associated with less microcirculatory disturbances,[40] lower cytokine release,[41] diminished hepatocellular injury,[39,40,42] and reduction of apoptosis[39] when compared with continuous clamping. Belghiti *et al.*[12] demonstrated the protective effect of intermittent clamping (15-min occlusion/5-min reperfusion) during liver resection in a randomized controlled trial. In this trial, the protective effect was notably and strikingly better in patients with liver steatosis; however, the drawback of this technique was the significantly higher blood loss during the periods of unclamping when compared to the group with continuous clamping.

Although another randomized trial failed to confirm the beneficial effects of intermittent portal triad clamping in cirrhotic patients,[43] this

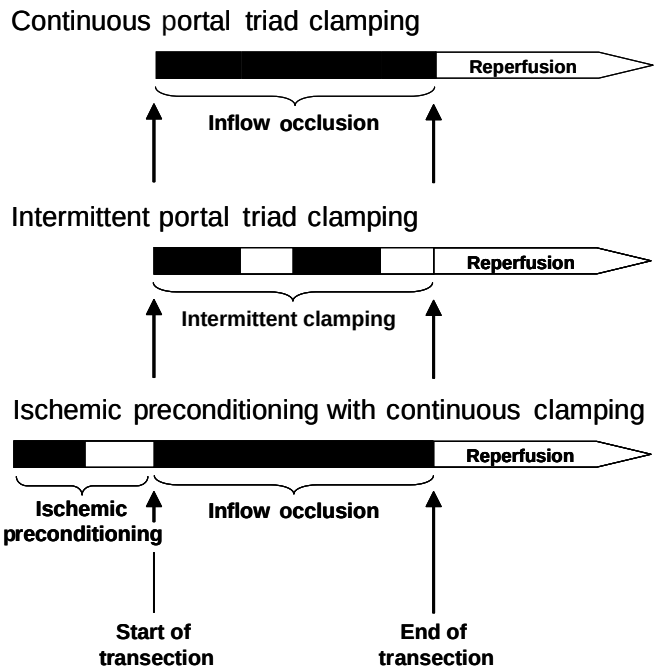

Fig. 6. Continuous inflow occlusion and protective strategies. Inflow occlusion (ischemia) and unclamping (reperfusion) are illustrated by black and white boxes, respectively.

technique has been adopted by many hepatobiliary surgeons as a protective strategy during liver surgery, especially in complex liver resections with predicted long parenchymal transection times (>60 min) and in patients with diseased livers.

Ischemic preconditioning with continuous inflow occlusion

Ischemic preconditioning consists of a brief period of ischemia (10–15 min) followed by a short interval of reperfusion (10–15 min) before transection under continuous inflow occlusion (Fig. 6). The current understanding of the underlying protective principle is that cells are exposed to various kinds of subinjurious stress, which triggers natural defence mechanisms against ischemia/reperfusion injury.

The protective phenomenon of ischemic preconditioning was first discovered in the myocardium,[44] and later also in other organs[11] including the liver.[45] Experimental studies have proposed various mechanisms to be responsible for the protective effects of ischemic preconditioning, including the inhibition of apoptosis.[39,45–49] A recent DNA microarray study in humans showed that ischemic preconditioning triggers the overexpression of mediators, counteracting the ischemia-induced proinflammatory and proapoptotic activation.[50] Clavien *et al.*[14] showed that the protective effect of ischemic preconditioning in patients undergoing major hepatectomy is also conferred through the preservation of the tissue adenosine triphosphate (ATP) content. For a more profound insight into the mechanisms of ischemia/reperfusion injury and protective strategies, please refer to the recently published review articles.[11,51]

The encouraging experimental findings stimulated translational research, and several randomized controlled trials investigating the protective effect of ischemic preconditioning were performed.[14,52–55] Although one clinical trial was negative,[52] the majority of studies demonstrated the beneficial effects of ischemic preconditioning for patients with and without cirrhosis undergoing liver resection under inflow occlusion.[14,53–55] In these studies, ischemic preconditioning with continuous inflow occlusion significantly lowered the postoperative markers of liver injury (aspartate aminotransferase [AST], alanine aminotransferase [ALT]) when compared with continuous inflow occlusion alone. One study also showed a better intraoperative hemodynamic stability when ischemic preconditioning was applied.[53] Similar to intermittent clamping,[12] ischemic preconditioning was also shown to be highly protective in the presence of hepatic steatosis; unfortunately, the protective effects of this strategy were lost in elderly patients.[14]

Intermittent portal triad clamping versus ischemic preconditioning

Intermittent clamping and ischemic preconditioning with inflow occlusion have been shown at the highest level of evidence to be superior to inflow occlusion alone.[12,14,53–55] However, the question arises as to whether both strategies are equally effective or whether one strategy is better than the other in certain clinical settings. In a murine model,

both strategies were found to be equally protective against ischemic injury up to 75 min of warm hepatic ischemia, with improved animal survival when compared with continuous inflow occlusion alone[39,56]; on the other hand, intermittent clamping was found to be superior to ischemic preconditioning when the duration of the ischemic insult exceeded 75 min.

A recently published randomized controlled trial comparing both types of protective strategies in noncirrhotic patients undergoing major liver resection showed similar findings.[57] In this trial, both of these strategies were equally effective in protecting against ischemic injury, but ischemic preconditioning with continuous inflow occlusion is associated with a lower blood loss and a shorter resection time. However, ischemic preconditioning appeared to have weaker protection in elderly patients and in livers with marked steatosis when compared with intermittent clamping. Based on the experimental and clinical data, intermittent clamping should be selected in elderly patients and in patients who require long clamping periods (>60 min) or with marked steatosis, while ischemic preconditioning is preferable in younger patients. Future studies should be conducted to compare the efficacy of these protective strategies in cirrhotic patients.

Continuous inflow occlusion under in situ hypothermia

Another strategy to enhance the hepatic tolerability to inflow occlusion and ischemia is the use of hypothermia.[58] Similar to ischemic preconditioning, the advantages of continuous clamping under *in situ* hypothermia are prolongation of safe ischemia times and prevention of bleeding, since this method does not require cyclic unclamping and reperfusion. *In situ* hypothermia during liver transection can be achieved by hypothermic perfusion cooling or simple topical (surface) cooling.[58] Simple topical cooling can reduce the hepatic core temperature to 20°C–25°C. Most experience with these techniques is reported from Asia on patients with HCC and cirrhosis.[58–61]

One principle of liver surgery in cirrhotic patients is to keep the inflow occlusion time as short as possible, since chronic diseased livers are more vulnerable to ischemia than livers with normal parenchyma.

The time of normothermic continuous inflow occlusion should not exceed 30 min in cirrhotic patients.[25,26] By simple surface cooling of the entire or the remnant liver, inflow occlusion times can be prolonged safely to 60–90 min in cirrhotic patients (Table 1).[60]

Conclusions

In liver surgery, excessive intraoperative blood loss and the need for blood transfusions are significant predictors of poor short- and long-term outcomes. The negative effects of bleeding can be avoided by the use of vascular control techniques during parenchymal transection. Continuous inflow occlusion (Pringle maneuver), selective inflow occlusion, and total vascular exclusion are the most used techniques of vascular control. The selection of the technique should be based on the tumor location, the complexity of liver resection, the underlying liver disease, and the patient's cardiovascular comorbidities. On the other hand, each of these vascular occlusion techniques, especially the nonselective techniques, is associated with ischemic insult in the liver remnant. In healthy livers, continuous inflow occlusion can be safely applied for up to 60 min, whereas cirrhotic livers do not tolerate continuous clamping well for more than 30 min.

To overcome these time limits of clamping, protective strategies have been developed during the last decade in order to allow safe liver parenchymal transections to be carried out for an extended inflow occlusion time in both healthy and cirrhotic livers. This can be achieved through intermittent portal triad clamping, ischemic preconditioning before continuous inflow occlusion, or *in situ* hypothermia of the liver. The selection of the most appropriate technique would depend on many factors such as the maximal expected clamp time, the underlying liver disease, the patient's age, and the surgeon's experience and preference.

Acknowledgment

We gratefully acknowledge the contribution of Stefan Schwyter for drawing the figures for this chapter.

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24

Techniques of Liver Transection

Eric T. Castaldo and C. Wright Pinson

Introduction

Numerous techniques exist for the division of hepatic parenchyma following proper exposure, mobilization, and hilar dissection. The finger fracture (blunt Kelly clamp or crush-clamp) technique, cavitational ultrasonic surgical aspirator (CUSA) dissection, staplers, water jet dissectors, the TissueLink dissecting sealer, radiofrequency energy devices, the LigaSure device, and the harmonic scalpel can all be used individually or in combination. All of these techniques share the same objectives: to quickly divide the hepatic parenchyma, minimize blood loss, and seal bile ducts in order to prevent postoperative biliary leakage. The specific techniques employed during parenchymal transection depend upon surgeon preference, experience, and available institutional resources.

Kelly Clamp Technique

The oldest, and perhaps simplest, of all parenchymal resection techniques is the Kelly clamp technique, also known as the finger fracture technique, crush-clamp technique, or digitoclasia. It begins with the scoring of Glisson's capsule with electrocautery along the planned plane of transection. The operator then uses a blunt instrument, such as a Kelly clamp or scissors, to work through the hepatic parenchyma. Electrocautery is used to control minor blood vessels. When larger blood vessels and bile ducts are encountered, they are individually isolated and controlled with either surgical clips, ligation, or suture ligation, and then divided; this is repeated until the parenchyma is fully divided along the resection plane. This technique can be seen in Fig. 1. This technique

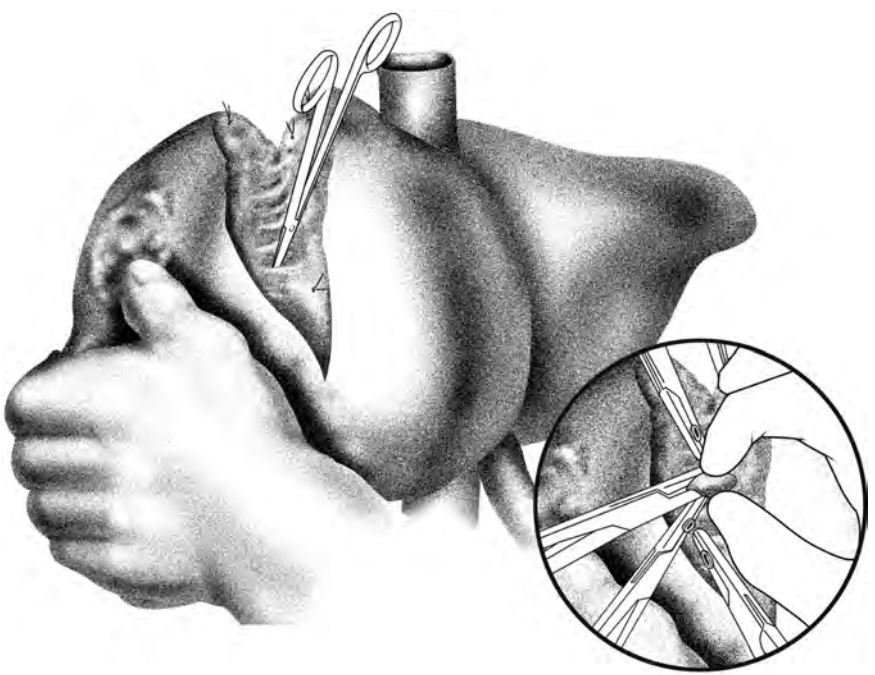

Fig. 1. Using the Kelly clamp technique, the jaws of the clamp are first used to crush the hepatic parenchyma; then, vessels are exposed and individually clamped and suture-ligated (inset).

has the advantages of being quick and of not requiring sophisticated, expensive instruments to carry out the transection, thus making it more cost-effective than other techniques.[1]

One potential disadvantage of this technique is the loss of operative precision (however, one randomized controlled trial noted that the crush-clamp technique resulted in increased precision and improved quality of hepatectomy[2]). Furthermore, this technique may be associated with increased blood loss compared to other techniques, although this is not completely established. Additionally, this technique typically requires portal inflow occlusion (Pringle maneuver). Finally, this technique is not easily used by laparoscopy.

Ultrasonic Dissection

The cavitational ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, CO) contains a hollow titanium tip which vibrates along its axis such that when the tip is brought into contact with tissue, mechanical energy is transferred, creating high- and low-pressure areas. When the pressure is below the vapor pressure of tissue fluid, vacuoles form within the cells that expand and collapse, generating forces that fragment the cell.[3]

This technique begins with scoring Glisson's capsule along the planned plane of resection. The CUSA is then used for lysing of hepatic parenchyma, while preserving the integrity of larger vascular and biliary structures (Fig. 2). As these structures are individually identified, they are ligated and divided. Smaller vessels are controlled with electrocautery. This continues until parenchymal transection is complete. Portal inflow occlusion can be used selectively with ultrasonic dissection.

Some ultrasonic dissection systems come with bipolar electrocautery or argon beam coagulation and a saline irrigation system as a component. In one retrospective review comparing ultrasonic dissection with bipolar electrocautery and argon beam coagulation, Nagano *et al.*[4] determined that ultrasonic dissection with argon beam coagulation was superior as it was associated with less blood loss and was faster.

Advantages of ultrasonic dissection are the potential for increased operative precision and less blood loss. One disadvantage of ultrasonic dissectors is that they are expensive and not available at many centers.

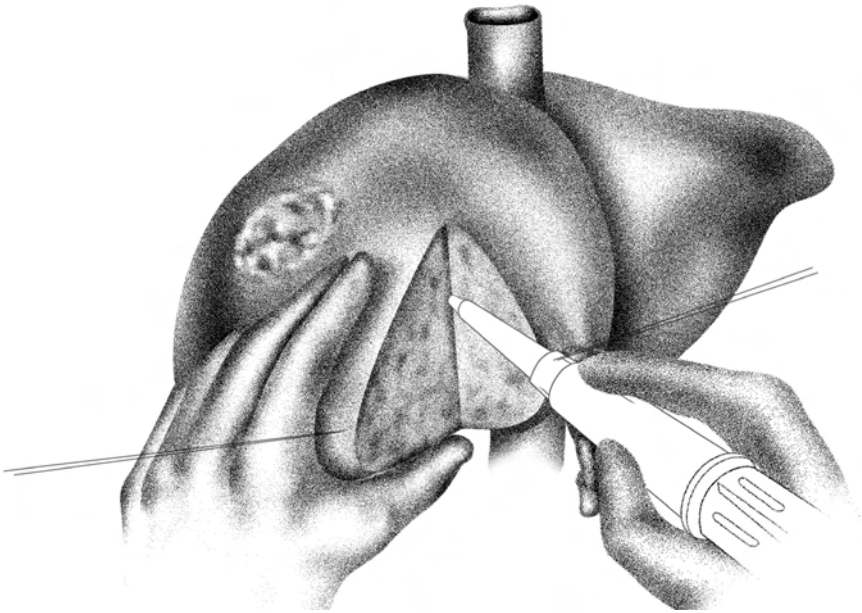

Fig. 2. Hepatic resection using the cavitational ultrasonic surgical aspirator.

Additionally, this technique of transection is often slower than the Kelly clamp technique. Finally, one last potential disadvantage is increased venous air embolism when using ultrasonic dissection. Koo *et al.*[5] demonstrated via intraoperative transesophageal echocardiography that the incidence and severity of venous air embolism during parenchymal transection using CUSA were greater than with the Kelly clamp technique; however, none of these were clinically significant in either group.

Staplers

Surgical staplers can be used in laparoscopic and open liver resections, and work by dividing hepatic parenchyma between two staple lines. Surgical staplers are typically either 30 mm, 45 mm, or 60 mm long. A stapler with a vascular load should be used. Longer staplers minimize the number of staple loads per procedure. Staplers can be fixed or have

a reticulating head, which can be very useful in laparoscopic resections. Stapling techniques are often used in conjunction with other techniques.

The resection begins with the scoring of Glisson's capsule along the planned plane of resection. The jaws of the stapler can be used in a crush-clamp–like technique similar to the Kelly clamp technique; if preferred, this step can be performed with a Kelly clamp instead. The jaws of the device are opened and closed across the parenchyma for crushing (Fig. 3). Then, the jaws are reopened and closed across the remaining biliary and vascular structures, and the stapler is deployed. This is repeated until the resection is complete.

Surgical staplers are most advantageous when gross dissection is needed away from important vascular and/or biliary structures, as is the case in left lateral sectionectomies or peripheral wedge resections. Another advantage of stapling devices is the speed in which resection can be performed. Staplers can be used not only for parenchymal

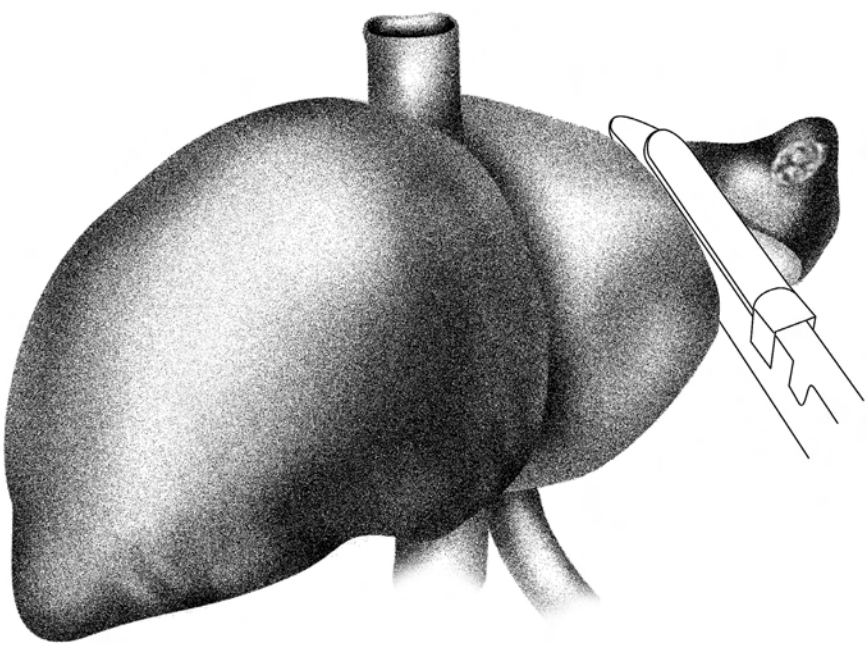

Fig. 3. Left lateral sectionectomy using surgical staplers with a vascular load to divide the hepatic parenchyma.

resection, but also for the division of extrahepatic portal and hepatic venous branches.[6] Staplers can also be used during laparoscopic hepatic resections.

One disadvantage of stapling devices is the cost. Devices with reticulating heads are more expensive than fixed head devices. Typically, several loads of the stapler are necessary, thus further increasing the cost. Despite this increased cost compared to the Kelly clamp method, stapler hepatectomy has been shown to be more cost-effective than the CUSA device in one retrospective study.[7] The same study showed a postoperative bile leak rate of 8% with surgical staplers. A high rate of bile leak was also demonstrated in another study at 13%.[8] Thus, the stapling technique may increase bile leaks.

Hydrojet

High-pressure water jet technology was originally developed for use in the steel and glass industries, where precise cutting and engraving are necessary. The hydrojet device (Hydro-Jet; ERBE, Tubingen, Germany) uses a highly pressurized, extremely thin stream of saline to divide hepatic parenchyma, while preserving the integrity of larger vessels and bile ducts. It uses the action of a laminar liquid jet, rotating like a drill at the surface of the applicator. The hydrojet delivers approximately 550–650 pounds per square inch of pressure for a liver with normal consistency. A cleavage plane is then created, where the liquid forces the tissues apart.

This method begins after scoring Glisson's capsule with electrocautery in the plane of resection. Selective inflow occlusion is at the discretion of the operator. Sutures can be placed on each inferior liver margin to provide tissue distraction. The water jet is used in a back-and-forth motion over 2–3 cm to divide the parenchyma until vessels and bile ducts are encountered (Fig. 4). These isolated structures are then divided with clips, ligatures, and/or bipolar cautery, much the same as in other methods. Intermittent stopping and suction are applied to clear the operative field of water buildup and for the reassessment for hemorrhage.[9] This continues until the resection is complete.

The main advantage of this technique is its precision and ability to preserve blood vessels and bile ducts, facilitating less operative blood loss.

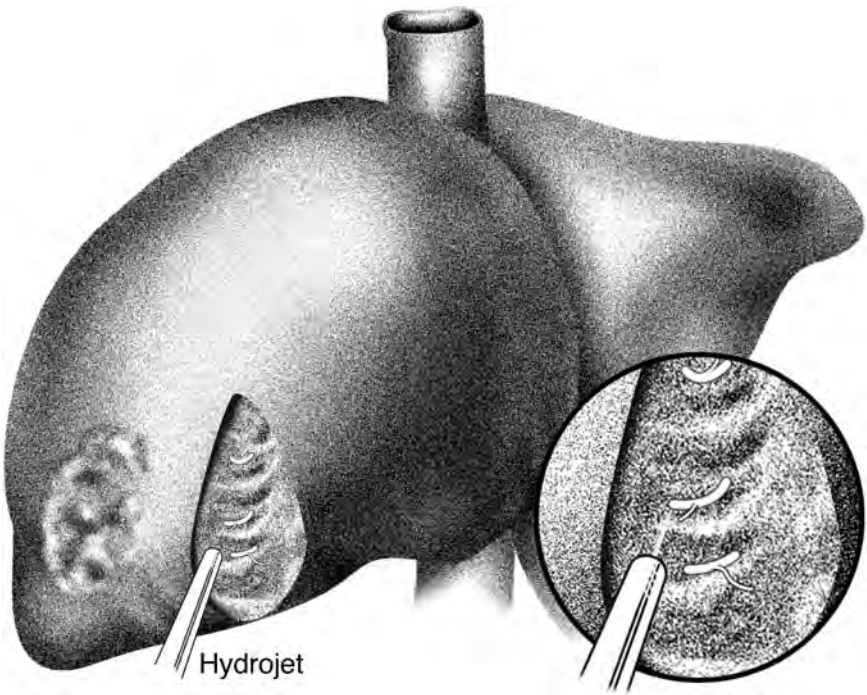

Fig. 4. Hydrojet dissection of hepatic parenchyma, exposing underlying blood vessels (inset), which are then isolated and divided.

The precise nature of the device limits trauma to surrounding tissues, and an integrated suction device allows for clear vision at the operative site. The largest single-center experience to date, evaluating 101 resections with this device, demonstrated only 14% of patients requiring perioperative heterologous blood transfusions.[9] This same group demonstrated water jet application when procuring grafts from live donors without inflow occlusion. This device has also been shown to be effective for performing laparoscopic liver resections.[10]

The main disadvantage of this technique is the cost associated with the materials and pump needed to create the high-pressure stream of saline for the device. This technique may also be slower than other methods of transection.[1] Finally, this device is not available at many centers.

Dissecting Sealer (TissueLink)

The dissecting sealer uses radiofrequency energy from a standard electrosurgical generator delivered to tissue through a conductive fluid, typically saline. The saline becomes the electrode and couples the radiofrequency energy at the tip of the device to the tissue, increasing the contact area and keeping the cut surface cool (below 100°C). This shrinks cellular collagen and seals smaller vessels and bile ducts.[11] This procedure can be used with or without vascular isolation of the liver. After scoring the liver capsule with electrocautery, the dissection begins. Small vessels and biliary structures are simply sealed and divided using the dissecting sealer; when larger vascular and biliary structures are encountered, these structures are either clipped or suture-ligated and divided. This is continued until the resection is complete.

One of the main advantages of this technique is the minimization of blood loss. Additionally, vascular inflow occlusion is not always necessary with this technique. Poon *et al.*[12] reported outcomes observed retrospectively in 10 patients. They reported no postoperative biliary complications with a median blood loss of 100 mL, despite no patients undergoing vascular inflow occlusion; no perioperative blood transfusions were required.

There are several disadvantages of this technique. The expense of these devices is one issue. Additionally, the speed with which hepatic transection can be performed is slower than that of other techniques; the median transection time as reported by Poon *et al.*[12] in the same 10 patients was 95 min (range, 45–180 min).

Radiofrequency Energy

Radiofrequency energy can be used in segmental or wedge resections.[13] Intraoperative ultrasound (IOUS) for tumor resection is necessary to clearly delineate the extent of the tumor, as radiofrequency energy hardens hepatic parenchyma and makes it difficult to feel tumor edges once applied. The steps in this technique can be seen in Fig. 5. First, an inner line is created on the liver capsule using electrocautery to mark the edge of the tumor; then, an outer line is created on the liver capsule in a

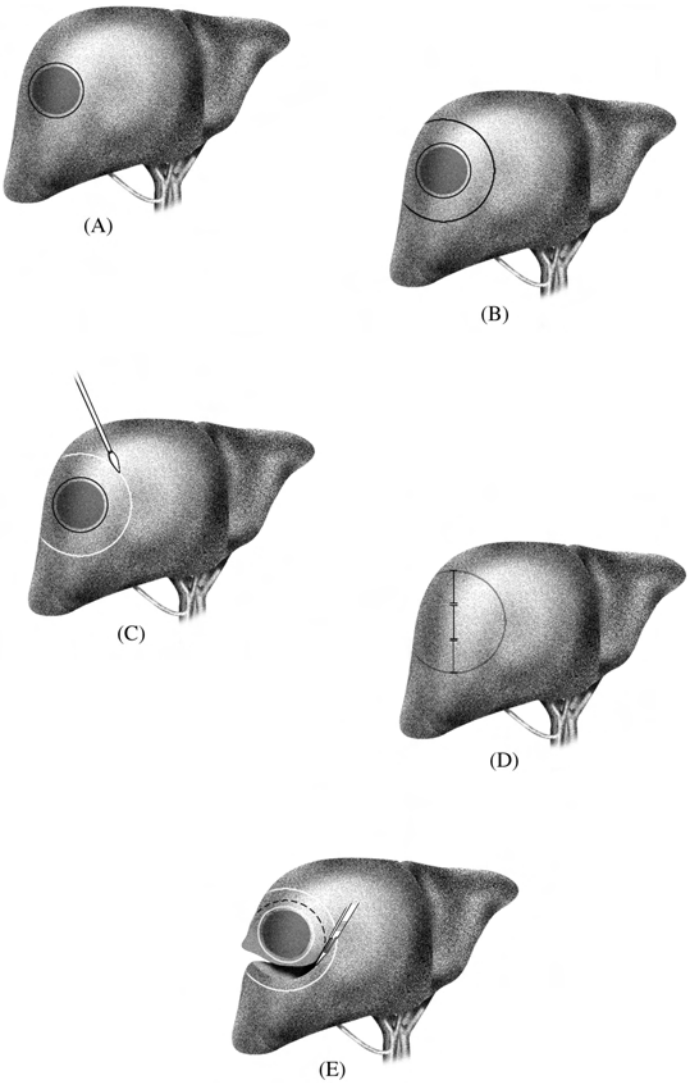

Fig. 5. Transection using radiofrequency energy. (A) First, the periphery of the tumor is marked with electrocautery. (B) Next, a circumferential outer line is created with electrocautery 2 cm from the inner line. (C) Then, the radiofrequency probe is inserted in the hepatic parenchyma along the outer line. (D) Each time the probe is used, it is inserted to the deepest desired point deployed, withdrawn 3 cm, and repeated until a cylinder of tissue is coagulated; this is then repeated circumferentially around the tumor. (E) Finally, the parenchyma is divided with a scalpel between the inner and outer lines.

similar fashion 2 cm outside the inner line. The outer line marks the insertion points of the radiofrequency probe. The radiofrequency probe is then inserted into the hepatic parenchyma along the outer line. Each time the probe is used, it is first inserted at the deepest desired point and the radiofrequency energy is deployed; then, it is withdrawn 3 cm and repeated to coagulate the next cylinder of tissue. This is repeated until a column of coagulated tissue is created through the surface of the liver. These steps are repeated circumferentially around the tumor until a zone of coagulative necrosis is created encompassing the tumor. The parenchyma is then divided with a scalpel midway between the first and second lines.

More recently, a modification of this technique has been developed called "in-line" radiofrequency ablation.[14] In this technique, a series of six 5-cm radiofrequency probes are incorporated into a device in a linear fashion such that a line of transection is created. After the tumor is isolated, parenchymal dissection takes place with the preferred method of the operator.

One advantage is that this technique has been shown to be very effective in minimizing blood loss. The original descriptors of this technique reported an average blood loss in 15 patients of only 30 mL.[13] In another study, the mean blood loss in 38 patients undergoing resection was 50 mL.[14]

One disadvantage of this technique is that the time needed for resection is long. Another disadvantage is the associated extra expense for using sophisticated instrumentation. Finally, the potential for postoperative biliary complications and/or intra-abdominal fluid collections exists. In a prospective analysis of 25 patients undergoing the in-line technique, 3 developed intra-abdominal fluid collections, including 1 who had a bile collection.[15]

LigaSure

The LigaSure device (Valleylab, Boulder, CO) is a bipolar vessel-sealing device connected to a unique power generator with a feedback control response system. A combination of pressure and energy delivered to

tissue through the jaws of the device creates a seal by melting the collagen and elastin in vessel walls, reforming it into a permanent seal. It can be used for blood vessels up to 7 mm in diameter.[16]

The initialization of parenchymal division for the LigaSure begins in much the same manner as the other methods described above. First, the plane of resection is created in Glisson's capsule using electrocautery in the standard manner. The blades of the device are inserted into the hepatic substance and the enclosed tissue is crushed between them several times, leaving blood vessels and bile ducts exposed. The structures are then grasped and power is applied. The jaws are released, and coagulated blood vessels and ducts are then divided with scissors.[17] This continues until the resection is complete. After completion, the remaining surface of the liver is inspected for hemostasis and/or bile leaks.

One potential advantage of this technique is minimization of blood loss in the noncirrhotic liver; however, whether this is a decided advantage remains unclear. In one study of 30 consecutive patients undergoing division with the LigaSure, the median blood loss was 250 mL[18] (however, in this same study, 5 patients required operative blood transfusions, 3 of whom had Child class B cirrhosis; and 4 additional patients required perioperative blood transfusions). This same study also reported no postoperative bile leaks. Another potential advantage is that this technique requires less suture ties and may be faster. One randomized clinical trial of 60 patients demonstrated significantly faster transection speed and significantly less suture ties for patients undergoing resection with LigaSure compared to patients using the Kelly clamp technique[19] (however, this same study failed to show a significant difference in blood loss or perioperative blood transfusions between the groups; additionally, there were no differences in the rates of postoperative bile leaks).

One disadvantage of this technique is its lack of utility in patients with cirrhosis, where parenchymal hemorrhage can be more difficult to control and may require an intraoperative change in the parenchymal division technique.[18] Another disadvantage is the increased cost associated with this technology.

Harmonic Scalpel

The harmonic scalpel (Ethicon, Inc., Somerville, NJ), first introduced in the 1990s, works through a controlled electric current transmitted via a transducer, which converts the current to mechanical ultrasonic vibration. The vibration is then transmitted through the rod of the device to the tip, the active blade, at a frequency of 23.5 kHz. When the pistol grip of the device is activated, the active blade clamps against the opposing pad, compressing the target tissue and generating friction. The friction creates heat and subsequent coagulation of the target tissue.[20]

This technique begins in the standard fashion, with the scoring of Glisson's capsule along the plane of resection using cautery. The harmonic scalpel is then carefully inserted into the hepatic parenchyma, and the tissue is coagulated and divided. Larger blood vessels or bile ducts are controlled with metallic clips or suture ligation. This continues along the plane of resection until completion. The remaining hepatic parenchyma is then inspected for hemorrhage or bile leaks.

One theoretical advantage of this technique is the minimization of blood loss. However, in a retrospective cohort comparing the harmonic scalpel and the Kelly clamp technique, no differences in blood loss or blood transfusion requirement were identified.[21] In another cohort study, the harmonic scalpel was noted to have a median blood loss of 820 mL and 28% of patients required perioperative blood transfusions.[22] Another advantage is its applicability in laparoscopic liver resections. In a prospective study of patients with tumors <5 cm located in the left or peripheral right segments with limited hepatic involvement, Cherqui *et al.*[23] reported that only 7% of patients required conversion to laparotomy. This same study also demonstrated improved blood loss, with a mean of 300 mL.

A disadvantage of the harmonic scalpel is the potential for an increased rate of biliary fistulas. This was demonstrated in a retrospective review, where a 24% bile leak rate was noted in patients undergoing harmonic scalpel parenchymal division, significantly higher than the 7% leak rate demonstrated in patients undergoing Kelly clamp division.[21] This study considered the potential for a learning curve effect; however, this could not be demonstrated as the leak rate per year never

changed. However, in a prospective study of 66 liver resections in 41 patients undergoing laparoscopic or open liver resection, no bile leaks were found.[22] Again, with sophisticated equipment comes increased cost and decreased availability.

Minimizing Blood Loss

Intraoperative blood loss is one of the most significant factors influencing morbidity and mortality in hepatic resection. In addition to the parenchymal division techniques, other techniques aimed at changing and/or controlling blood flow to the liver during dissection exist.

Application of clips

The proper application of clips is necessary to ensure adequate hemostasis during liver resection. Proper clip placement should follow six steps: (1) placing the clip applier across the middle of the exposed vessel or bile duct so that the tips of the clip are free; (2) pushing the clip applier against the liver surface on the patient side; (3) angling the clip applier to obtain maximum contact of the clip and the hepatic parenchyma; (4) closing the clip applier; (5) releasing the clip applier; and (6) disengaging the clip applier and removing it without tearing the clipped structure.[24]

Wedge resection with parenchymal compression

Peripheral tumors can be resected with minimal blood loss by means of parenchymal compression with clamps. After full mobilization of the liver and capsular scoring of the resection plane with electrocautery, a large vascular clamp or a Storm–Longmire clamp (Fig. 6) can be placed in a more central position than the planned plane of resection. If one of these clamps fits, then the patient is placed in the Trendelenburg position and a temporary Pringle maneuver is applied for 2 mins. The compression clamp is then placed, and resection proceeds according to one of the methods described above.

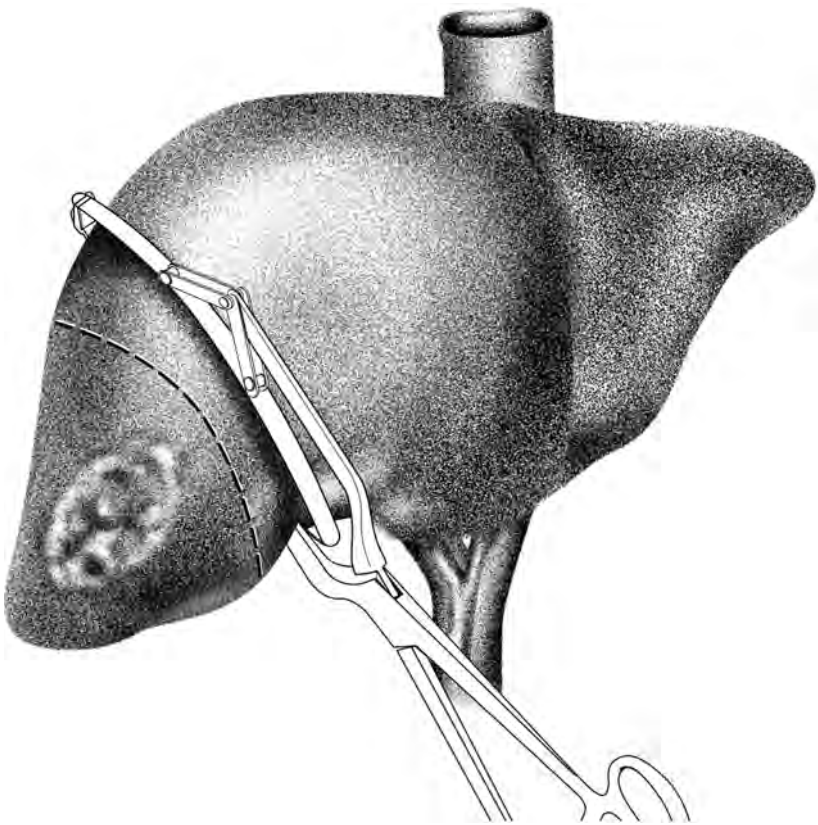

Fig. 6. Parenchymal compression using a Longmire clamp prior to a peripheral wedge resection.

Vascular isolation

First described in 1908,[25] the Pringle maneuver is considered the gold standard for minimizing blood loss during hepatic resection and has been described elsewhere.[26–28]

Control of the inferior vena cava (IVC) may be necessary for large tumors adhering to the vena cava or its confluence with major hepatic veins. The infrahepatic IVC is dissected free from its surrounding tissues, and umbilical tape is placed circumferentially around it between the

inferior surface of the liver and the renal veins. Care should be taken to avoid tearing the right adrenal vein.

Controlling the suprahepatic IVC is equally important and necessary. This can be achieved from the intra-abdominal position by completely dissecting the suprahepatic vena cava from the surrounding structures inferior to the diaphragm; a vascular clamp or umbilical tape can be used to isolate this portion of the vena cava. If this is not possible, control of the suprahepatic IVC can alternately be performed intrapericardially by incising the diaphragm and the pericardium and circumferentially dissecting the IVC free at the level of its entrance into the right atrium. If this cannot be done from an intra-abdominal position, it may be necessary to control the IVC in the same manner after median sternotomy.

Total vascular isolation

Vena cava clamping in addition to the Pringle maneuver can create a state of total vascular isolation in the liver during difficult hepatic resections, allowing for reduced blood loss during parenchymal transection (Fig. 7). This can reduce back-bleeding through the vena cava and the hepatic veins. However, total vascular isolation leads to venous stasis in the intestines, kidneys, and lower body, and can result in a state of hemodynamic instability. For these reasons, total vascular isolation should be reserved for patients with tumors near the vena cava or hepatocaval junction.[29]

One prospective randomized study comparing patients undergoing major hepatic resection under either the Pringle maneuver or total vascular isolation demonstrated that intraoperative blood loss and postsurgical hepatic enzyme levels were similar between the two groups.[30] However, 14% of patients randomized to the total vascular isolation arm developed hemodynamic instability and required removal of vena cava clamps. Additionally, total vascular isolation was associated with significantly increased clamp time and increased total operative time. Venovenous bypass, commonly used in liver transplantation, can be used for patients who experience the hemodynamic instability.

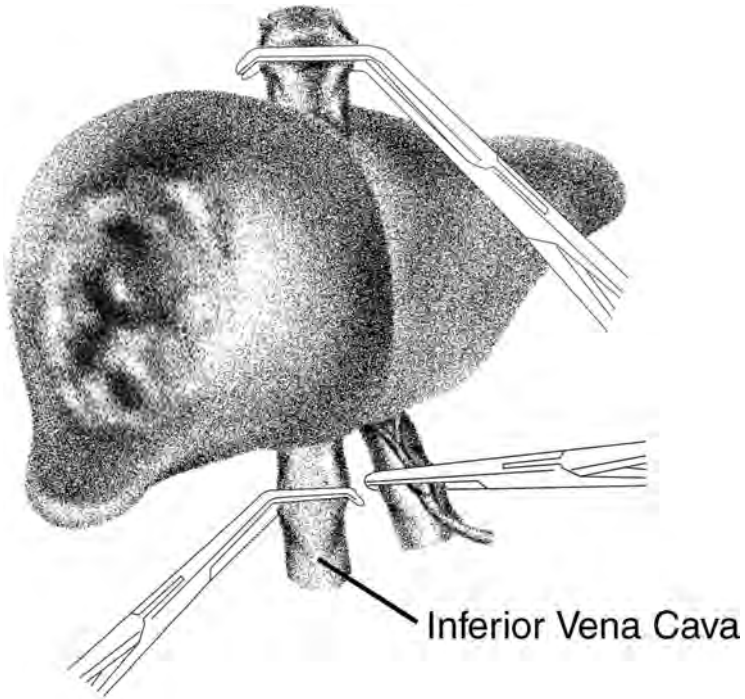

Fig. 7. Total vascular isolation of the liver prior to hepatic transection.

Low central venous pressure

Another well-accepted technique aimed at decreasing blood loss during hepatic transection is lowering central venous pressure (CVP). This can be achieved through various pharmacologic means (limiting intravenous infusions) or through patient positioning in the Trendelenburg position. Low CVP decreases hepatic congestion and limits back-bleeding from the transected hepatic substance.

A prospective evaluation of 20 patients undergoing major hepatic resection performed by Johnson *et al.*[31] noted a strong correlation between blood loss and CVP: when the caval pressure was $\leq$5 mm Hg, the mean blood loss averaged 363 mL and was always $<$500 mL; between 6 mm Hg and 12 mm Hg, the mean blood loss averaged 1259 mL; and $\geq$13 mm Hg, the mean blood loss was 2703 mL.

In a similar study, Wang *et al.*[32] randomized 50 patients undergoing hepatic resection for hepatocellular carcinoma (HCC). They noted a dramatic decrease in intraoperative and intrahepatectomy blood loss for patients whose CVP was maintained at 2–4 mm Hg. Although no difference existed in the proportion of patients requiring blood transfusions, there was a significant difference in the volume of blood transfusions administered to the patients with low CVP.

Comparisons of Liver Transection Techniques

There have been only a handful of prospective randomized comparisons of hepatic transection methods, and the results have been mixed. Lesurtel *et al.*[33] demonstrated in a prospective randomized trial that the crush-clamp technique resulted in a higher transection velocity, lower blood loss, and lower postoperative blood transfusions compared to the ultrasonic dissector, hydrojet, or dissecting sealer. However, the crush-clamp technique in this study was always performed under portal inflow occlusion, whereas the other techniques were not, thus potentially biasing the blood loss and transfusion outcome measures. Additionally, there were no differences in postoperative morbidity between the groups. Finally, a cost analysis was performed, revealing the Kelly clamp technique to be the most cost-effective and the CUSA technique to be the most expensive.

Takayama *et al.*[34] compared crush-clamp and ultrasonic dissection in a randomized prospective trial, and found no difference in blood loss or transection speed between the two methods. In another prospective randomized trial comparing ultrasonic dissection and the crush-clamp technique, no difference in blood loss, transfusion requirements, parenchymal division time, or total operative time was shown.[5] Another prospective trial evaluated hydrojet and CUSA, demonstrating that hepatic transection with the hydrojet was associated with significantly less length of parenchymal resection time, inflow inclusion time, and intraoperative blood transfusions.[35] In a prospective trial of eight patients where half of the liver resection was with the in-line radiofrequency technique and half with the ultrasonic aspirator, Haghighi *et al.*[36] noted significantly less blood loss with the radiofrequency technique; they

also noted no difference in the time required to perform parenchymal transection between the two techniques.

In a retrospective review, Fan *et al.*[37] determined that ultrasonic dissection was superior to the crush-clamp technique, as it resulted in less blood loss, less blood transfusion requirement, lower hospital morbidity and mortality, and improved tumor-free margin. Another retrospective review looked at the incidence of bile leakage following hepatic parenchymal transection with CUSA, Kelly clamp, or microwave tissue coagulation (not previously described)[38]; here, the authors determined that the Kelly clamp technique was associated with the least amount of postoperative bile leaks and shorter hospital stays. In another retrospective review, blood loss was found to be significantly less in patients who had a resection using a combination of CUSA and harmonic scalpel (not previously described) when compared to the Kelly clamp technique[39]; this same trial showed that the Kelly clamp method had more bile leaks and intra-abdominal fluid collections and was significantly faster.

It is difficult to ascertain which method of hepatic transection is the best. The only evident truth is that, on a cost basis, the Kelly clamp technique is the least expensive due to the lack of requiring anything more than basic surgical instrumentation. In terms of postoperative biliary complications, it appears that the stapler and the harmonic scalpel may carry the highest risk. However, when trying to determine which method of transection is quickest and has the least amount of blood loss, the picture grays. With many different studies reaching various and sometimes differing conclusions, it is likely that the Kelly clamp under inflow occlusion technique offers similar or improved blood loss and parenchymal transection speed as the other more technologically advanced methods, and therefore should be familiar to all surgeons performing hepatectomies.

In conclusion, there are many effective operative techniques available for surgeons to perform hepatic transection. Each has specific advantages and disadvantages. Furthermore, surgeons should be familiar with different methods of minimizing blood loss, such as hepatic inflow occlusion, total vascular isolation, low CVP dissection, and the application of clamps capable of parenchymal compression. The choice of

technique is operator-dependent, dependent on patient circumstance, and subject to the resources available at individual institutions. One needs to develop capability with one or more of these techniques.

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Radiofrequency-Assisted Liver Resection

Long R. Jiao and Nagy A. Habib

Introduction

Surgical advances generally follow either a scientific discovery or a technological breakthrough, for example magnetic resonance imaging or joint replacement. Over the past few years, the advent of new energy sources such as radiofrequency has had an increasing impact on surgical practice, notably in the field of liver tumors.

Radiofrequency ablation (RFA) is now widely accepted as an effective modality for treating liver tumors that are unsuitable for resection.[1] It is based on the conversion of radiofrequency waves into heat, leading to coagulative necrosis[2]; and it can be delivered either percutaneously or at open operation. Although RFA is effective in the management of liver tumors, it is merely one of many palliative modalities available to clinicians. Foci of intact tumor cells are present on histological evaluation of previously ablated liver tumors, indicating incomplete destruction of the cancer by this technique.[3] Surgical resection, therefore, remains the definitive method of cure for liver tumors.

Over the past few years, a new technique for liver resection assisted with radiofrequency has been developed at the authors' unit, expanding the role of radiofrequency in liver surgery from mere tumor ablation to routine hepatic resection.[4] By using the radiofrequency probe to develop a plane of coagulative necrosis along the intended line of parenchymal transection, we have been able to perform both major and minor liver resections with this technique in order to avoid intraoperative hemorrhage and the previous need for postoperative admission to an intensive care unit.[5] It offers a new method of bloodless resection without the need for sutures, ties, staples, tissue glue, or hypotensive anesthesia; the liver tissue is simply divided with a scalpel through the zone of necrosis. There have been very few cases of postoperative bile leakage or liver failure. However, the major disadvantage of this technique is that it is slow for most often-impatient surgeons. To solve this problem, Professor N. A. Habib has developed a new resection device, the Habib 4X (Emcision Ltd, UK), which can considerably reduce the length of time taken to achieve coagulative necrosis and hence the operative time.

Principles

Radiofrequency thermal ablation works by converting radiofrequency waves into heat. The alternating current passing down from an uninsulated electrode tip into the surrounding tissues generates changes in the direction of ions, and creates ionic agitation and frictional heating (Fig. 1). The tissue heating then drives extracellular and intracellular water out of the tissue, resulting in the final destruction of the tissue as a result of coagulative necrosis.[2] RFA has long been used in neurosurgery for either tumor ablation or treatment of functional neurological conditions, and in cardiology for ablation of abnormal pathways and restoration of normal rhythm.[6–8] With advances in technology, new radiofrequency generators have been made; this has had a wide impact on minimum invasive surgery. There has been increasing interest in the use of RFA both in urological and hepatobiliaripancreatic surgeries.[9–11]

The diameter of the lesions generated by monopolar radiofrequency is largely dependent on the tip temperature and the power created in the tissue. By maintaining the tip temperature of the probe at 25°C–35°C with perfusion of chilled saline, Goldberg *et al.*[12] have

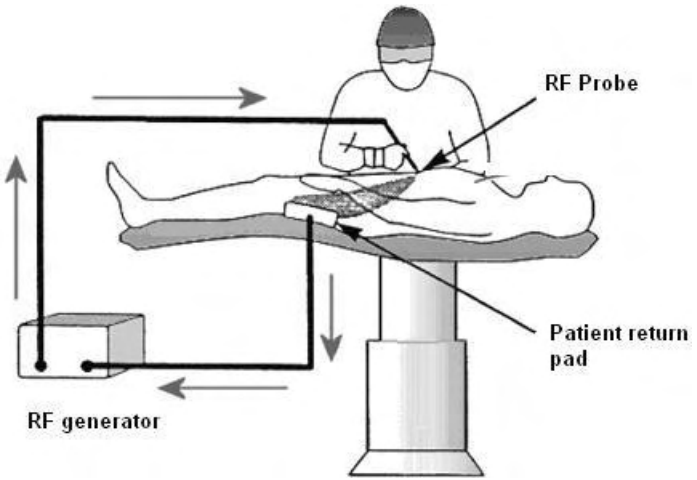
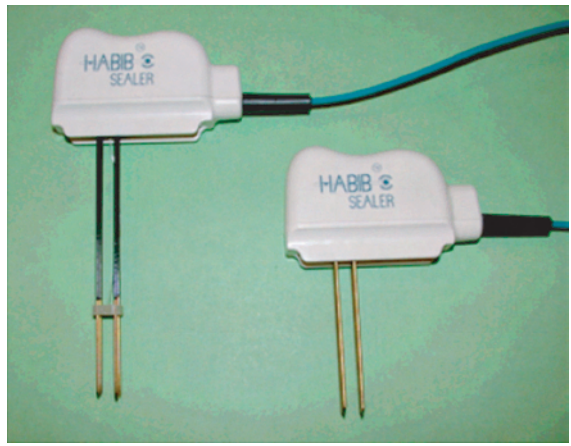


Fig. 1. Schematic illustration of a typical radiofrequency (RF) circuit.

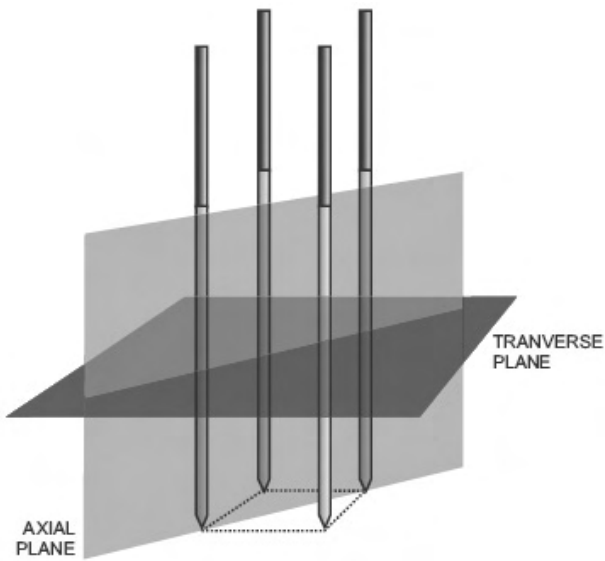
obtained maximal tissue destruction in porcine liver *in vivo.* Since this technique creates a 2.4-cm-diameter zone of necrosis without inducing tissue charring, it should be able to treat large tumors with fewer insertions of the probe. For radiofrequency-assisted liver resection, we routinely use a single cooled-tip monopolar probe in order to generate the maximum diameter of coagulated tissue for hemostasis and safe coagulated resection margins.

Design of the Habib 4X

The new-generation Habib® 4X is a bipolar device that eliminates complications from electrical conduction. Since there is no possibility of a conduction injury and the current need not be lessened, there is a marked decrease in operative time. Two versions are currently available: the hand-held sealer available for open surgery, and a smaller laparoscopic device. Both the open and laparoscopic sealers consist of an array of four electrodes in a square arrangement (Fig. 2A). There is a long version with corresponding long electrodes (120 mm) to access deeper tissue planes, and a short version with short electrodes (60 mm) for more superficial tissue coagulation. The electrodes are made of stainless steel



(A)



(B)

Fig. 2. The Habib 4X. (A) Long and short probes. (B) Four needles are arranged in a 2 × 2 array with the two pairs of needles.

covered with a nonstick coating (Tomlinson Tube & Instrument Ltd, Warwickshire, UK) with a polished titanium nitride nonstick coating (Tecvac Ltd, Cambridgeshire, UK; Integrated Surgical Sciences Corp., Sedalia, CO) to facilitate insertion and removal from the hepatic tissue. The long electrodes are sufficient to reach distal regions of the parenchyma; however, the active portion is restricted to the distal 40 mm of the probe in order to allow rapid heating. The entire length is not heated, as the energy required would be too great and would compromise the time to coagulate the tissue. The proximal portion of the probe is insulated with a polytetrafluoro ethylene (PTFE) coating. The short probe device is designed to coagulate superficial vessels and ducts, and for more superficial tumorectomies.

In both devices, the four needles are arranged in a 2 × 2 array with the two pairs of needles connected together, and each pair is connected to a single terminal of a bipolar RF generator (Generator 1500X; RITA Medical Systems, Inc., Fremont, CA) (Fig. 2B). The probe is introduced in a serial fashion to produce a zone of coagulated areas (Fig. 3).

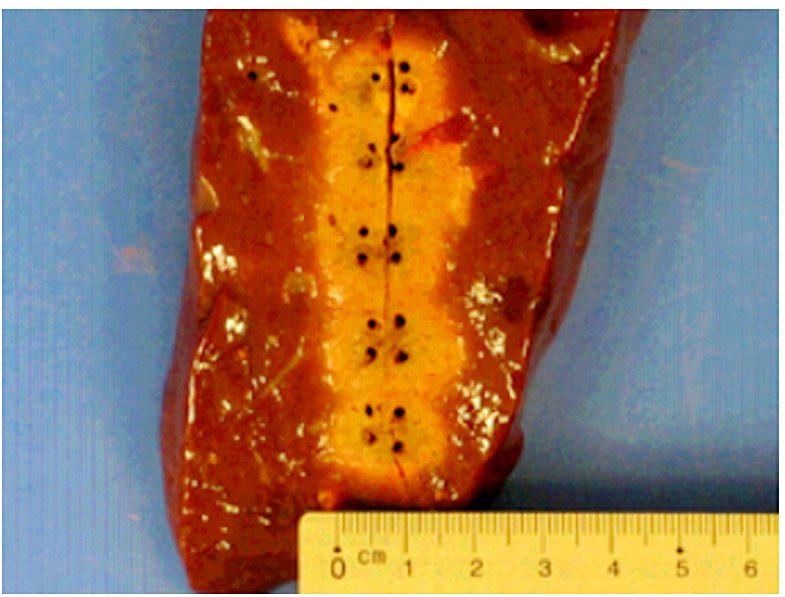


Fig. 3. A zone of ablated areas with the Habib 4X.

Operations

Preoperative assessment

A careful preoperative assessment and evaluation of patients with liver tumor is crucial in order to determine the best treatment option for individual patients and to prevent postoperative morbidity and mortality. A multidisciplinary approach has been increasingly adopted as a routine practice in the West for management of patients with liver cancers, consisting of a team of surgeons, physicians, oncologists, radiologists, and anesthetists.

Preoperative assessment includes the evaluation of both the patient's general fitness for surgery and the liver tumor. The latter is composed of a detailed examination of the site, size, and location of the tumor as well as any possible extrahepatic involvement for those with malignant cancer. Modern imaging techniques — including ultrasound with or without contrast, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans — should be accurate enough to provide adequate information required preoperatively. Further assessment with intraoperative ultrasound (IOUS) adds invaluable information on the relationship between liver anatomy and tumor, and on the detection of some lesions occasionally missed in preoperative images.

Operation

The fundamental success of liver surgery in minimizing postoperative morbidity and mortality lies in a meticulous preoperative assessment and the optimization of any underlying medical condition.

Position of patient

Following general anesthesia, the patient is positioned supine with both arms carefully placed to the side with folded towels. This should be done with great caution to ensure that the arms are not tucked in too tightly so as to prevent neuropraxia. The abdomen is prepared with antiseptic

solution just beneath the nipple line anteriorly and to the posterior axillary line on the right side.

Incision

Depending on the site and size of the liver tumor, the surgeon should decide on the best incision for the patient. The key is to have an adequate exposure and mobilization of the liver. We routinely start with a small upper midline incision to perform laparotomy in order to ensure that there is no extrahepatic disease. Having done so, the incision is extended to the right subcostal margin to form a J-shaped incision, which suffices for any major liver resection.

Examination and mobilization of the liver

Having completed a formal laparotomy to exclude any extrahepatic disease in patients with hepatic cancer, examination of the liver is carried out first by inspection, then by palpation, and finally by IOUS. Mobilization of the liver is dependent upon the type of liver resection and the location of the liver tumor. For major liver resection involving more than three segments, the liver is fully mobilized by dividing the falciform ligament, left and right triangular ligaments, and anterior leaf of coronary ligament. For resection of lesion in the left liver, mobilization of the left liver is usually sufficient by freeing the left triangular ligament from the diaphragm. The same approach is applied to free the right triangular and coronary ligaments from the diaphragm for resection of less than two segments such as bisegmentectomy of segments 5 and 6, anterior sectionectomy, or posterior sectionectomy.

Right hepatectomy

Dissection

After mobilization of the entire liver, cholecystectomy is performed first. Then, dissection is carried out to identify the right hepatic artery

between the common bile duct and the portal vein at the hilus by gentle retraction of the cystic duct stump to the left side in order to assist the opening of the plane between these two structures. Having done so, the right hepatic artery is ligated.

Conventionally, the right branch of the portal vein is ligated and divided; however, with the radiofrequency-assisted technique, we have modified this technique without the need for division. The portal vein dissection is performed upwards to the bifurcation. The right branch of the portal vein is freed and encircled by a vessel loop. The dissection then continues further centrally to the right portal vein and its branching. A tie (3-0 Vicryl) is passed around the right portal vein (RPV) (Fig. 4); following this, the RPV is ligated. To prevent slipping, a transfixing suture can be applied when necessary (Fig. 5). The RPV is thus not divided and no further dissection is required. For radiofrequency-assisted liver resection, dissection of the hepatic vein is not usually necessary.

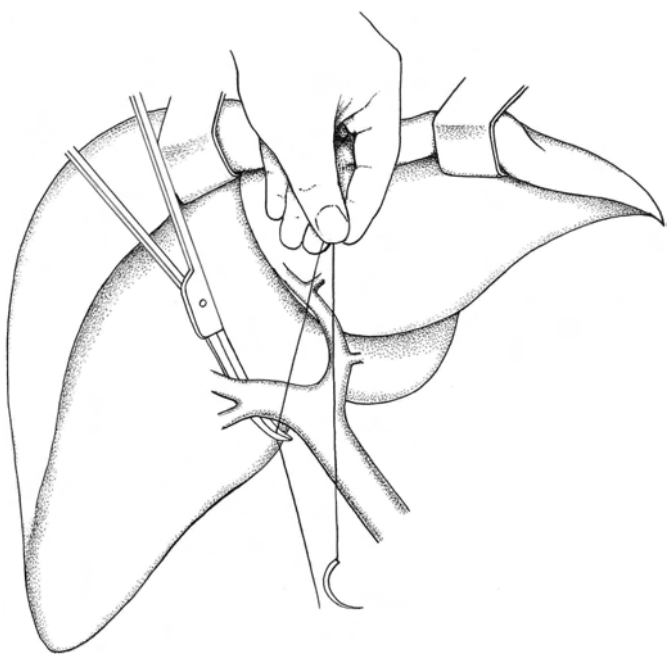


Fig. 4. Slinging of the right portal vein.

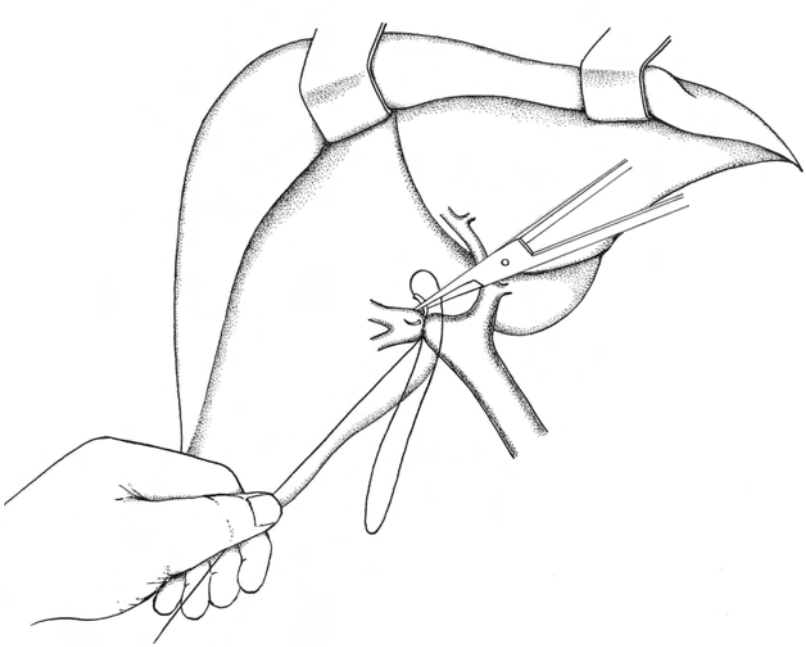


Fig. 5. Ligation and transfixation of the right portal vein without division.

Transection of liver parenchyma

A detailed description of radiofrequency-assisted liver resection with either a single probe or the Habib 4X is as follows:

1. Cooled-tip single-probe device (Fig. 6)

Step 1. A first or an inner line is made on the liver capsule with an argon diathermy to mark the demarcation between the right and left livers. This step is important to do at this time because after the use of RF, the parenchyma is hardened and it becomes difficult to visualize this line.

Step 2. A second or outer line, again using argon diathermy, is made on the liver capsule 2 cm outside (away from) the inner line to mark the site where the probe is positioned to achieve coagulative necrosis.

Step 3. Coagulative necrosis is made along a line that follows the second or outer line using the cooled-tip RF probe and a 500-kHz RF generator

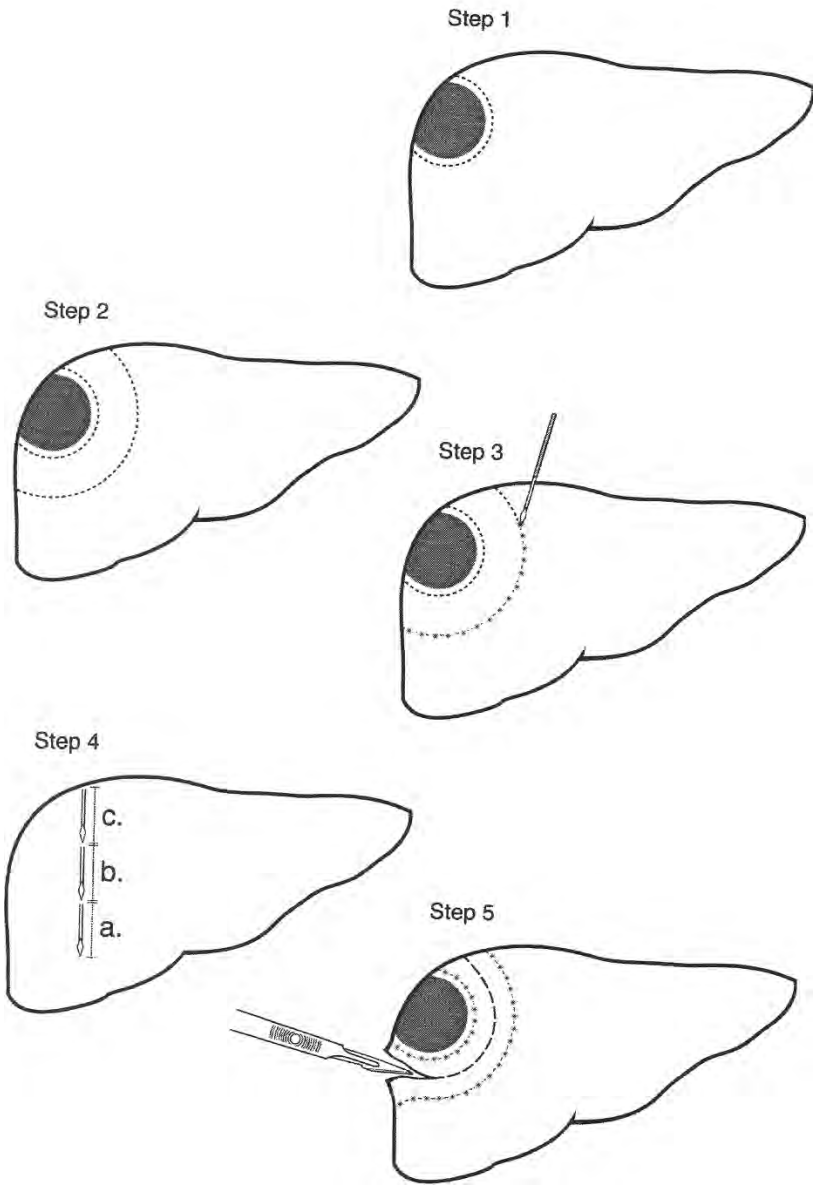


Fig. 6. Five steps to achieve liver resection using the radiofrequency energy probe.

(Model RFG-3D; Radionics Europe, N. V., Wettdren, Belgium), which produces 100 W of power and allows measurements of the generator output, tissue impedance, and electrode tip temperature. The probe contains a 3-cm exposed electrode, a thermocouple on the tip to monitor temperature and impedance, and two coaxial cannulae through which chilled saline is circulated during RF energy application in order to prevent tissue boiling and cavitation immediately adjacent to the needle.

Step 4. The number of probe applications that are required to obtain a zone of necrosis is related to the depth of the liver parenchyma that is to be resected. For example, to obtain a zone of necrosis in a core of tissue 1 cm in radius by 3 cm in depth, each application of RF energy will need to be applied for about 60 seconds. Thus, for a core of tissue 12 cm in depth, four applications will be needed in vertical succession.

Application of the RF energy should begin with the area deepest and farthest from the upper surface of the liver, checking that each probe is correctly positioned with an ultrasound. The preferred technique is to have the tip of the probe piercing the liver capsule of the inferior surface of the liver, and to feel the tip with the middle finger of the left hand while holding the probe with the right hand. The areas of coagulative necrosis can be monitored using IOUS to show the change in tissue impedance and the formation of microbubbles in the tissue. Once the deepest 3 cm of tissue is coagulated, the probe is withdrawn by 3 cm to coagulate the next cylinder of tissue and so on until the upper surface of the liver is reached. Each application requires about 60 seconds of RF energy. For example, a cylinder of tissue 12 cm in depth requires four applications, each application coagulating 3 cm of tissue and taking about 4 minutes to produce.

Once an area is coagulated, the probe is withdrawn completely and placed 1–2 cm away from the previous application. This allows complete coagulation of a band of parenchyma extending along the second line. The point of entry of each probe should be kept close to each other (i.e. 1 cm) to achieve some overlap of the areas to be coagulated so as to ensure that the coagulation is complete. Just prior to each probe removal, the saline infusion is stopped in order to increase the temperature close to the electrode. This results in coagulation of the needle tract during

withdrawal, and reduces the possibility of bleeding from the probe tract and liver capsule. Pringle's maneuver is not needed.

Step 5. The liver parenchyma is divided using a scalpel. The plane of division should be situated midway between the first and second lines so as to leave a 1 cm resection margin away from the tumor and to leave *in situ* 1 cm of burned coagulated surface. Coagulative necrosis from inside the resection margin can be applied in order to stop any potential point of bleeding and to increase the safety margin, particularly if the resection is to remove cancerous tissue. A drain is placed at the site of resection. The abdomen is subsequently closed in layers.

2. Habib 4X device

Steps 1 and 2 are identical to the single radiofrequency probe device as above. Then, the Habib 4X is applied to create a plane of coagulative necrosis along the intended line of parenchymal transection. The final division of liver parenchyma is done again, as above, with a surgical scalpel (Fig. 7).

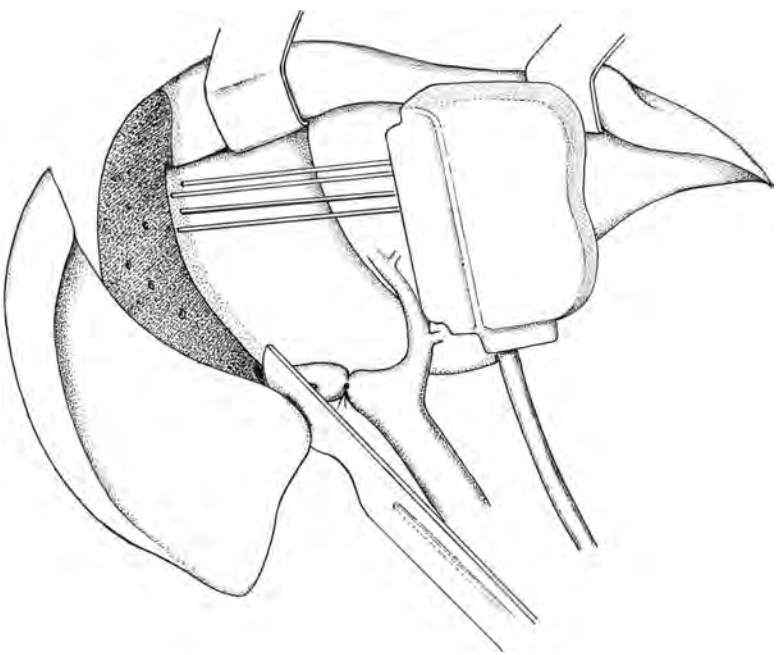


Fig. 7. Transection of liver parenchyma following ablation with the Habib 4X.

Left hepatectomy

Dissection

This is similar to that for right hepatectomy. The left hepatic artery and portal vein are dissected and ligated without division, as described above.

Transection of liver parenchyma

This is the same as for a right hepatectomy.

Left lateral sectionectomy

Dissection

This is normally performed without any difficulty by freeing the left triangular ligament. The lesser omentum is then divided to completely free the left liver, taking care to avoid inadvertent damage to the aberrant left hepatic artery, which often runs in the lesser omentum. For radiofrequency-assisted liver resection, conventional dissection along the falciform ligament to identify the arterial and portal branches to segments 2 and 3 is not required.

Transection of liver parenchyma

This is the same as for a right hepatectomy.

Tumorectomy or segmentectomy

For tumorectomy, full mobilization of the liver is not usually required with radiofrequency-assisted liver resection. The steps described above for right hepatectomy are the same, but special attention is paid to step 1 in order to carefully mark the area of resection prior to the application of radiofrequency. This is extremely important because after application of radiofrequency, the parenchyma is hardened and it becomes difficult to feel the tumor edge. Also, IOUS fails to visualize the tumor edges after radiofrequency application due to the increased echogenicity resulting from radiofrequency.

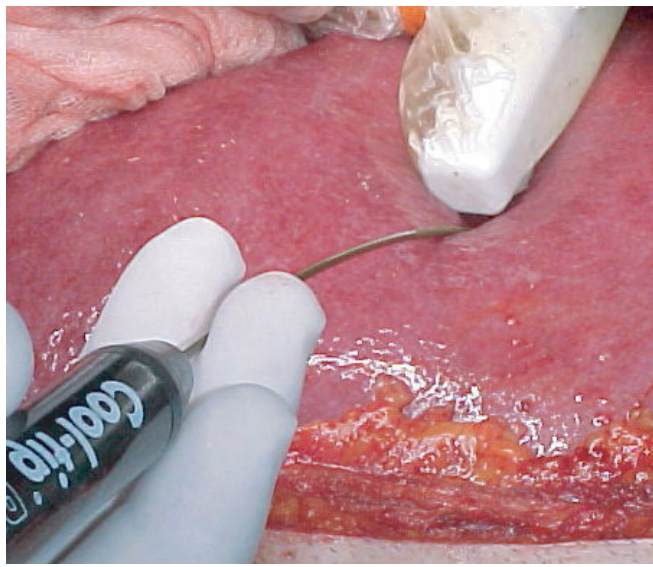
For anatomical segmentectomy, a new technique has been developed with radiofrequency at the authors' unit. The liver is mobilized according to the size and site of the lesion to be excised. IOUS is repeated to identify the segmental or subsegmental arterial and portal branches feeding the area including the tumor (Fig. 8). The coagulative desiccation of these feeding vessels is then induced with application of cooled-tip radiofrequency. First, the probe containing the electrode is placed under IOUS guidance at the level of the vessels; this produces destruction of these vessels by inducing thrombosis and creating a zone of desiccation in a core of tissue. The intrahepatic parenchymal change induced by RF can be monitored by using IOUS, revealing an absence of Doppler signal and a change in the color of this area (Fig. 8B). Following the application of RF to destroy the feeding vessels to that segment, an area of marked discoloration on the surface of the liver becomes obvious (Fig. 9). Finally, liver resection is carried out with a surgical scalpel without any form of hepatic inflow occlusion.

Postoperative Care

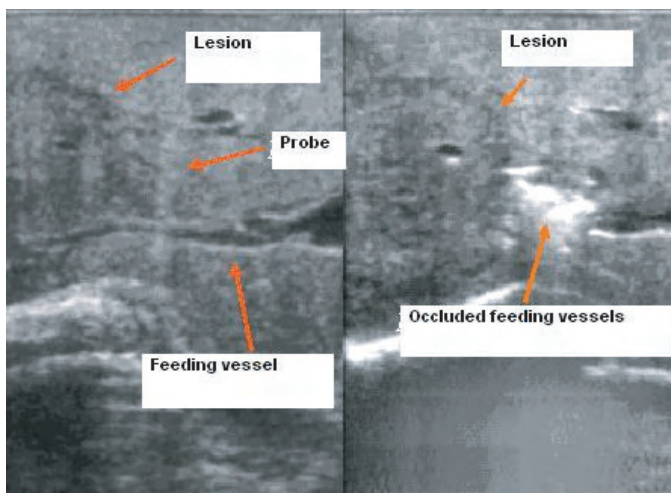
Postoperative care should be directed at the prevention and early intervention of any possible complication. Management of fluid and electrolyte balance can be difficult and challenging, particularly in patients with pre-existing chronic liver disease. Early review by intensivists and renal physicians can be extremely valuable in the prevention of renal failure. Regular chest physiotherapy is also important to avoid respiratory complications commonly occurring with right hepatectomy. We advocate early eating, drinking, and mobilization within 24 hours in our postoperative patients.

Complications

With the cooled-tip single-probe radiofrequency device, intraoperative blood loss should be minimum, with reported figures being less than 200 mL and a transfusion rate of less than 5%.[5] The most common complication is chest-related, such as chest infection and pleural effusion.[5] Biliary leak is uncommon. We routinely place an FG30 Robinson drain



(A)



(B)

Fig. 8. Application of a single RF probe to the liver parenchyma (A) under intraoperative ultrasound guidance (B).

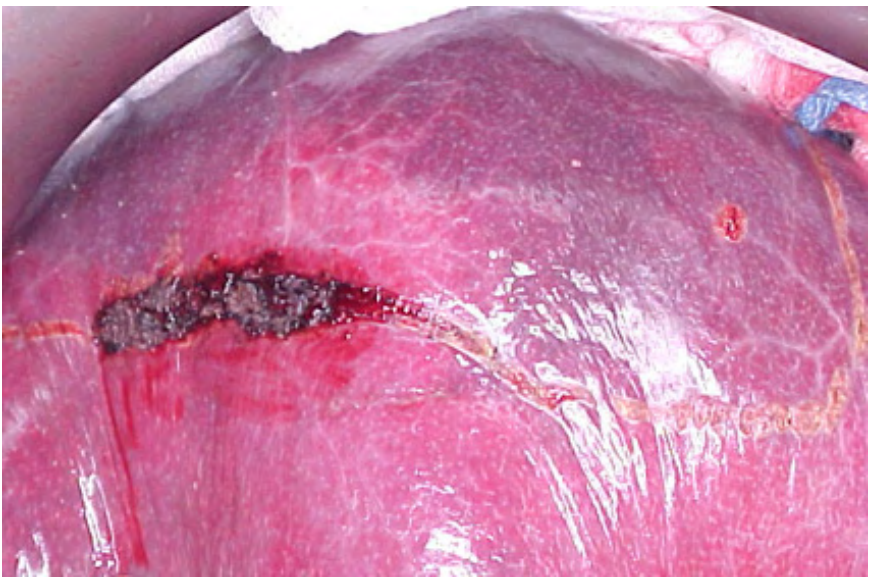


Fig. 9. Demarcation of the segment on the surface of the liver following RFA of the feeding vessels.

along the resection margin to prevent intra-abdominal collection, and we treat it early should this occur.[13] Patients are usually discharged home within 10 days.

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26

Cytoreductive (Tumor-Debulking) Surgery

Eric C. H. Lai and W. Y. Lau

Introduction

Treatment for patients with hepatocellular carcinoma (HCC) is determined by the extent of the tumor, the liver functional reserve, the general condition of the patient, and the available resources.[1–5] Of the therapies aiming at cure, liver resection and liver transplantation remain the best choice, although local ablative therapy in the form of radiofrequency ablation (RFA) is becoming established as a form of curative treatment for small HCCs <3 cm.[1–5] Unfortunately, only 10%–30% of HCCs are amenable to curative surgical resection at the time of diagnosis, as most patients with HCC are still diagnosed at an advanced and unresectable stage. Advanced HCC includes large-sized tumor, multifocal bilobar tumors, tumor with main portal vein tumor thrombus, and extrahepatic spread of the disease. Without specific antitumor treatment, the prognosis is very poor. The median survivals for patients with unresectable early and advanced tumors are 6–9 months and 1–2 months, respectively.[1–5]

For HCCs that are not suitable for curative treatment, nonsurgical and surgical interventions are available for palliative care. Progress has also been made in multimodality therapy, which has the potential to increase the quality and quantity of survival for patients with advanced HCC. These palliative interventions can be divided into systemic therapy such as chemotherapy, immunotherapy, or therapy using human hormonal analogs; regional therapy such as transarterial chemotherapy (TAC), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE); and local ablative therapy such as RFA, percutaneous alcohol injection (PAI), and microwave coagulation therapy (MCT).[1–10] Cytoreductive surgery[11,12] — also termed tumor-debulking surgery,[2,3,13] tumor mass reduction surgery,[14] volume reduction surgery,[15] or reductive surgery[16] — is another potentially effective component of a multidisciplinary treatment approach to HCC in carefully selected patients.

This chapter illustrates the rationale for cytoreduction and the current role of cytoreductive surgery for HCC.

Rationale for Cytoreduction

Cytoreductive surgery aims at the removal or destruction of all macroscopic tumors, allowing microscopic foci to persist while at the same time preserving as much functional liver tissue as possible.[17,18]

The results of experimental studies suggest that cytoreduction has important potential benefits.[17–19] Reduction of tumor burden increases the sensitivity of the remaining tumor to chemotherapy and radiotherapy due to improved perfusion, cellular distribution of oxygen and nutrient within the tumor, and increased growth fraction of the tumor cells. The smaller tumor bulk requires a decreased number of necessary chemotherapeutic cycles or radiation doses for tumor eradication; as a result, the likelihood of developing resistant clones also decreases. In addition, cytoreductive surgery has the potential benefit of relieving symptoms and improving quality of life.[17–19]

However, cytoreductive surgery has its own potential hazards. Surgery increases the number of circulating cancer cells and produces

transient immunodepression, which promotes cancer cell implantation. In addition, the healing process stimulates growth factors, and the transient immune suppression due to the surgery-induced stress enhances tumor growth. Cytoreductive surgery also has the disadvantage of delaying other potentially beneficial nonsurgical treatment; this can be detrimental if the patient fails to recover from the surgery and the tumor continues to grow.[17–19]

McCarter and Fong[18] suggested four general guidelines to identify those patients who may benefit most from cytoreduction: (1) symptomatic tumors; (2) slow-growing tumors; (3) tumors that respond to other therapies; and (4) surgical procedures that can be performed safely. The group most suitable for cytoreductive therapy is symptomatic patients. Patients with metastatic neuroendocrine carcinoma of the liver often present with disabling endocrinopathies. Cytoreductive surgery can relieve symptoms and prolong survival. The combination of cytoreductive surgery and perioperative adjuvant therapy has gained increasing attention in recent years. Theoretically, perioperative therapy can eradicate residual tumor cells. The combined surgical and chemical cytoreductive therapy has been suggested as the standard of care for peritoneal dissemination from advanced ovarian, appendiceal, and colorectal carcinomas as well as diffuse malignant peritoneal mesothelioma.[17–20]

In general, most surgeons would agree that partial hepatectomy for HCC should only be carried out when the surgery is curative and the risks of operative morbidity and mortality are reasonably low. In the past two decades, the increased understanding of liver segmental anatomy as well as the improvement in surgical techniques and perioperative care have led to a dramatic decrease in operative mortality and an improvement in surgical outcome. It is with this increased safety that cytoreductive surgery becomes possible and worthwhile in HCC. Furthermore, the development of effective local ablative therapy has facilitated surgeons to reduce the tumor burden even further during the operation. Cytoreductive surgery can be followed by other nonsurgical treatments to deal with the micrometastases or the small residual tumor volume.

Outcome of Cytoreductive Surgery for HCC

Cytoreductive surgery has been shown to prolong survival and provide excellent symptomatic relief for good-surgical-risk patients in nonrandomized studies.[11–16,21–24] In 1994, Lau *et al.*[11] reported the first comparative study on the survival of patients who received cytoreductive surgery ($n = 26$) or systemic chemotherapy ($n = 26$) for unresectable HCC. In the cytoreductive surgery group, the largest diameter of the tumor ranged from 2 cm to 20 cm, with a median of 8 cm. The number of tumors present ranged from 2 to 10, with a median of 2. Histological evidence of cirrhosis was present in 70% of patients. Cytoreductive surgery was carried out with partial hepatectomy, cryosurgery, MCT, or absolute alcohol injection. The results were compared with a case-control group of patients who received systemic chemotherapy. This study showed a significant benefit in the cytoreductive surgery group (median survival, 10 months vs. 2.3 months). Three other comparative studies also showed significantly better survival of patients who received cytoreductive surgery (Table 1).[12,21,22] Ku *et al.*,[16] in a recent single-arm study ($n = 25$), reported a 5-year survival rate of 42% in patients with multiple and advanced HCCs who underwent cytoreductive surgery and percutaneous isolated hepatic perfusion.

All of these results should be interpreted with caution because there are variations in the reasons for inoperability and in the liver functional status of the patients in each of these studies. The variations in the adjuvant therapy regimens used in the various institutions at different time periods also contribute to differences in the results. Further randomized controlled trials are required to validate the true effects of cytoreductive surgery in the treatment of HCC.

Cytoreductive surgery followed by adjuvant therapy was shown to give better survival than without adjuvant therapy. The subgroup analysis of Nagashima *et al.*[12] showed that the absence/noneffectiveness of adjuvant therapy was a significant factor for early postoperative death. In the subgroup analysis of the prospective randomized trial by Li *et al.*,[24] patients who underwent palliative hepatectomy with adjuvant TACE had significantly better survival than those without adjuvant therapy (1-, 2-, 3-, and 4-year survival rates of 68.3%, 32.3%, 21.5%, and 21.5%, respectively, vs. 38.9%, 0%, 0%, and 0%, respectively).

Table 1. Results of comparative studies of cytoreductive surgery for HCC. A, partial hepatectomy for the main tumor + intraoperative local ablative therapy for the smaller tumor nodules in the liver remnant; B, partial hepatectomy for the main tumor + postoperative adjuvant regional chemotherapy; C, partial hepatectomy for the main tumor + intraoperative local ablative therapy for the smaller tumor nodules in the liver remnant + postoperative adjuvant regional chemotherapy.

Reference	Treatment group (Treatment)	Treatment group (*n*)	Control group (Treatment)	Control group (*n*)	Survival of treatment group	Survival of control group
11	A or C	26	Systemic chemotherapy	26	1-, 3-year survival — 46%, 7%; median survival, 10 months	1-, 3-year survival — 8%, 0%; median survival, 2.3 months
12	A, B, or cytoreductive surgery only	28	TACE	25	1-, 3-, 5-year survival — 78.6%, 48.7%, 48.7%	1-, 3-, 5-year survival — 64%, 22.9%, 17.1%
21	A or B	15	TACE, systemic chemotherapy, TACE + systemic chemotherapy, cryotherapy, tamoxifen, or no treatment	63	1-, 3-year survival — 65%, 35%; median survival, 19.5 months	1-, 3-year survival — 36%, 10%; median survival, 7.1 months
22	B or C	28	TAC, TACE, or PAI	43	1-, 3-, 5-year survival — 58.2%, 27.1%, 21.7%	1-, 3-, 5-year survival — 34.3%, 4.7%, 4.7%

Modalities of Cytoreductive Surgery

There are three modalities of cytoreductive surgery that are commonly used for unresectable and advanced HCC:

1. Partial hepatectomy for the main tumor + intraoperative local ablative therapy for the smaller tumor nodules in the liver remnant;
2. Partial hepatectomy for the main tumor + postoperative adjuvant regional chemotherapy; and
3. Partial hepatectomy for the main tumor + intraoperative local ablative therapy for the smaller tumor nodules in the liver remnant + postoperative adjuvant regional chemotherapy.

It is still unknown which is the best modality of cytoreductive therapy. Except in one prospective randomized trial, there is no comparative study to look at the efficacy of the different treatment modalities. Taniai *et al.*[25] randomized 30 patients with multiple and advanced HCC who underwent reduction hepatectomy (defined as resection of the main tumor, or of the main tumor plus the satellite tumors around the main tumor; hemihepatectomy, $n = 16$; extended hemihepatectomy, $n = 3$; segmentectomy, $n = 7$; subsegmentectomy, $n = 4$) in conjunction with either intraoperative local ablative therapy with MCT/RFA ($n = 15$) or postoperative adjuvant TACE ($n = 15$). The 3- and 5-year overall survival rates in patients who underwent partial hepatectomy and intraoperative local ablative therapy were 35.7% and 7.7%, respectively; while in those patients who underwent partial hepatectomy and postoperative adjuvant TACE, they were 35.0% and 0%, respectively. The survival rates did not differ significantly between these two groups of patients.

Cytoreduction by Radiofrequency Ablation (RFA)

RFA has recently gained attention as a promising technique for the treatment of HCC. It induces temperature change by using a high-frequency alternating current applied via electrodes placed within the tissue to generate areas of coagulative necrosis and tissue dessication.[7]

RFA of HCC can be accomplished by an open, laparoscopic, or percutaneous approach. Open and laparoscopic approaches have the potential advantages of being more precise in staging the disease, in treating larger tumors by using the multiple probe application techniques, in treating lesions near an adjacent organ by either dissecting away or resecting the organ, in treating lesions inaccessible percutaneously, and in detecting additional tumors not seen by preoperative imaging through the use of intraoperative ultrasound (IOUS). RFA is commonly used in patients with small HCC confined to the liver, especially when the tumors are unresectable due to poor general condition of the patient or compromised liver function. The application of RFA has a number of potential advantages in patients with unresectable HCC. The procedure is relatively safe and well tolerated, and its complication rates in most series have been low.[26,27]

RFA for large or multifocal HCCs is being investigated as the alternative modality of cytoreduction. However, the size and number of tumors are important factors determining the local recurrence rate after RFA. Apart from the larger tumor volume, large HCCs more frequently have irregular borders and satellite lesions. With the conventional monopolar technique, the radiofrequency (RF) power decreases in proportion to the square of the distance from the electrode; tissue temperature also decreases rapidly with increasing distance from the electrode. Therefore, a precise tailoring of the size and shape of the thermal lesion is important in RFA for large HCC. A number of precisely calculated overlapping coagulations is necessary for large HCC.[28–30] The treatable tumor volume is also limited by the problem of charring and the "heat sink" phenomenon.

In order to overcome the size limitation in RFA, numerous modified electrodes and techniques have been developed. These include the use of saline injections during RFA, cooling of the electrode tip, bipolar RF device, complex electrode geometry, and vascular occlusion during RFA.[31–35] Temporary interruption of hepatic blood flow using the vascular occlusion technique has been shown to increase the efficacy of interstitial thermotherapy with a significant increase in lesion volume. The vascular occlusion causes reduction of heat dispersion, thus increasing the range of therapeutic thermal coagulation. However, there is a

lack of randomized or nonrandomized controlled studies showing the survival benefit of RFA for advanced HCC. The technique of RFA for large HCC is still being refined. Randomized controlled trials for an optimized RFA technique would be needed to establish its potential benefit.

Cytoreduction for Extrahepatic Disease

Synchronous extrahepatic metastases are less common than intrahepatic metastases in patients with disseminated HCC. Pulmonary metastasis is the most common type of extrahepatic spread of HCC. In general, HCC with extrahepatic metastasis is regarded as an advanced disease with extremely poor prognosis. A few small retrospective studies suggested that prolonged survival can be achieved by aggressive surgical resection of both the primary and the metastatic tumors in patients with isolated metastases to the lung, adrenal gland, or peritoneum.[36–47] However, due to limited evidence, it cannot be recommended as a routine practice. Only highly selected patients should be considered for this aggressive surgical approach in experienced centers, provided the following criteria are fulfilled: (1) the intrahepatic primary tumor can be treated with hepatectomy or local ablative therapy; (2) there is an isolated and resectable extrahepatic disease; (3) other metastases have been excluded with adequate imaging assessment; and (4) the surgery should be carried out in patients with good surgical risk. One of the major reasons for the inferior result of cytoreductive surgery for extrahepatic metastases for HCC when compared with ovarian and colorectal carcinoma is that there is still no effective systemic therapy for HCC.

Challenges of Cytoreductive Surgery for HCC

The major challenges of cytoreductive surgery in HCC are that only a selected group of patients would benefit, and that the indication for cytoreductive surgery has not been clearly defined. The data in the medical literature are too limited to have a meaningful analysis of the factors that are predictive of good results in cytoreductive surgery. The available data suggest that patients with small tumors, fewer tumor nodules,

absence of tumor venous thrombus, better liver functional reserve, and better response to adjuvant therapy would have a better outcome after cytoreductive surgery.[12,48–50] Those patients who have a good response to cytoreductive surgery are more likely to have tumors that are biologically more favorable. Furthermore, any further improvements in cytoreduction in extending the survival or disease-free interval in patients with advanced HCC would depend on the development of an effective adjuvant therapy; unfortunately, the currently available adjuvant therapy in HCC is of limited effectiveness.

Conclusions

It is unclear whether the combination of cytoreductive surgery with other nonsurgical interventions for patients with advanced HCC gives a survival benefit when compared with nonsurgical palliative therapy alone. One clear message is that cytoreductive surgery has a role to play in the multimodality approach for unresectable and advanced HCC, and it contributes to improve survival in a selected group of patients. This treatment strategy can be considered as one of the options in selected patients with low operative risks and reasonable liver function in experienced centers. Further prospective randomized trials are required to validate this aggressive surgical approach.

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Cryosurgery

George Petrou and David L. Morris

Introduction

Primary hepatocellular carcinoma (HCC) is the most common liver cancer in the world. HCC is also the most common cancer attributable to death in the world. The incidence of HCC varies geographically because of variations in the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. As HBV, HCV, and alcohol are commonly associated with HCC, it is likely that the incidence of HCC in both the Eastern and Western worlds will increase.

The prognosis for HCC remains poor, as most patients present at an advanced stage. Therefore, most patients require palliative treatments. Surgery still remains the best curative treatment for HCC. Two surgical procedures have emerged: partial liver resection and liver transplantation. In liver transplantation, selecting HCC patients with the Milan criteria[1] or the University of California San Francisco criteria,[2] 4-year survival rates of 75% for small HCCs have been demonstrated.

Although liver transplantation has an excellent long-term survival rate, its use is restricted because of shortages in donors and strict inclusion criteria which make most patients with HCC ineligible.[3] However, this may soon change with the development of living donor liver transplantation, which is emerging as a feasible alternative.[4]

Partial liver resection is a curative treatment with a long-term survival rate ranging from greater than 30% to as high as 70% in carefully selected patients.[5–8] Despite this, partial liver resection is only offered to a minority of patients as most are rejected because of tumor location, multifocal liver disease, portal vein invasion, inability to achieve an adequate tumor-free margin, extrahepatic metastases, and inadequate functional hepatic reserve. As most HCCs are associated with cirrhosis, postoperative morbidity and mortality are considerable and are commonly related to hemorrhage, liver failure, hepatorenal syndrome, and sepsis.[9]

A variety of treatments are reported for unresectable HCC. These have generally produced good palliation of symptoms without making a significant impact on survival. Also, few have been assessed in randomized trials; therefore, their efficacy is not well established. Percutaneous ethanol injection of small solitary HCCs (<5 cm) appears to be a useful treatment. Transarterial chemoembolization (TACE) by intrahepatic artery infusion of lipiodol in combination with cytotoxics or radioisotopes (iodine-131) has produced good tumor response in the majority of patients treated, with few long-term survivors.[10,11]

In light of these limitations, other local ablative techniques have emerged as alternative therapies for patients with unresectable HCC and patients with resectable HCC but poor functional liver reserve to tolerate a partial hepatectomy. Open or percutaneous ablative therapies have now extended the boundaries, as patients with multiple HCCs and/or bilobar disease can be treated with curative intent using a single-stage or two-stage combination of resection/ablation liver surgery. The type of ablative therapy used is largely institution-dependent. Cryotherapy has been extensively used for the *in situ* imaging-controlled destruction of liver tumors, mainly colorectal cancer liver metastases, neuroendocrine tumors, and HCCs. The advantage of cryotherapy in HCC is that extensive liver resection is not required. This has therefore broadened the

scope of liver surgery to cirrhotic patients with HCC in an era where liver transplantation is not widely available.

The History of Cryosurgery

The use of low temperature to treat malignant tumors was first described by an English physician named James Arnott (1797–1883). He applied crushed ice saline solutions to large cutaneous ulcerating cancers and observed a reduction in size, pain, and hemorrhage. He was the first to report the use of extreme cold locally to destroy tumor tissue.[12] He treated breast cancer, uterine cancers, and skin cancers. Although palliation was his main aim, he recognized the potential of cold for curing cancer.[13]

The first cryosurgical system capable of delivering liquid nitrogen to trocar-like probes with an insulated shaft and a conductive metal tip was described by Cooper and Lee in 1961,[14] and the ability of the device to produce an avascular cryolesion in the liver was demonstrated in a cat model in 1993.[15] The innovative design of the probes allowed surgeons, for the first time, to contemplate treating lesions deep within the parenchyma of the liver with minimal trauma to the liver.

During the following 20 years, cryosurgical treatment of tumors at various organ sites such as rectum, breast, skin, lung, brain, prostate, uterus, oral cavity, pancreas, and liver were reported.[16] The lack of a method to adequately monitor the freezing process in the organ resulted in an imprecise and incomplete destruction of tumors deep in the liver, which translated to high rates of local recurrence. Confounding this, the morbidity reported by accidental freezing of adjacent organs in prostate cryotherapy[17] delayed its more widespread application.

With the introduction of intraoperative ultrasound (IOUS) as an accurate method of guiding cryoprobe placement and monitoring ice ball formation in the liver,[18–20] along with the development of more sophisticated high-powered cryomachines and smaller cryoprobes with better insulated shafts, a number of centers have now adopted this ablative technique for the treatment of both primary and secondary liver tumors.[21–26]

Mechanism of Tissue Destruction by Freezing

During the freezing of cells, intracellular and extracellular ice formation occurs. Intracellular ice formation causes injury to cellular membranes and intracellular structures, resulting in cell death. Intracellular ice formation is only achieved through fast freezing or freezing to very low temperatures.[27] Slower freezing rates result in the formation of extracellular ice, causing an increase in extracellular osmolarity; the osmotic gradient results in cellular dehydration.[26] The ensuing changes in the intracellular milieu — i.e. changes in pH, ionic concentration, and denaturation of proteins — are lethal.[28] In addition, mechanical interaction between extracellular ice crystals and cells leads to the deformation of cells and rupture of cell membranes, which is also lethal.[29] Despite this, it is well reported that cells may, to a certain extent, survive after thawing.[30,31]

In vitro freezing of cells

Many investigators have performed *in vitro* experiments using different tumor cell lines to establish the lethal temperature for tumor cells being frozen and the optimum freezing protocol. Zacarian[32] showed that 45% of HeLa cells survived freezing at −35°C to −40°C for 1 hour. A total of 0.3%–1% of Walker carcinoma cells frozen to −35°C were still viable, whereas all of the cells died at −40°C.[28] Although these data suggest that freezing to very low temperatures is necessary to ensure cell death, the temperatures reached at the tumor edge in clinical application of hepatic cryotherapy are usually not nearly as low. We believe that little of the effect of hepatic cryotherapy can be attributed to direct cell damage, as measured by *in vitro* freezing of cells.

In vitro freezing of tissue

Early attempts at studying the effects of the speed and final temperature of freezing of tissue on cellular damage had difficulty in separating these parameters. Rubinsky and coworkers[33,34] developed a method of controlled freezing of tissue slices on microscopic slides moving along

a temperature gradient between two constant temperature bases. They were able to freeze both animal and human liver tissues with a constant cooling rate. Their experiments revealed that high cooling rates resulted in intracellular ice formation and immediate cell death, representing the clinical situation of live tissue very close to the cryoprobe. Lower cooling rates resulted in cellular dehydration and extracellular ice formation with large ice crystals propagating along sinusoids, expanding them by a factor of two in diameter. It is speculated that this expansion may lead to the destruction of liver microvasculature, resulting in ischemic necrosis of surviving cells in the frozen region.[32,35] This observation explains the mechanism of cellular destruction in the periphery of the ice ball in the clinical setting, where the temperatures reached are not as low and cooling rates are slower. This is the most likely explanation for the greater sensitivity of tissue to freezing *in vivo* compared with *in vitro* cell data.

The freezing of human liver tumor slices with this system revealed that tumor tissue is more resistant to cellular dehydration and vascular disruption than normal liver during slow freezing, with HCCs being harder to destroy than colorectal liver metastases.[33] This observation emphasizes the importance of conducting experimental work in hepatic cryotherapy on animal models with tumor-bearing livers.

In vivo freezing of tumors

Animal models

Very few studies have used animal models of liver tumors to evaluate cryotherapy, all of them using a rat model.[36–40] Most of these investigators used sarcomas implanted into the liver. The histological changes following cryotherapy of tumors appeared more slowly; and in partially frozen tumors, the line of demarcation between frozen and unfrozen tumors was less distinct than in normal liver tissue, with altered but viable tumor cells in the border zone. Many frozen tumors also showed surviving tumors at the periphery of the lesion.[33] Jacob *et al.*[41] compared cryotherapy, using a double freeze–thaw cycle and achieving temperatures of at least −60°C at the tumor edge, with infarction and resection

of tumor-bearing rat liver. Resection and cryotherapy were equally effective and superior to infarction in achieving local tumor control. Only one study used a colorectal cancer cell line implanted in rat liver[38]: six rats had their tumors resected, and in another six rats a double freeze–thaw cycle was used to freeze the tumors with a surrounding margin of normal liver; in both groups, one of six tumors treated recurred locally.

Looking at these studies, it seems very likely that different tumors have different resistances to freezing. The lethal freezing temperatures of liver cancers commonly treated by cryotherapy have, to date, not been adequately investigated. Furthermore, it is still unknown whether a margin of surrounding normal liver tissue needs to be frozen with the liver tumor; however, it appears logical for this to be the case. It is also unknown whether double or even triple freeze–thaw cycles are necessary for adequate tumor destruction.

Human liver tumors

Colorectal liver metastases are the most widely experimentally studied liver tumor in humans. Liver metastases that have been frozen and resected do not show a clear demarcation of the tumor into frozen and unfrozen areas macroscopically as in normal liver tissue; however, microscopically there is clear delineation of the tumor into frozen and unfrozen areas. In the frozen areas, coagulative necrosis with nuclear pyknosis and loss of nuclear detail was present; the cytoplasm also had an indistinct granular appearance with indistinct cell borders and shrinkage of cells.[42] Histological changes consistent with necrosis after freezing were more striking in tumor tissue than in normal liver tissue, even after one freeze–thaw cycle. Commonly frozen tumor lesions treated up to 5 months later revealed histologically only a fibrotic scar.[43]

Single Versus Double Freeze–Thaw Cycles

Double freeze–thaw cycles are more efficient in killing tumor cells in suspension[44] and tissue.[26] It is believed that repeat freeze–thaw cycles in an animal model allow the production of larger ice balls in the

liver and faster ice ball growth, probably due to microvascular damage and deprived blood flow in the previously frozen region, resulting in increased thermoconductivity. The repeatedly frozen liver tissue shows marked signs of immediate cell damage.[45] The zone of necrosis in the liver at different times for ice balls of the same size is greater[46,47] with double freeze–thaw cycles.

Although the advantages of double freeze–thaw cycles are obviously apparent in the experimental model, they may be associated with higher morbidity. Double freeze–thaw cycles result in greater hepatocellular injury, as measured by serum aspartate aminotransferase (AST) on the first postoperative day.[44,48] They are also associated with a larger platelet drop in the early postoperative period.[49] Furthermore, double freeze–thaw cycles are associated with the potentially fatal cryoshock phenomenon.[23] The authors' unit regularly performs double freeze–thaw cycles with hepatic cryotherapy and advocates its usage.

Hepatic Inflow Occlusion

Our experience with hepatic inflow occlusion is that it allows a faster freezing time and creates a larger maximum-sized ice ball.[46,50] This is useful when large liver tumors need to be treated. Furthermore, the resulting zone of cryonecrosis for ice balls of the same size, measured 1–21 days following cryosurgery, is considerably larger if hepatic inflow occlusion is used.[44] Hepatic inflow occlusion is achieved before cryotherapy of the liver lesion commences by clamping the hepatoduodenal ligament (Pringle's maneuver). The duration of clamping should not exceed 1 hour, but it may be reapplied after a recovery period of 15 minutes.

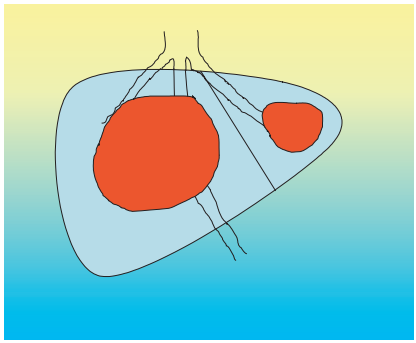
Patient Selection: Indications for Hepatic Cryotherapy in HCC

The largest experience of HCC treated with cryotherapy is from China,[19,21] where HCC was the first indication for cryotherapy. Cryotherapy has several advantages that make it an attractive potential treatment choice in this disease. It is a local ablative treatment that destroys only a small amount of normal tissue around the tumor, and is

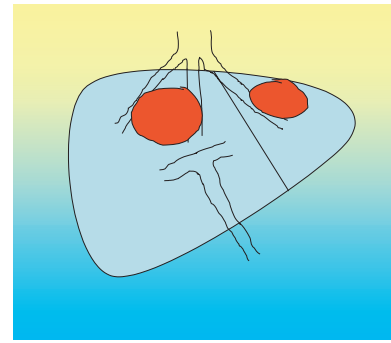
ideal for patients with cirrhosis who have limited hepatic reserve. It is also suitable for the treatment of patients with multifocal HCCs of the liver. Several groups have published their experiences of hepatic cryotherapy for HCC.[19,21,51–55] Most groups use hepatic cryosurgery in patients without extrahepatic disease, but with unresectable liver disease, due to the following (Fig. 1):

1. Multiple bilobar tumors, where cryotherapy allows local destruction of the tumors and preservation of functional liver tissue. The number of liver tumors treatable per patient is debatable, but in general our experience is up to four HCC lesions. We have also completed a combination of resection of large HCCs from one side of the liver followed by cryotherapy of smaller lesions on the other side;
2. Proximity to major intrahepatic vessels, where cryotherapy may still allow destruction of the tumor without injury to the vessel;
3. Involved or inadequate margin following liver resection. In this situation, cryotherapy of the resection edge prevents edge recurrence (Fig. 2)[24]; and
4. In cases where the tumor is resectable but the patient is unfit for major liver resection; or in cases of severe liver cirrhosis, where liver resection may not be tolerated because of insufficient hepatic functional reserve.

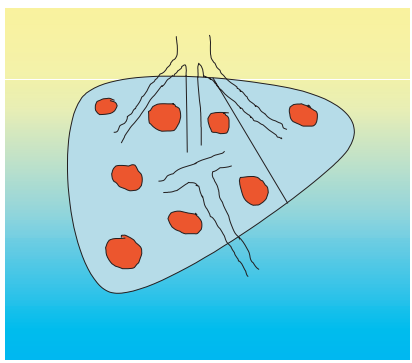
We have considered that tumors greater than 6 cm are unsuitable for cryotherapy, although the use of concurrent multiple probes may allow their treatment (Fig. 3). From our broader experience with the treatment of colorectal liver metastases, the number of lesions present is clearly of importance. In a selected group of patients where we were successful in completely destroying all liver disease, the number of hepatic lesions was not prognostic; whether this is applicable to HCC, where liver recurrence is common, is not known. Our experience with cryotherapy in colorectal liver metastases has also revealed the diameter of the liver lesion to be treated of highly prognostic significance for recurrence. Our disappointing early results with lesions greater than 3 cm led to a change in our approach, whereby larger lesions are resected where possible. This has resulted in a significantly lower recurrence rate, and we have applied this same philosophy to cryotherapy treatment of patients with HCC.[56]



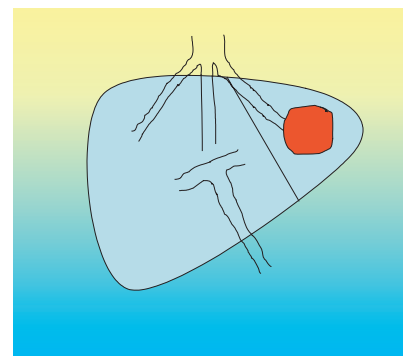
May be treated with a combination of cryosurgical ablation to the smaller lesion and regional therapy to the remaining liver.



Not suitable for resection because of proximity to all hepatic veins. Cryosurgery may allow destruction of tumor without injury to veins.



Cryosurgery may treat multiple bilobar tumors with a combination of resection and cryoablation to preserve liver parenchymal volume.



Cryosurgery may treat resectable HCC when the patient is not fit for surgery or liver function is insufficient to withstand resection.

Fig. 1. Indications for hepatic cryosurgery in patients with nonresectable HCC.

Techniques

Preoperative investigation and preparation

Patients with potentially resectable or ablatable HCC that fall outside liver transplant criteria due to tumor size or number are worked up for curative resection and or cryosurgery via analysis of their Child–Pugh score and serum alpha-fetoprotein (AFP) levels. Preoperative imaging

includes lipiodol computerized tomography (CT) of the liver, lung CT, and bone scan to assess resectability and exclude systemic disease. The diagnosis of HCC is made from interpreting a combination of preoperative imaging and AFP levels. A multidisciplinary meeting with a specialist surgical team and a radiologist is desirable to accurately determine the diagnosis, resectability, and management plan. We prefer to avoid percutaneous needle biopsy for fear of tumor seeding. If both CT and AFP levels are nondiagnostic, then a radiology-guided percutaneous biopsy is completed to define the etiology of the lesion.

Surgical technique

Equipment and personnel

We use the LCS System (Cryogenic Technology Ltd, Belper, UK) or the ERBE Cryo 6 (Elektromedizin, Tübingen, Germany) for all of our cryotherapy work in Australia (Fig. 4). These are large-capacity systems

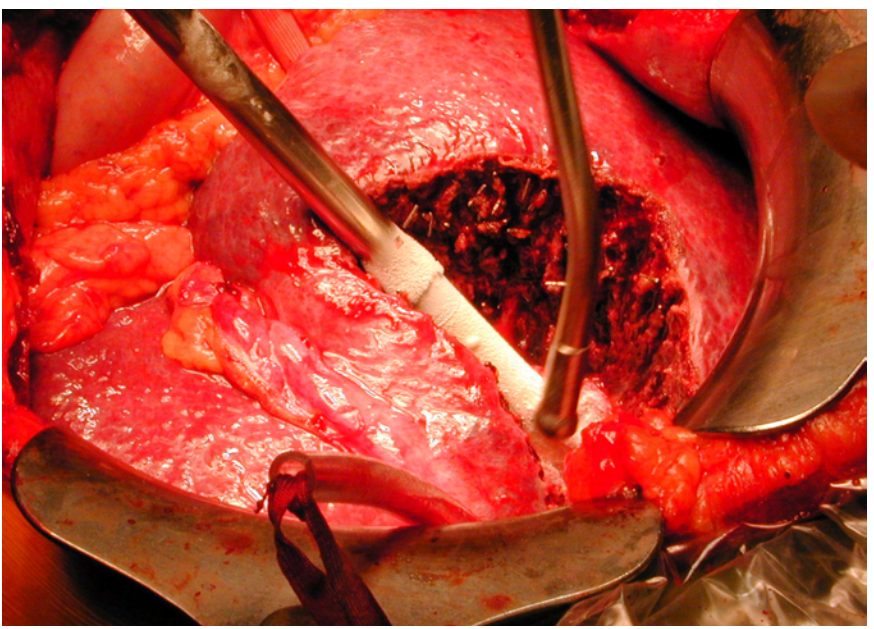


Fig. 2. Cryotherapy of resection edge in a cirrhotic liver to improve surgical margin.

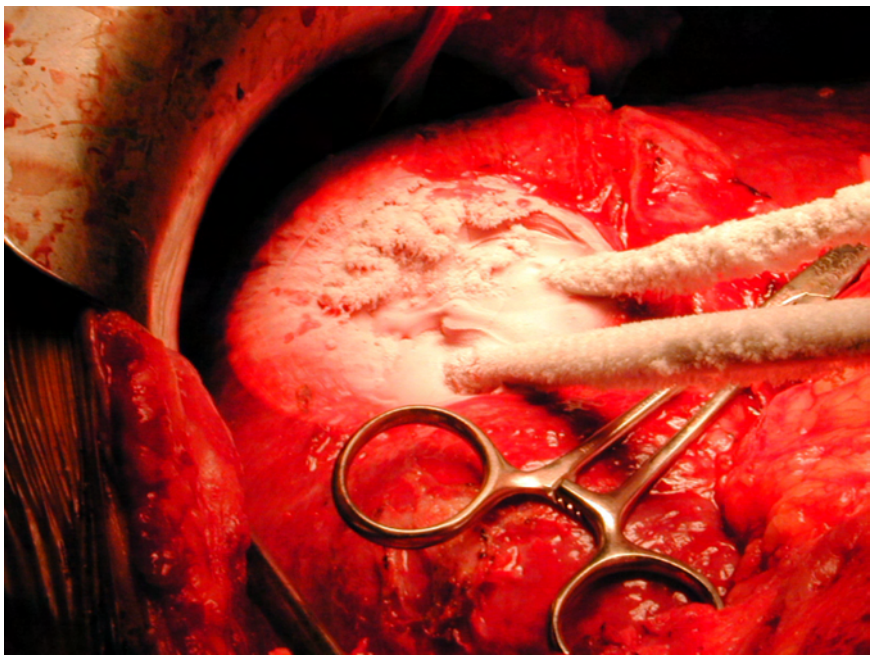


Fig. 3. Cryosurgery using concurrent multiple probes may quickly ablate larger HCCs.

designed specifically for hepatic cryotherapy to deliver liquid nitrogen to the tip of a triple lumen probe applied to the lesion to be frozen. Large ice balls form in the tissue surrounding the probe. The shaft of the probe is insulated, allowing precise destruction of deeply placed hepatic lesions without significant thermal damage to overlying liver tissue. We use three probes at present: 5-mm and 9-mm insulated trocar probes, and a flat plate probe. The machine allows the simultaneous use of two probes, although four linear machines are now available and would be an advantage for hepatic work. A unique thaw system has been incorporated in the specially engineered probe to allow quicker probe detachment after freezing. Heated nitrogen gas is used in the thawing process. Liquid nitrogen (30 L) is stored in a double-walled, vacuum-insulated storage vessel (Dewar) with the system. This is filled from a storage tank on site under pressure before the cryotherapy procedure. The Dewar pressure is maintained at 40 psi during cryotherapy, but pressures up to 55 psi

Fig. 4. The ERBE Cryo 6 (Elektromedizin, Tübingen, Germany).

can be used. Lowering the pressure to a minimum of 25 psi is a method of preserving liquid nitrogen during a long freeze for a large lesion, but we believe that the flow rate is probably of importance in achieving ice balls of adequate size for large lesions.

We use three types of probes. The first flat probe can be applied to surface lesions, while the two long trocar-tipped probes are inserted into the center of lesions. The larger 9-mm probe results in faster freezing, but clearly leaves a large defect on extraction when compared to the smaller

5-mm probe. We now seldom use the flat plate probe to treat liver HCC lesions because of the limited depth of ice ball that it achieves; it is, however, useful during liver resection to ablate an inadequate margin.

The freeze cycle should commence at 40 psi. This pressure is maintained for at least 5 minutes before it can be reduced if a long freeze cycle is anticipated. Exhaust gas is vented through a tube from the proximal part of the probe; this is necessary as the exhaust gas can freeze objects in close proximity. Therefore, the patient, skin, viscera, and assistants should be protected from exhaust tubing. A hand-held gauze sling, to avoid contact with the patient, supports the inlet and exhaust tubes. We use a polystyrene-insulated receptacle attached to the exhaust tubing in order to avoid damaging theater floors by contact with the exhaust gas.

The probes and exhaust tubing are sterilized by autoclave, gas sterilization, or immersion. Probes are sterilized by immersion for 10 minutes in gluteraldehyde solution. It is important that the immersion liquid is excluded from the inside of the tubes and probes by blocking off the tubes with stoppers and running gas through the system prior to using liquid nitrogen; failure to do so results in immediate blockage by frozen liquid on contact with the gas. The line assemblies are sterilized in a similar manner, and then the equipment is rinsed with sterile water. Prior to the first freeze, we test-run the probes in a container of saline to be sure that there is no leak of gas. A probe fracture would expose the patient to the possibility of gas embolism, although as soon as the ice ball is created the path of least resistance for gas is out the exhaust channel. We have not yet seen a probe failure in several thousand freeze/thaw cycles in both our animal and clinical experience.

The personnel required to operate the system safely include the surgeon and assistant, scrub nurse, and one technician. The technician should be well trained in the operation of the LCS 2000 System and should be able to connect the various pipes during the procedure.

Operative approach

This is best done via an extended right subcostal, bilateral subcostal (rooftop), or triradiate incision. The liver should then be completely mobilized. After the exclusion of extrahepatic diseases, intraoperative ultrasound (IOUS) of the liver is completed.

Intraoperative ultrasound (IOUS) (Fig. 5)

Ultrasound is used to detect and assess intrahepatic disease, guide accurate placement of the cryoprobe, and visually monitor freezing. The extent of liver malignancy is assessed using an IOUS system with

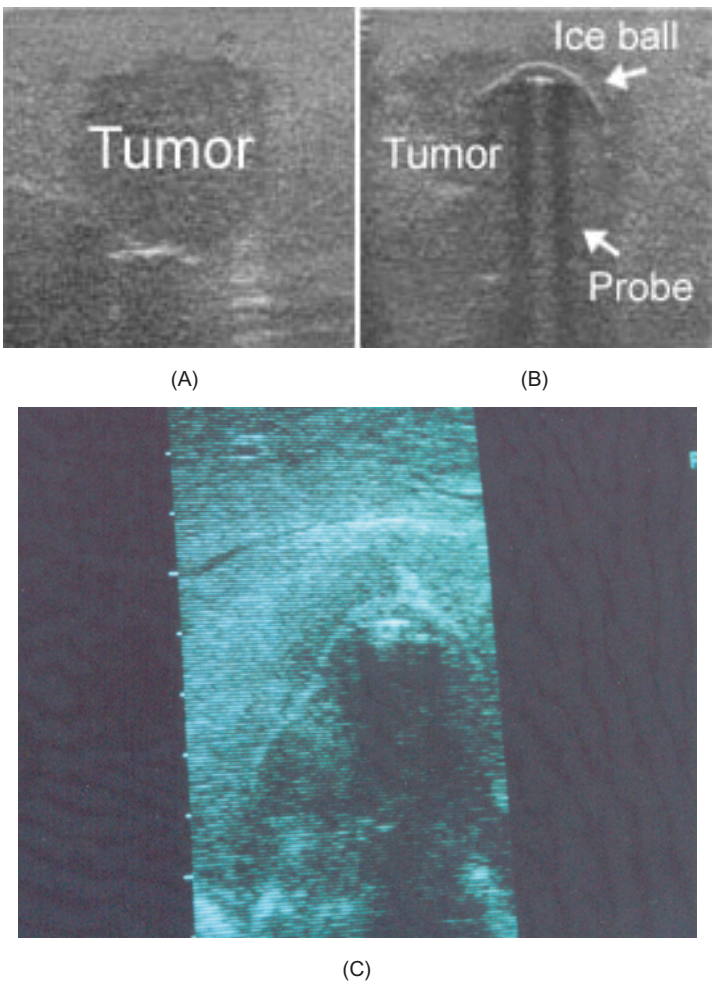


Fig. 5. (A) Ultrasonographic appearance of the live tumor before freezing as a hypoechoic mass. (B) The ice ball appears on IOUS as a hypoechoic area with a hyperechoic rim. The margin of freezing is easily observed. (C) The edge of the ice ball still within the tumor. Freezing will continue until it is 1 cm outside the tumor.

a sterilizable linear array or mechanical sector probes. The liver is examined systematically, using the modern definition of Couinaud segments.[57] HCC tumor masses are identified and their characteristics are recorded in terms of site, size, and echogenicity. The relationship of the tumor to the major vascular structures is noted.

The ultrasonic characteristics of frozen liver are well described *in vivo*.[26] The ice ball appears as a hypoechoic area with a hyperechoic rim, representing complete reflection of the ultrasound waves at the solidification interface between frozen and unfrozen tissue with posterior acoustic shadowing. This allows precise monitoring of the growth of the ice ball using real-time IOUS.[58] At full thaw, the previously frozen region appears hypoechoic compared with the surrounding liver, allowing precise assessment of treated and untreated areas. The size of ice balls as measured by IOUS correlates accurately with the size of the macroscopically visible cryolesion in the liver specimen. Therefore, a definite margin from the liver tumor can be precisely measured.[42,59]

Cryoprobe placement and freezing process

For small lesions on the liver surface, a trocar probe may be applied directly without penetration of the tumor. For large lesions on the liver surface, a trocar is inserted into the tumor under direct vision. For lesions deeply placed within the liver substance, which cannot be easily palpated, a spinal needle is directed under ultrasound guidance into the center of the tumor. The cryotherapy probe is inserted through the liver substance, using the spinal needle as a guide for both angle and depth. The process is clearly visualized with ultrasound. Multiple attempts at tumor access must be avoided with the larger cryoprobes. In addition, the track of the probe is chosen to avoid damage to major vessels and ducts. The inlet valve on the liquid nitrogen is opened to the maximum, and the freezing process commences. At this point, gauze swabs hold the inlet and outlet tubes away from the patient's body, protecting it from cold injury. Cold gas from the exhaust should not come into contact with any object, which may be damaged by cold. The ice ball growth is then monitored using ultrasound. It appears very clear as a dense black image (very hypoechoic). Freezing continues until the ice ball is seen to

exceed the tumor margin by 1 cm. During this time, the cryoprobe is supported to avoid mechanical stress on the ice ball caused by movement of the liver with respiration. The average time taken to freeze a 5-cm-diameter lesion is 30 minutes. The freezing time may be decreased by applying an atraumatic vascular clamp across the entire hepatoduodenal ligament (Pringle's maneuver). We use this method for periods of up to 1 hour and use this routinely for central, deep, or large lesions. We avoid this method in patients with poor hepatic functional reserve for fear of precipitating liver failure.

After achieving complete freezing of the lesion, we allow the edge of our ice ball to thaw by approximately 1 cm. In passive thawing between double freeze/thaw cycles, no gas is used. We do not allow lesions to completely thaw before refreezing as this would take a very long time, but more importantly is probably causally associated with the potentially fatal cryoshock syndrome. The second freeze should be allowed to go at least to the edge of the first. We then pass treated nitrogen gas through the probe system, which allows removal of the probe before the ice ball defrosts. Ice balls are always allowed to completely thaw before closing the abdomen, as it is impossible to assess hemostasis until thawing is complete. The cryoprobe can be removed when rotatory movement indicates that thawing has occurred around the probe. Precut fingers of oxidized cellulose foam are placed in the tract vacated by the probe. Liver sutures (chromic catgut) are used to control hemorrhage from the thawed ice ball in about 50% of cases. Major bleeding can occur from cracks, and these can be temporarily controlled by pressure or packing. The surgeon using cryotherapy should have adequate training to deal with the more severe forms of iatrogenic liver trauma. At the end of cryotherapy and thawing, a thorough check is made for hemostasis. We routinely place a suction drain above and below the liver.

The postoperative follow-up includes regular checks of AFP and CT of the abdomen. The CT appearance of a cryolesion is characteristic and changes during its histological evolution.[60,61] An experienced radiologist is needed to differentiate between normal cryolesions and pathological findings such as tumor recurrence or abscess formation.

Cryotherapy close to blood vessels

Gage *et al.*[62] suggested in 1967 that cryotherapy could be applied to tumors close to critical blood vessels supplying vital organs when he showed the resistance of large blood vessels to freezing in a dog model. As the proximity of hepatic tumors to major vessels (e.g. the portal vein, inferior vena cava, or hepatic veins) is used as one of the criteria for resectability, it would be ideal if those unresectable lesions could be ablated with cryotherapy. However, it has been argued that tumors immediately adjacent to large blood vessels might be subject to inadequate freezing due to the "heat sink" effect of the flowing blood in the vessel.[40,63] To overcome this problem, hepatic inflow occlusion or temporary occlusion of hepatic veins might be used to reduce the blood flow. When the cryoprobe is placed immediately adjacent to the vessel, providing high cooling rates in this region can result in complete destruction of the tumors abutting the major vessels. However, we have certainly experienced the local recurrence of tumors close to large blood vessels following cryoablation.

Laparoscopic cryosurgery

The safety of laparoscopic cryotherapy has been assessed in an animal model,[64] and a technique for clinical application has been described.[65] Cuschieri *et al.*[52] published a series of 22 patients treated by hepatic cryotherapy. They used a cryosurgical unit especially designed with very small implantable trocar-tip–type needle probes. A total laparoscopic approach, including laparoscopic IOUS, was used in six patients with accessible lesions in liver segments II–VI. A laparoscopic hand-assisted approach involving a small subcostal incision was used in four patients for lesions in the posterior-lateral sector of the right liver. No significant perioperative morbidity related to the laparoscopic approach was described. The proportion of patients who may benefit from this minimally invasive technique is not yet established. Critical assessment of the safety and efficacy of this technique will be important in establishing its place.

Morbidity and Mortality Following Hepatic Cryosurgery (Table 1)

Although hepatic cryotherapy is generally considered to be safe, there are some adverse effects that one must be familiar with in order to avoid serious morbidity.

Intraoperative hypothermia

Hypothermia as low as 33.7°C has been reported during hepatic cryotherapy.[66] We have not noted a clear relationship between the magnitude of the fall and the duration of surgery or total freeze time. Warming devices, such as the Bair Hugger and wrapping of the limbs with woolly bandages or warm blankets, have been useful in preventing excessive hypothermia. These are useful and inexpensive intraoperative adjuncts, which prevent the risk of cardiovascular complications such as conduction disturbances and arrhythmias. These complications become more common as the core body temperature drops.

Cardiac rhythm disturbances

Intraoperative arrhythmias have been reported in patients who have had cryotherapy of lesions close to the inferior vena cava (IVC).[67,68] In our sheep model, freezing of the liver close to the IVC without occluding it did not freeze the IVC and no arrythmias occurred. If the IVC was occluded, severe ventricular tachycardia occurred during the thaw; this was related to hyperkalemia.[67]

Cracking of the treated lesion

Cracks in the liver capsule may develop when the ice ball is allowed to extend to the liver surface, and are due to the thermal stress occurring during the rapid freezing and thawing process. Cracks are fairly common in hepatic cryotherapy and may require suturing in about 50% of patients.[69] Most of the cracks are easily controlled, and significant hemorrhage from cracks is rare. In an Australian series, cracking occurred in

Table 1. Published series of morbidity and mortality following hepatic cryosurgery.[a]

Reference	Year	No. of patients	Mortality	Cracking of ice ball	Bleeding	Nephropathy	Chest infection	Pleural effusion	Biloma/ Fistula	Abscess
72	1993	113	0	—	0	—	—	—	0	0
23	1995	145	0	—	0	—	—	—	0	0
73	1991	32	0	—	0	—	—	—	0	1 (3)
63	1993	64	0	5 (8)	2 (3)	—	—	—	2 (3)	2 (3)
24	1993	86	3 (3)	1 (1)	1 (1)	3 (3)	—	—	1 (1)	1 (1)
74	1995	140	6 (4)	—	10 (7)	3 (2)	—	7 (5)	6 (4)	2 (1)
26	1996	110	2 (2)	—	10 (9)	1 (1)	28 (25)	4 (4)	9 (8)	2 (2)
71	1994	100	1 (1)	—	3 (3)	—	—	—	—	—
54	1997	155	1 (1)	39 (25)	—	1 (1)	—	—	1 (1)	—
75	1997	63	0	—	0	—	3 (5)	—	0	0
76	1998	116	1 (1)	—	4 (4)	5 (4)	8 (7)	4 (3)	4 (3)	5 (4)

[a]Numbers in parentheses are percentage values.

8 of 26 patients; 5 of these 8 patients required blood transfusion of 1–4 units, and one of these five patients with a very soft tumor that literally shattered required abdominal packs overnight to control bleeding.[66]

Fever

Increased temperatures as high as 39°C during the early postoperative days, lasting for less than 1 week, are a common finding following hepatic cryotherapy and might represent a response to the tissue necrosis produced. Blood cultures and other investigations for localized infection or systemic sepsis are usually negative.

Pleural effusion and chest infection

Transient pleural effusion is a common finding, probably representing a secondary response to subdiaphragmatic irritation caused by freezing close to the diaphragm. However, in only 4%–18% of patients is thoracocentesis necessary (Table 1). Basal atelectasis and pneumonia occur due to inadequate ventilation of basal alveoli, and require a course of chest physiotherapy.

Subphrenic or hepatic abscess

Despite the large amount of necrotic liver tissue produced by cryotherapy, subphrenic or hepatic abscess is an uncommon complication, occurring in less than 2% of patients (Table 1). However, late intrahepatic abscess formation at the cryosite has been reported as long as 5 months after treatment.[70]

Biloma or bile fistula

Bile ducts are susceptible to freezing injury, and freezing of extrahepatic bile ducts leads to bilomas or bile fistulas. Bilomas are a fairly frequent complication, occurring in almost 3% of patients. These are usually managed nonoperatively via percutaneous radiological-guided drainage. Large-volume bile leaks may be treated effectively with endoscopic retrograde cholangiopancreatography (ERCP) and endobiliary stenting or

sphincterotomy. Bilomas seem to develop more frequently when the liver resection edge with an involved or inadequate margin is frozen, due to damage of small bile ducts at the cut surface.[26,68]

Postoperative changes in serum liver function tests (LFTs) and platelet count

The most striking postoperative change in serum LFTs is the transient increase in transaminases, usually normalizing within 7 days.[21,23,58,66] The serum aspartate aminotransferase (AST) level on the first postoperative day seems to be a good measure of hepatocellular injury, correlating with the amount of frozen tissue. Double freeze–thaw cycles cause a greater rise in AST level on the first postoperative day when compared to patients treated with a single freeze–thaw cycle. This shows that double freeze–thaw cycles create greater hepatocellular injury.[48]

A significant decrease in platelet count following hepatic cryotherapy has been observed in animal models and in almost all patients. It has been shown that the AST level on the first postoperative day is a good predictor of the expected platelet decrease, with its most common nadir on the third postoperative day; and patients treated with double freeze–thaw cycles had a greater drop in platelet count postoperatively.[49] The decrease in platelet count also seems to correlate with the amount of liver tissue injury.

Cryoshock

Cryoshock is the syndrome of multiorgan failure experienced by few patients after hepatic cryotherapy. Patients suffer from severe coagulopathy and disseminated intravascular coagulation (DIC), similar to septic shock but without evidence of systemic sepsis. This was responsible for the death of two patients who had large central lesions frozen in the Pittsburgh series,[25] where colorectal liver metastases were treated with hepatic cryosurgery. Severe DIC necessitating repeated transfusions of fresh frozen plasma, cryoprecipitate, platelets, and tranexamic acid was observed in 2 out of 100 patients in another series.[71] It was speculated that toxic substances derived from the necrotic liver tissue might

be responsible for this effect; however, data explaining the pathophysiological mechanisms of cryoshock are lacking and poorly understood.

Efficacy of the Treatment of HCC with Cryosurgery (Table 2)

Drawing a firm conclusion on the efficacy of cryosurgery in the treatment of HCC is difficult, as the literature is limited. The widely practiced multimodal treatment of HCC also makes commenting on cryosurgery alone as a treatment for HCC complicated. Superimposed on this is the lack of randomized controlled trials comparing the various thermal ablative techniques in the treatment of HCC.

Zhou's group in China is credited with the largest reported experience of treating HCC with cryosurgery. They have published many series, as is seen in Table 2. One of the largest series reported on 167 patients with survival rates at 1, 3, and 5 years of 74%, 48%, and 32%, respectively.[79] They recognized that tumors less than 5 cm had a better prognosis compared with tumors larger than 5 cm (5-year survival rates of 48% and 25%, respectively). Several modalities of treatment were used in conjunction with Zhou's publication, including cryosurgical ablation followed by resection of the frozen tumor, cryosurgery

Table 2. Published series of long-term survival data of cryosurgery for HCC.

Reference	Year	No. of patients	Survival (%)		
			1 year	3 years	5 years
21	1988	60	52	21	11
77	1992	87	61	32	20
72	1993	107	—	—	22
23	1995	145	69	49	35
85	1997	235	78	54	40
78	1998	245	78	54	40
25	1995	136	85	40	20
84	2002	15	90	79	79
83	2004	14	80	57	48
Morris *et al.* (unpublished)	2006	20	65	40	20

and hepatic artery ligation and/or perfusion, synchronous resection of the main liver tumor mass, and cryosurgical ablation of smaller residual tumor masses. Although other smaller reported series (Table 2) have not been able to emulate as excellent long-term survival figures, it is unanimous that a long-term survival of at least 20% should be expected.

Zhao *et al.*[51] reported a median survival of 21 months for patients with unresectable HCC undergoing cryosurgery. Pearson *et al.*[80] achieved complete tumor necrosis, as assessed by avascularity shown on posttreatment imaging in 60%–85% of tumors treated with cryotherapy. Despite this, it is now well established that incomplete tumor eradication can occur owing to either large tumor size or close proximity to a large vessel with its "heat sink" phenomenon.

Crews *et al.*[81] treated eight HCC patients with intraoperative cryoablation. They reported no tumor progression after 18 months. In a recent series by Adam *et al.*[82] who compared cryosurgery and radiofrequency ablation (RFA) in 36 patients with unresectable hepatic malignancies, they found no significant difference between the two groups with respect to tumor progression. Their results supported superiority in favor of treating HCC with cryosurgery when compared to other liver malignancies.

One of the major advantages of cryosurgery in the treatment of HCC is that many patients have cirrhosis with impaired liver function. Cryosurgery has an advantage of safety over liver resection in these patients, as the perioperative mortality in cirrhotics is about three times higher than in patients without cirrhosis. Patients with Child–Pugh class B or C cirrhosis would generally cope better with nonresectional therapies. As long as the HCC is small (less than 6 cm), cryosurgery is a reasonable option for unresectable HCC. No randomized controlled trials comparing cryosurgery with RFA exist to date in this patient cohort.

Conclusions

The incidence of HCC worldwide is increasing. Without a definitive treatment, most patients will die of this disease within 12 months. To date, neither regional nor systemic chemotherapy alone has made a

significant impact on long-term survival, but liver resection or ablation can prolong overall survival in selected patients. More importantly, only a small proportion of patients are suitable for liver resection, and even less are suitable for liver transplantation because of donor shortages. Cryosurgery alone or in combination with hepatic resection and/or hepatic intra-arterial chemotherapy is another important tool, which considerably increases the scope of patients who can be treated with a curative intent.

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Liver Transplantation

Chao-Long Chen and Allan M. Concejero

Historical Overview and Introduction

Due to the lack of alternative treatment and a dismal life expectancy, patients with unresectable hepatocellular carcinoma (HCC) formed part of the initial experiences with liver transplantation. These experiences showed poor outcome. With newer chemotherapy but doubtful effectiveness, and with a multimodality approach in the 1980s, liver transplantation was relegated to a second-line treatment measure.[1–4] The largely ineffective neoadjuvant studies, which included large and multifocal tumors, and the long waiting time made liver transplantation for HCC impractical. This dilemma prompted the development of locoregional treatment modalities such as transarterial embolization (TAE) and transarterial chemoembolization (TACE),[5–10] ethanol injection,[11–13] radiofrequency ablation (RFA),[14,15] and cryoablation.

Later experience from Italy, Spain, France, and Germany showed that excellent results could be achieved in patients with proper selection. Renewed enthusiasm for liver transplantation resurfaced by the 1990s

with rigid selection criteria, improved organ allocation, and shorter waiting time for donor livers.

Liver transplantation now offers the best chance of cure for selected patients with unresectable HCC. However, not all patients with unresectable HCC are suitable for transplantation. An improved outcome of liver transplantation for HCC greatly depends on recipient selection and accurate tumor staging, both of which rely heavily on diagnostic imaging. The role of adjuvant and neoadjuvant treatment approaches needs further evaluation in the overall objectives of disease removal and liver replacement. The purpose of this chapter is to review the status of liver transplantation for HCC.

Epidemiology

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, with increasing incidence.[16] It is also the seventh most common cause of cancer-related deaths worldwide.[17] HCC accounts for 80%–90% of primary hepatic malignancies. Mixed hepatocholangiocarcinomas are rare.[18–20] HCC is also responsible for more than one million new cases per year worldwide.[21–23] It is three times more common in men than in women. Untreated HCC has a median survival of 6 months from diagnosis because most patients are in the advanced stage of the disease when recognized. In addition, 80% to 90% of patients with HCC have underlying cirrhosis, most commonly due to hepatitis virus or alcohol, thus making surgical extirpation of the tumor less likely. Cirrhosis contributes to a 3%–10% increase in the annual HCC incidence among cirrhotic patients.[23]

Chronic inflammatory disease due to repeated or persistent infection, cytotoxic injury, and necrosis leads to increased cell division and mutation. This pattern leads to long-standing cholestasis, which in turn leads to an ordered bile duct proliferation or typical ductular reaction, and is associated with progressive accumulation of extracellular matrix, starting from the portal tracts and extending to the other areas of the lobule. This is characterized by hepatic inflammation as well as the activation of hepatic stellate cells and other mesenchymal cells, including portal myofibroblasts which participate in the deposition of

extracellular matrix components and contribute to the development of fibrosis.[24–27] Biliary fibrosis from long-standing cholestasis eventually results in cirrhosis.[28–30] Liver cirrhosis is considered to be an irreversible process characterized by excess extracellular matrix deposition in the liver with scar formation and destruction of normal liver architecture.[25,26,31] These processes are associated with loss of cell growth control: from adenomatous hyperplasia to atypical hyperplasia, which undergoes transformation to overt malignancy.[23]

In Asia, the distribution of HCC is mostly related to the hepatitis B virus (HBV); whereas in the United States and Europe, nearly 50% of HCCs are associated with the hepatitis C virus (HCV).[19–23,32] HCV appears to be an independent risk factor in Japanese and European patients.[33–35] The risk of HCC appears maximal at 20 to 30 years after HBV infection. HCC also develops in individuals with cirrhosis from genetic hemochromatosis. Although uncommon, HCC may also occur in autoimmune disease of the liver, primary biliary cirrhosis, Wilson's disease, and congenital liver diseases like biliary atresia. Chromosome abnormalities and specific gene mutations have been described, but a unifying molecular concept has not yet emerged. A variety of environmental risk factors for HCC include chlorinated hydrocarbons, nitrate compounds, radiation, pesticides, aflatoxin, smoking, betel nut use,[36–38] oral contraceptives, and several drugs and steroids.

As with other types of malignancies, vascular invasion is the strongest predictor of tumor recurrence and correlates with tumor number and size in HCC. Elevated serum alpha-fetoprotein (AFP) levels are useful in making a diagnosis if they are high or if the values increase with time.[39] Elevated AFP levels also occur in hepatitis, germ cell tumors, and pregnancy. In severely cirrhotic patients, it may be difficult to interpret the value of a single AFP determination. The prognosis for AFP-negative HCC patients is claimed to be better than that for AFP-positive HCC patients.[39,40] Des-gamma-carboxy prothrombin (DGCP) has been reported to be a useful marker in HCC, particularly in patients with moderate-to-severe advanced cirrhosis, and it may also have prognostic significance.[41,42] Assaying for AFP messenger RNA has been under study for its clinical significance.

Clinical Presentation and Diagnosis

The process of making a diagnosis and of surveillance involves deciding the level of risk of HCC. If the risk is high enough to trigger the diagnosis and need for surveillance, what screening tests should be applied and how frequently should surveillance be made? Patients with HCC usually present with abdominal pain, a palpable liver mass, or deterioration in liver function in patients with chronic liver disease; or the tumor is found incidentally during a routine medical examination. Signs of chronic liver disease may be present, such as jaundice, ascites, splenomegaly, spider angiomata, and caput medusae.

Although inadequate as a screening test, AFP still has a role in the diagnosis of HCC since, in cirrhotic patients with a liver mass, an AFP level greater than 200 ng/mL has a very high positive predictive value for HCC.[43] Furthermore, a persistently elevated AFP level has been clearly shown to be a risk factor for HCC.[44,45] Another serological test used to diagnose HCC is the DGCP test. Most reports have evaluated the use of this test as a diagnostic mode rather than for surveillance. It has been used as a marker for portal vein tumor invasion in some studies. Other tests that have been used as screening methods include the ratio of glycosylated AFP to total AFP, alpha-fucosidase, and glypican.[44–47]

For a patient with a liver mass and marked elevation of AFP, the diagnosis of HCC is straightforward and may obviate the need for liver biopsy confirmation. The practice of routine biopsy in patients suspected of having HCC is controversial because of the potential for needle-tract seeding after such an invasive procedure.[48] The decision to perform a biopsy is further weighted by the tumor grade, which is an important prognostic factor in HCC candidates for transplant. However, patients having one or more hepatic masses with no or only mild AFP elevation may require biopsy for diagnosis. Multiple immunohistochemical stains using monoclonal antibodies are used to differentiate the diagnosis of HCC from cholangiocarcinoma, metastatic carcinoma, and benign tumors.[49,50] The hepatocyte paraffin monoclonal antibody is sensitive, but not specific, for HCC.[51]

Many patients are referred for liver transplantation after a liver biopsy has proven the presence of malignancy. Surgical resection is the treatment of choice for HCC in noncirrhotic patients or in patients who

have cirrhosis but with adequate liver function reserve, normal bilirubin, and without significant portal hypertension. These patients with adequate functional reserve tolerate major resections with low morbidity. In cirrhosis, patients for resection have to be carefully evaluated to diminish the risk of postoperative liver failure and death. Today, the 5-year survival rate after resection exceeds 50%. Patients with unresectable tumors due to advanced cirrhosis or multicentricity of tumor, but without signs of metastatic disease or gross vascular invasion, are candidates for liver transplantation.[47,52–56]

Diagnostic Imaging Evaluation

The focus of any imaging modality in liver transplantation is to answer fundamental questions. These questions include the precise location of the tumor in the liver; characteristics of the lesion, including the size and number of lesions as well as the margins of the lesion; the relationship of the tumor with the liver vascular and biliary structures; and any associated findings that may give clues as to the extrahepatic spread of the liver tumor (Fig. 1).[57]

The precise location of the tumor allows preoperative planning for anatomical or nonanatomical resections. Tumor localization is also critical in locoregional therapies like percutaneous ethanol injection (PEI), RFA, and cryoablation for patients on the transplant waiting list.

Because of the restrictive criteria used in liver transplantation, accurate preoperative assessment and staging rely heavily on diagnostic imaging. The imaging test most widely used for screening is ultrasonography. Ultrasound has been reported to have a sensitivity of between 65% and 80% and a specificity greater than 90% as a screening tool.[58] However, these performance indices decrease in nodular cirrhotic patients. Moreover, ultrasound is difficult in obese patients and is operator-dependent. Finally, lesions <1 cm are difficult to detect by ultrasound, particularly in a cirrhotic liver.[59–63]

The exact delineation of the tumor and its characteristics are best provided with dynamic multidetector contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) (Fig. 2). Dynamic multidetector contrast-enhanced CT relies mainly on the

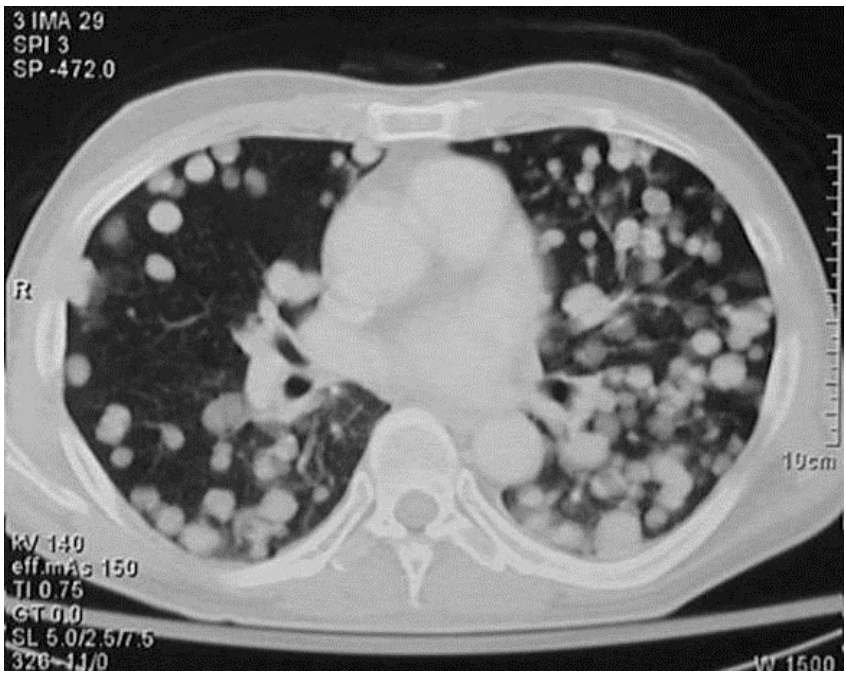
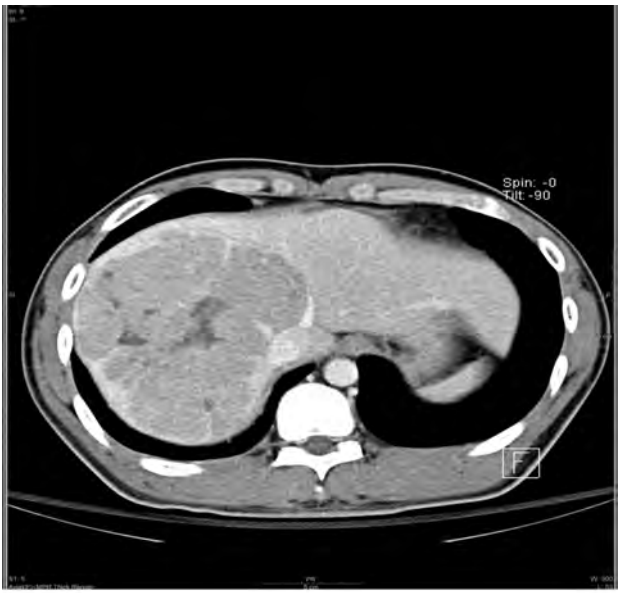
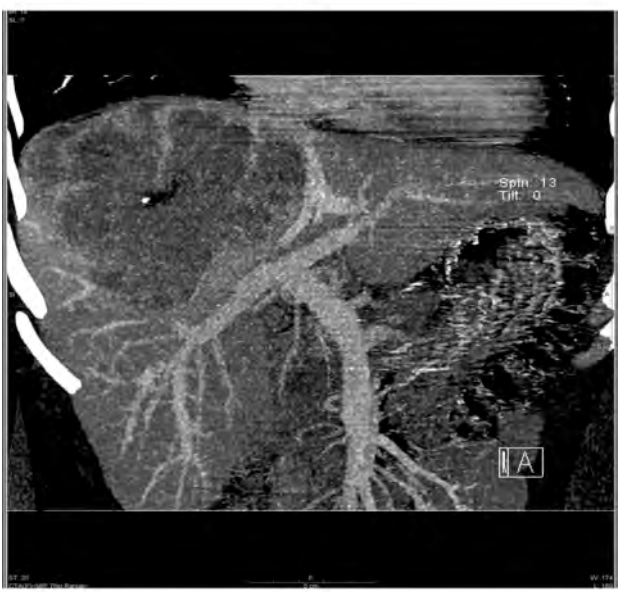


Fig. 1. Pulmonary metastases from hepatocellular carcinoma.

hypervascularity of tumors which are enhanced during early arterial phase scanning; also, most of the tumors show a hypodense lesion in the portal venous phase scanning. Because of inappropriate arterial phase scan timing in different patients, hypervascular tumors cannot always be easily detected.[64] In superparamagnetic iron oxide (SPIO)-MRI (SPIO is a tissue-specific contrast medium that is taken up by Kupffer's cells of the liver, resulting in a loss of the liver parenchymal signal on T1-weighted [T1W] and T2-weighted [T2W] MRI), hepatic neoplasms that do not contain functional Kupffer's cells, such as HCCs and metastases, do not lose the signal when compared with the normal liver parenchyma. Consequently, there are significant differences in T2/T2* relaxation between normal parenchymal tissue and tumors, resulting in increased lesion conspicuity and detectability (Fig. 3).[65] Several studies reported that SPIO-MRI is more sensitive and has a better diagnostic accuracy than spiral CT scan in detecting



(A)



(B)

Fig. 2. Conventional CT (A) and CT angiography imaging (B) are complementary in showing the precise location of the tumor and its relationship with vascular structures.

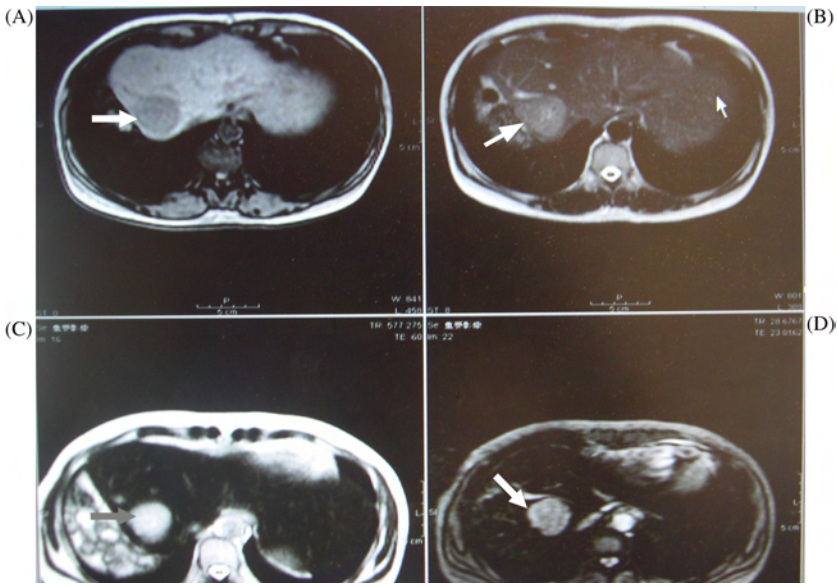
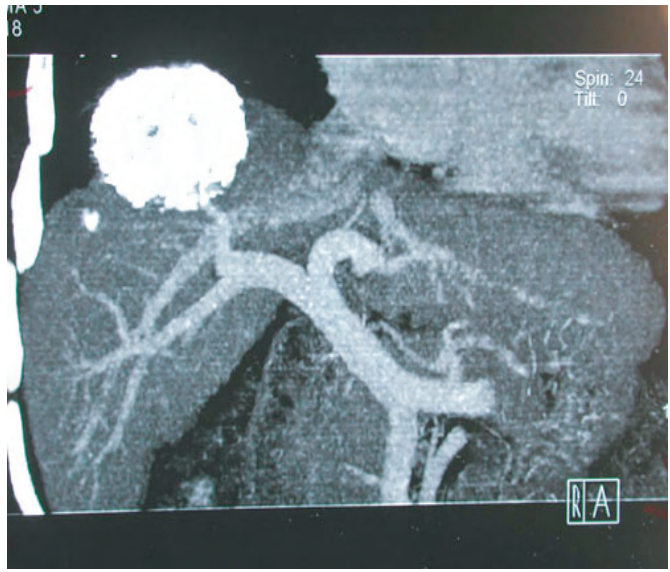


Fig. 3. SPIO-MRI shows Kupffer's cell uptake of iron oxide by the normal liver parenchyma in a case of post–right hepatectomy. Outpatient follow-up showed elevated AFP. Liver MRI showed a 3.7 cm × 3.4 cm × 3.7 cm mass over segment 4 near the resection margin. The mass demonstrated low signal intensity in T1W image (A), and was slightly hyperintense in T2W images (B, C). SPIO-enhanced MRI T2W image showed a drop of signal of the normal liver parenchyma and brighted out the hepatic mass (D). The arrows point to the tumor.

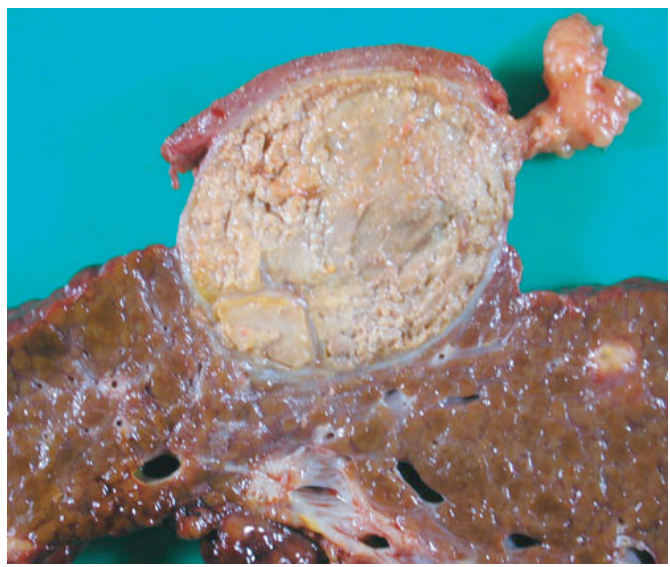
small hypervascular HCCs.[66,67] SPIO-MRI is also superior to dynamic multidetector contrast-enhanced CT in detecting liver metastases.[68,69] Positron emission tomography (PET) is helpful in the evaluation of extrahepatic metastases.

Of special interest in liver transplantation when requesting for imaging investigation for a transplant candidate are the vascular structures and their anatomical relationships. Aside from confirming whether a candidate is acceptable within chosen criteria based on imaging, the anatomical variations of the hepatic artery, hepatic vein, portal vein, and inferior vena cava (IVC) are also important. The vascular anatomy is often assessed using CT angiography or magnetic resonance angiography (Fig. 4).

In non-HCC transplant candidates, extensive thrombosis in the portal vein may preclude transplantation or allow for preoperative planning



(A)



(B)

Fig. 4. (A) CT angiography shows the relationship between tumor and vascular structures, depending on contrast-phase images taken. (B) The actual tumor specimen is shown at explant pathology.

to look for an alternative source of portal inflow. In HCC patients, however, a portal vein thrombus close to a tumor may be considered a tumor thrombus and precludes transplantation. Occlusion of the hepatic artery depending on the length of occlusion decides whether a candidate may receive a graft from a live donor or wait for a deceased donor graft. Patency of the hepatic artery is of particular importance in patients who have undergone repeated transarterial embolizations (TAEs) and are planning to receive a partial liver graft from a live donor because the graft artery is short (Fig. 5).

The presence of collateral vessels, arterioportal shunting, and splenorenal shunting are some of the important vascular changes that need to be evaluated in an HCC cirrhotic patient undergoing pretransplant work-up (Fig. 6).

Staging (TNM, Okuda, CLIP, BCLC)

Any staging system should classify patients into subgroups with significantly different outcomes, and should help to direct therapy.[46] Several staging systems have been developed for HCC. Historically, HCC has been classified according to the tumor-node-metastasis (TNM) or Okuda staging system. The TNM system by the American Joint Committee on Cancer is recommended by the International Joint Agency of the American College of Surgeons, and has undergone several revisions since 2002 (Table 1).[70] However, critics of this system argue that it does not have an adequate prognostic accuracy because it is biased to pathologic findings and the liver function is not considered. This is important because accurate staging and selection of liver transplant candidates are based on imaging, not pathologic findings.

As preoperative TNM staging relies heavily on imaging modalities, it may understage as many as 30% of patients. Candidates at stage I or stage II benefit most from transplantation. The Okuda classification takes into account tumor size (either by imaging or at surgery) and liver function (serum albumin and bilirubin levels, and the presence of ascites) to determine stage I, II, or III disease. It allows the identification of end-stage disease patients, but is unable to stratify patients with early or intermediate cirrhosis.[46] The Child–Turcotte–Pugh model for end-

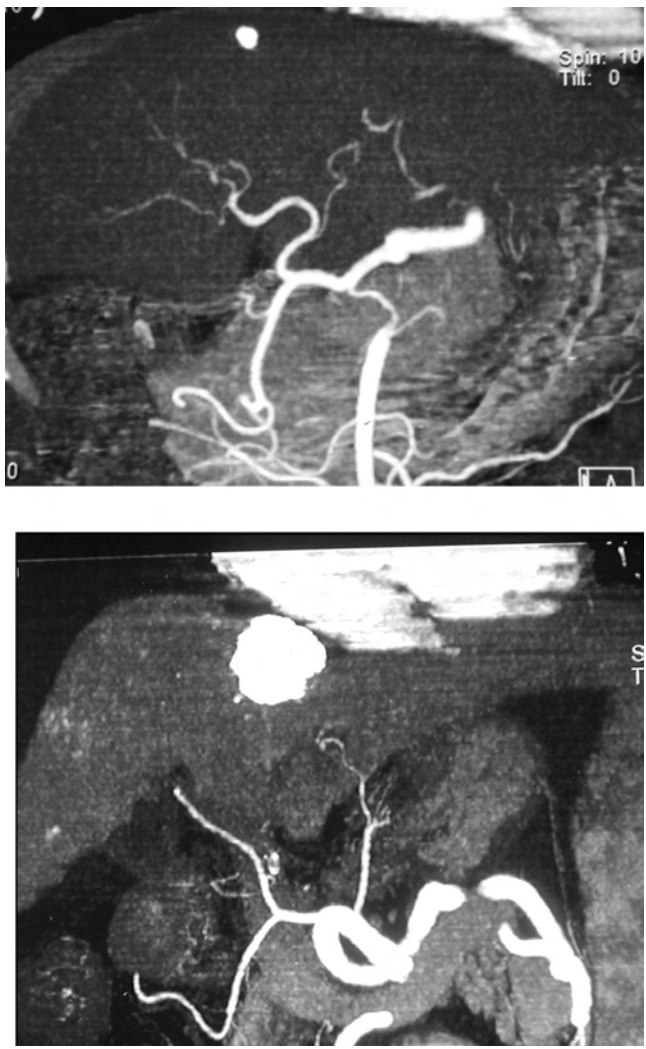
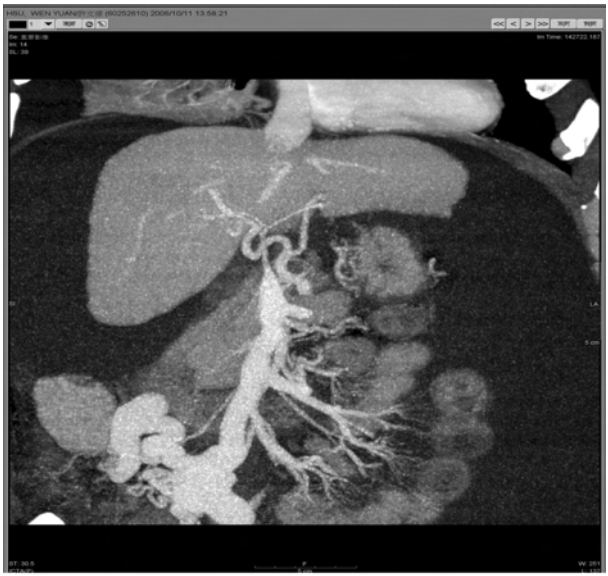
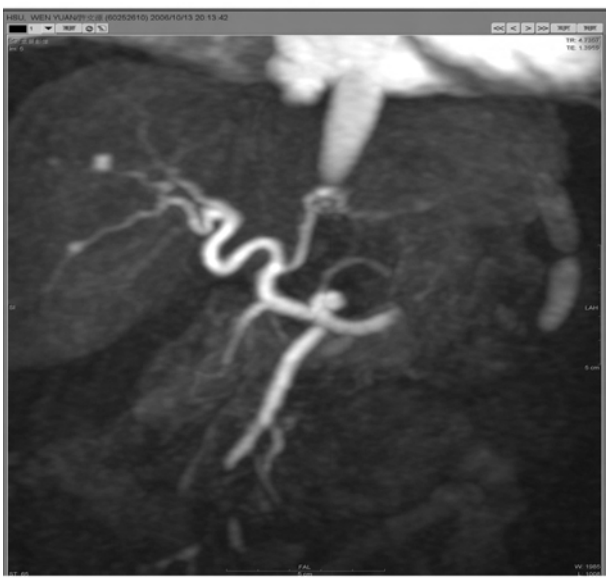


Fig. 5. CT angiography is excellent in demonstrating the hepatic artery, and obviates the need for conventional arteriography.

stage liver disease systems considers only liver function.[71,72] The scheme developed by the Cancer of the Liver Italian Program (CLIP) takes into account the Child–Turcotte–Pugh class, tumor characteristics, AFP



(A)



(B)

Fig. 6. CT angiography shows diminuted hilar and intrahepatic portal vein. (A) Mesenteric collaterals and shunting develop with portal vein occlusion. (B) Highlighted image of the diminuted portal vein.

Table 1. Tumor-node-metastasis (TNM) staging system based on the American Joint Committee on Cancer (6th ed.).

Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor without vascular invasion
T2	Solitary tumor with vascular invasion or multiple tumors not more than 5 cm
T3	Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or tumor(s) with perforation of the visceral peritoneum
Node	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	With regional lymph node metastasis
Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	With distant metastasis
Stage Grouping	*Interpretation*
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage IIIA	T3 N0 M0
Stage IIIB	T4 N0 M0
Stage IIIC	Any T N1 M0
Stage IV	Any T Any N M1

levels, and portal vein thrombosis. The computed CLIP score correlates with median and 1-year survivals (Table 2).[73,74]

These systems of staging are mostly helpful in identifying end-stage patients with a poor prognosis, but do not take into account the effects of previous treatments. Furthermore, they do not indicate optimal forms of treatment for the different stages. The Barcelona Clinic Liver Cancer (BCLC) staging system has recently been validated in U.S. and Italian patients (Fig. 7). It was developed based on the combination of data from different independent studies representing different disease stages

Table 2. Cancer of the Liver Italian Program (CLIP) scoring system.

Score	**0**	**1**	**2**
Child–Pugh stage	A	B	C
Tumor morphology	Uninodular and extension ≤50%	Multinodular and extension ≤50%	Massive or extension >50%
AFP (ng/mL)	<400	≥400	
Portal vein thrombosis	No	Yes	

Score-Survival Interpretation

CLIP Score	**Median Survival (months)**	**1-Year Survival (%)**
0	35.7	84
1	22.1	66
2	8.5	45
3	6.9	36
4–6	3.2	9

and treatment modalities. It includes variables related to tumor stage, liver function, physical status, and cancer-related symptoms. It identifies patients with early HCC who may benefit from curative therapies, and patients at intermediate- or end-stage disease who may benefit from palliative treatments.[75–80] Molecular markers were not used in any of the staging systems.

Prognostic Factors and Selection Criteria

The need to obtain the optimal benefit from the limited number of donor livers that are available has prompted the maintenance of strict selection criteria to list patients with early HCC who have the highest likelihood of long-term survival after transplant. Findings that appear to be important in prognosis include clinical status, liver function, tumor characteristics (size, number, satellite nodule, histologic grade,

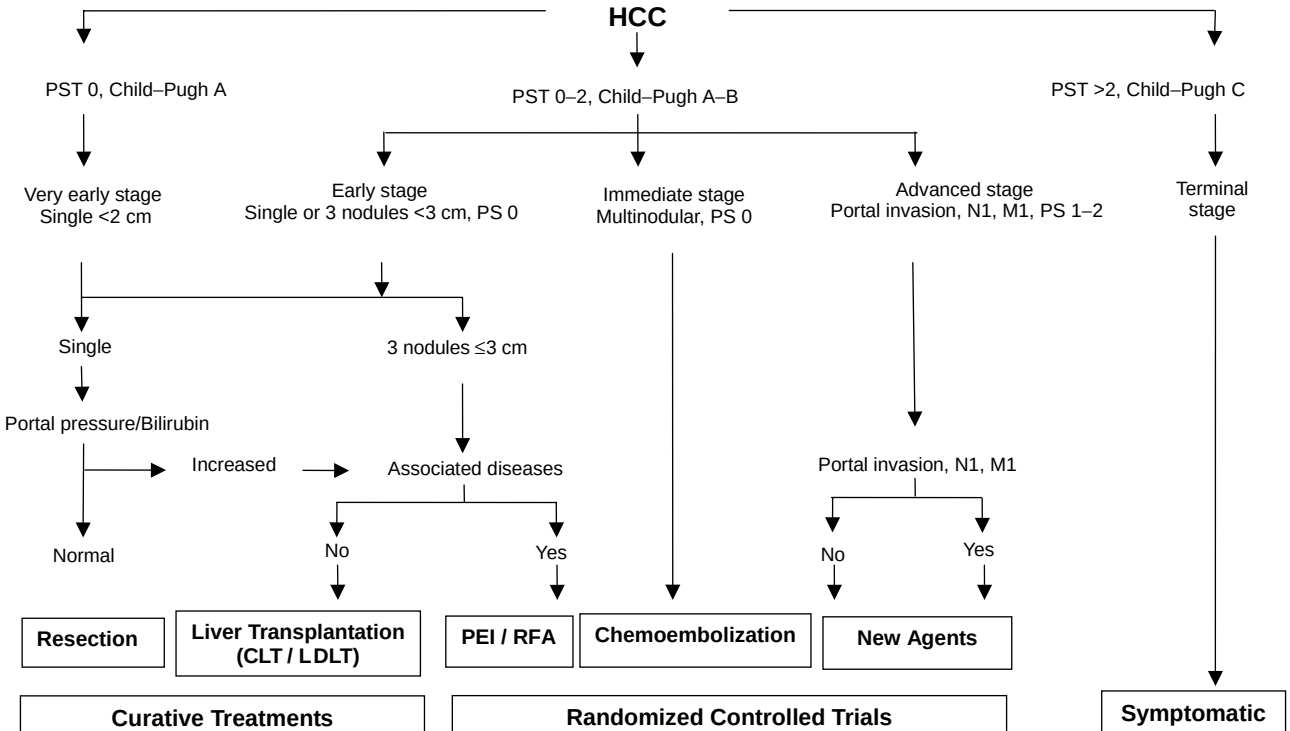


Fig. 7. Strategy and treatment assignment based on the Barcelona Clinic Liver Cancer (BCLC) system. PST, performance status test; CLT, cadaveric liver transplantation; LDLT, living donor liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation. From Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology* **42**:1208–36, 2005. Reprinted with permission.

node involvement, vascular invasion), and serum levels of AFP and DGCP.[81–84]

The Milan criteria framed by Mazzaferro and colleagues[81] showed that excellent results could be achieved in patients with a solitary tumor <5 cm or with up to three nodules smaller than 3 cm (Table 3). The 5-year survival in these patients exceeded 70%. For patients with disease beyond the Milan criteria (which is not extensive) and with no gross vascular invasion or extrahepatic spread seen on radiologic imaging, the survival was comparable to patients transplanted for disease within the standard Milan criteria.

Henceforth, the University of California, San Francisco (UCSF) criteria by Yao *et al.*[85] in 2002 has been advocated to extend the Milan criteria (Table 3). Using the definition for an acceptable 2-year survival to be greater than or equal to 70%, patients meeting the UCSF criteria but exceeding the Milan criteria had a 2-year survival of 86%. Advanced tumor exceeding the UCSF criteria also served reasonably well as a surrogate marker for poorly differentiated tumor grade and microvascular invasion. The UCSF criteria better predicted acceptable posttransplant outcome than the Milan criteria. It is clear that there is some room to expand the criteria, but at present there are limited data to define the new limits. Most published studies that support expansion of the criteria are based on an analysis of explanted livers where the information is not available before transplant.[46]

The most powerful predictor of tumor recurrence in the absence of extrahepatic spread is vascular invasion, be it microscopic or macroscopic.[86,87] Furthermore, vascular invasion runs parallel with

Table 3. Milan and University of California, San Francisco (UCSF) criteria for liver transplantation.

Milan criteria[81]	**UCSF criteria**[85]
1 tumor ≤ 5 cm or Up to 3 tumors, all < 3 cm	1 tumor ≤ 6.5 cm or Up to 3 tumors, all ≤4.5 cm and total tumor diameter ≤8 cm

tumor size and number.[88] Tumor differentiation and molecular markers have been described as influencing poor prognosis, but these remain to be validated. Tumor differentiation has been proposed to be a predictor of microscopic vascular invasion, but its assessment requires biopsy or a previous liver resection.

The development of living donor liver transplantation (LDLT) has stimulated the discussion about expanding the tumor burden limits for HCC patients. Unlike organs from deceased donors, living donation is not regulated by organ distribution and allocation. Transplantation can be done with almost no delay and staging would be recent. Reports from Asia suggest that the outcome of LDLT is the same as with deceased donation. However, the results of patients transplanted for HCC using the Milan criteria versus the extended criteria are different.[89–92] At present, there are few data to support utilizing the expanded criteria.

Organ Allocation (MELD, UNOS)

In 2001, the U.S. Department of Health and Human Services approved HCC as an indication for liver transplant.[93] However, the TNM staging system does not consider the severity of the underlying liver disease and it correlates poorly with survival of patients with HCC. The Model for End-stage Liver Disease (MELD) was implemented in February 2002. The MELD score is based on total serum bilirubin level, serum creatinine, and prothrombin time international normalized ratio to calculate a risk score for mortality while on the waiting list. This model has an excellent ability to predict mortality during a 3-month waiting period.[94–98] Initially, patients with HCC were given additional points for them to receive an organ immediately and to shorten the waiting time so as to avoid tumor progression, eventually leading to waiting list dropout; this system gave an unfair advantage to patients with HCC. Later, adjustments to the MELD score were accepted by the United Network for Organ Sharing (UNOS) for patients with stage II HCC (Policy 3.6.4.4 Liver transplant candidates with hepatocellular carcinoma, under Policy 3.6 Organ distribution: allocation of livers; www.unos.org). The MELD scores continue to be adjusted as experience with this new system is acquired. Outside the U.S., there are few

organ allocation schemes. The European Society for Organ Transplantation (ESOT), comprised of 12 individual organ exchange organizations representing most of Europe and Scandinavia, is another example of an organ utilization model.

Shortening the waiting times by expanding the donor pool has been explored. This includes the use of marginal donors such as donors aged more than 50 years old, donors with fatty livers, viral hepatitis B core antibody–positive[99] and viral hepatitis C antibody–positive donors, non–heart beating donors,[100–102] and donors with extended stay in the intensive care unit. In a recent multivariate study, the use of livers from older donors was associated with increased biliary complications.[103] Split liver transplants, domino transplants from patients with familial amyloid polyneuropathy, and live liver donation are other ways to enlarge the donor pool.[104]

The use of LDLT has been advocated extensively in Asia, where the sociocultural background results in few organ donations.[105–110] The use of living donors has also been reported in centers in the U.S., South America, and Europe.[89–91,105–110] To combat the major ethical issue of organ trading, most live liver transplants utilize living related donors.

Orthotopic Liver Transplantation

Surgical resection offers the best chance of cure for patients with HCC. Unfortunately, in cirrhotic patients with large and multiple or bilobar tumors at the time of initial presentation, surgery is not feasible and the overall survival is short.[111] Liver transplantation is now accepted as the optimal therapeutic measure because it removes not only the tumor, but also the underlying cirrhosis that may progress to dysplasia and HCC in the future.[112] A number of studies have shown encouraging patient survival after liver transplantation for early HCC. The UNOS policy for organ allocation in patients with HCC favors those potential recipients with a limited number and diameter of tumor nodule(s) as defined by the Milan criteria.[81] Liver transplantation can therefore be offered with a good chance of success to only a relatively small proportion of patients.

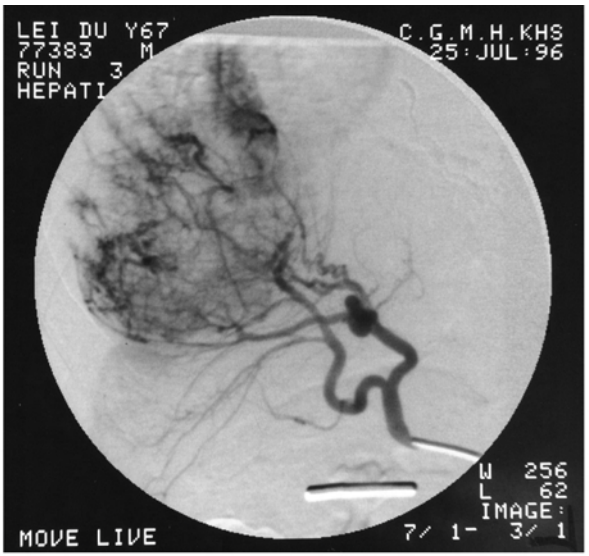
Enthusiasm in liver transplantation for patients with HCC has increased since the mid-1990s because of improved survival. However, strict selection criteria have been largely responsible for the better outcome in patients.[113–119] Other factors that may play a role in improving survival are locoregional therapies which include transarterial lipiodol embolization and chemoembolization (Fig. 8); ethanol injection; RFA; cryoablation[5–15,120]; and systemic adjuvant and neoadjuvant treatments consisting of preoperative, intraoperative, and postoperative chemotherapy. The results of chemotherapy have been largely equivocal.[121,122] The superiority of any one treatment over the other is unclear, and the optimal multimodality approach for HCC is unknown. Notably, however, most transplant candidates have had previous treatment with any of the abovementioned regimens before being referred for transplant evaluation.

With stringent selection criteria, some centers are now downstaging HCC patients prior to transplantation to fit accepted criteria. Successful tumor downstaging can be achieved in the majority of carefully selected patients in order to enable them to undergo transplantation, but longer follow-up is needed to further assess the risk of HCC recurrence after transplant (please also see Chapter 32). Recurrence usually occurs within 2 years after transplant in 60%–70% of recipients. The common sites of recurrence are in the liver allograft, lungs, and bone.

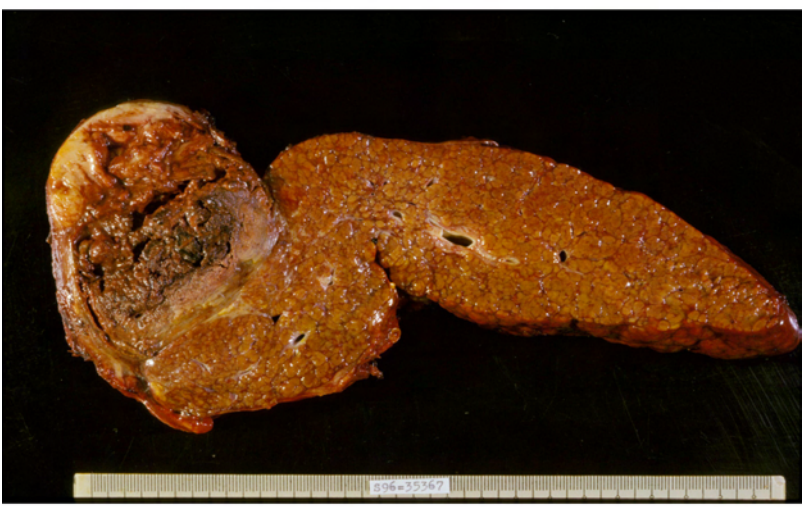
UNOS data between 1987 and 2001 confirmed the steady improvement in patient and graft survivals.[123,124] The reasons for improvement have been largely attributed to better patient selection, identification of prognostic factors, use of adjunctive therapy, newer immunosuppression regimen, and improvements in intensive and anesthesia care (Table 4).

Living Donor Liver Transplantation (LDLT)

LDLT is unique because of the ethical challenge it poses to putting a healthy individual's life at jeopardy in trying to save another's. LDLT was developed to alleviate organ shortage because of a markedly limited deceased donor organ graft supply, and to decrease mortality while on the waiting list.[125] Initially, LDLT was performed only in pediatric recipients using a left lateral section graft. With experience, the



(A)



(B)

Fig. 8. (A) Selective transarterial lipiodol embolization and chemoembolization are common forms of locoregional tumor control pretransplant. (B) Extensive tumor necrosis is seen on explant pathology after transarterial embolization. From Chen CL, Chen YS, Goto S, *et al.* Successful transplantation in a patient with ruptured large hepatocellular carcinoma with diaphragmatic invasion. *Surgery* **127**:228–9, 2000. Reprinted with permission.

Table 4. Outcome of orthotopic liver transplantation in the era of the Milan criteria.*

Study	No. of Patients	Actuarial Survival (%)	
		1 year	5 years
Mazzaferro *et al.* (1996)	48	90	75 at 4 years
Pichlmayr *et al.* (1998)	126	54	27
Bechstein *et al.* (1998)	52	88	71
Llovet *et al.* (1999)	58	84	74
Iwatsuki *et al.* (2000)	344	73	49
Figueras *et al.* (2000)	85	84	60
Yao *et al.* (2001)	70	91	72
Hemming *et al.* (2001)	112	78	57
Tamura *et al.* (2001)	53	79	61
Jones *et al.* (2001)	120	90	71
Margarit *et al.* (2002)	103	81	58

*Modified from Stone MJ. Transplantation for primary hepatic malignancy. In: Busuttil RW, Klintmalm GB (eds.), *Transplantation of the Liver*, 2nd ed., Elsevier Saunders, Philadelphia, PA, 2005, pp. 219. Used with permission.

indications for LDLT have been extended to adult recipients, whereby a right graft is mainly used due to volume requirement. Hepatitis virus–related liver cirrhosis with or without HCC is now the most common indication for adult LDLT.

Decision analysis — taking into account the risk of dropout while on the waiting list, the expected survival of the recipient, and donor risk — suggests that LDLT is a cost-effective approach if the waiting time exceeds 7 months. Although the mortality risk for the donor is low at 0.3%–0.5%, complications may develop in 20%–40% of donors. LDLT should be undertaken by expert surgeons to ensure the lowest donor morbidity and the optimal outcome for recipients.[46] Living donor hepatectomy can be done with minimal blood loss, thereby obviating the need for blood transfusion in donors with its potential consequences.[126,127]

LDLT improves access to transplant.[107,114,128] Because LDLT is not restricted by waiting time and organ allocation from a deceased donor, it offers a substantial advantage for patients with early-stage

HCC who would otherwise have to wait for several months or years for a deceased donor. This is supported by analytical studies that demonstrated the theoretical advantage of LDLT over deceased donor liver transplant (DDLT) based on the latter's long waiting time and dropout rate.[129,130] Despite this theoretical advantage and direct survival advantage of LDLT over DDLT, a higher recurrence rate was observed in an LDLT series reported by Lo *et al.*[128] This observation contradicts an earlier series by Gondolesi *et al.*,[107] who reported that the incidence of recurrence as well as patient survival and freedom from recurrence in LDLT were comparable to results after DDLT.

The observed higher HCC recurrence rate in LDLT when compared to DDLT may be due to the histologic differentiation of the tumor. Since the patient comes with a donor and transplantation is "fast-tracked", there may not be enough time for the tumor to exhibit its biologic behavior or aggressiveness as would have been seen if the patient was allowed the waiting time for tumor progression.[131] Another theory for the high recurrence rate is due to tumor-enhancing effects of cytokines, growth factors, and transcription factors associated with liver regeneration in LDLT.[131] Researchers have associated this theory together with the recurrence of HCV after LDLT. This theory requires the presence of an extrahepatic microscopic tumor at the time of transplantation, since almost all patients are within the standard Milan or UCSF criteria and the surgical techniques are also almost the same.

Again, discussions about expanding the tumor burden limits for HCC patients and extending the criteria for transplantation have been stimulated by living donation. In any case, long-term data are awaited.

Other Issues

Surgical resection has traditionally been and still is the first option offered to HCC patients with resectable tumors without significant portal hypertension and acceptable liver function. This strategy of offering resection as the first treatment option, reserving transplantation for disease recurrence, avoids the unnecessary risks of the early use of immunosuppression. Others advocate early transplantation without resection because recurrence is influenced by tumor characteristics, not

by immunosuppression. Salvage transplantation has been advocated for patients with high pathological risk of recurrence after surgical resection as manifested by microvascular invasion and/or presence of satellite nodule.[132] Age *per se* is not an absolute contraindication to transplant, although an age greater than 60 years is a negative prognostic factor for survival in patients with incidental tumors.[133]

Viral reinfection of the graft either by HBV or HCV is a major concern after transplant, and appears to be the only aspect where preventive treatment is important posttransplant. There are several effective strategies for the prevention of HBV reinfection, including pretransplant and posttransplant use of lamivudine (adefovir and entecavir for mutants), use of hepatitis B immune globulin, and to some extent hepatitis B immunization. However, the situation in patients with HCV is different. The response rate to the combined use of pegylated interferon and ribavirin is less compared to the pretransplant situation. If viral replication persists, it causes damage to the new liver, leading to cirrhosis and ultimately affecting graft and patient survival.[46]

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29

Local Ablative Therapy

Tito Livraghi

Introduction

Percutaneous local ablation therapies (PLATs) are performed using a direct image-guided approach through the liver parenchyma. PLATs may be based on the use of means capable of destroying the tissue chemically, such as with percutaneous ethyl alcohol injection (PEI) or percutaneous acetic acid injection (PAI); or physically, as with interstitial laser photocoagulation (ILP), radiofrequency (RF), or percutaneous microwave coagulation therapy (PMCT). PEI, the first of the PLATs to be proposed, was independently conceived at the University of Chiba in Japan and at the Vimercate Hospital (Milan) in Italy. The first study in an international journal appeared in 1986.[1] On the basis of its rationale and the results obtained, the other techniques were subsequently designed.[2–5]

The range of indications for PLATs is becoming wider than for surgery and intra-arterial therapies. Indeed, whereas for some years only patients with up to three small (3 cm in size) or single (<5 cm in size) lesions were treated (and this still applies at many centers),

with the introduction of the "single-session" procedures under general anesthesia,[6] even patients with lesions greater in number or larger in size are now being treated. This chapter considers only PEI and RF ablation (RFA), which is currently considered the gold standard because of its recent results.

Principles and Techniques

PEI and RFA are generally performed under ultrasound (US) guidance because this real-time control allows faster execution, precise centering of the needle or electrode on the target, continuous monitoring of ethanol or vapor bubble distribution, and determination of the appropriate amount of ethanol or energy to give each time.

Percutaneous ethanol injection (PEI)

Alcohol acts by (1) diffusing within the cells, causing immediate dehydration of cytoplasmic proteins with consequent coagulation necrosis followed by fibrosis; and (2) entering the circulation, inducing necrosis of endothelial cells and platelet aggregation with consequent thrombosis of small vessels followed by ischemia of the neoplastic tissue. Two characteristics of HCC favor the toxic action of ethanol: hypervascularization, and the different consistencies of neoplastic and cirrhotic tissues. Since the neoplastic tissue of HCC is softer than the surrounding cirrhotic tissue, ethanol diffuses within it easily and selectively; while at the same time hypervascularization facilitates its uniform distribution within the rich network of neoplastic vessels.

Conventional PEI is performed in multiple sessions in an ambulatory regimen or, when the tumor is more advanced, in a single session under general anesthesia with the patient hospitalized. The former technique is generally used for a single HCC <4–5 cm in diameter or for multiple HCCs with two or three nodules ≤ 3 cm in diameter. The number of sessions is approximately twice the lesion diameter in centimeters.[7] The latter technique is adopted for more advanced HCCs, single or multiple, that do not occupy more than 30% of the hepatic volume and with no neoplastic thrombosis in the main portal branches or in the hepatic veins.[8] PEI is also performed in selected patients with segmental or

subsegmental portal thrombosis, injecting 1–3 mL of ethanol directly into the thrombus.[9]

More detailed technical information about the procedures are available in several studies.[7–12]

Radiofrequency ablation (RFA)

The treatment of thermoablation with RF exploits the conversion of the energy of an electromagnetic wave into heat. A generator is used to convert normal energy supplied by an electric alternating current of 90 Hz into an RF band of 500 kHz. The current is linked to an active electrode in the form of a needle, which is inserted into the tumor so that the body becomes part of the electric circuit, and is dispersed with a passive electrode in the form of a plate, which is applied to the skin of the patient. In this way, a resistive type of heating is produced, particularly around the exposed point of the needle electrode, due to ionic agitation of the tissue electrolytes that follow the change in direction of the alternating current. Heat is generated by means of impedance (resistance) that the surrounding tissue opposes to the flow of current, so that heat is not generated at the tip of the electrode but within the tissue. The heat produced is given by the difference between the heat generated around the extremity of the electrode and dispersed heat, whose entity depends on the conductivity of the tissue and dissipation by convection due to blood circulation (sink effect). In the presence of a physical and electrical homogeneity, the heat generated around the noninsulated extremity of the electrode is regulated by the distance from the tip, by the intensity of the current, and by the duration of the application.

The most widely used instruments are made by three companies: Radiotherapeutics, Sunnyvale, CA; RITA Medical Systems, Mountain View, CA; and Radionics, Burlington, MA.[13,14] Each of the devices uses a different needle design, wattage, and algorithm. The first two devices use an expandable electrode 1.9 mm in diameter which, once positioned in the tumor, opens out into several retractable curved electrodes around the target like an umbrella. The technique determines a reproducible area of necrosis about 3–5 cm in diameter. The third device utilizes a cold perfusion electrode with a diameter of 1.2 mm, and the tip is exposed for 2–3 cm.[15] By avoiding early increments of impedance linked to

carbonization, such electrodes permit application of a greater power with respect to conventional electrodes. To obtain cooling, a physiological solution brought to 2°C–5°C is circulated within two coaxial lumens situated in the electrode. The technique determines a reproducible area of necrosis of 2.4 cm in diameter. A recently constructed electrode with three cooled tips, permitting a higher current deposition, determines more than 4.5 cm of coagulation necrosis.[16]

To ulteriorly increase the necrotic area obtained with the aforementioned techniques, interruption of the tumor arterial supply by means of occlusion of the hepatic artery with a balloon catheter or the feeding arteries with gelatin sponge particles was proposed.[17]

At the author's center, the therapy plan foresees the completion of treatment in only one session, with an eventual retreatment after the first control of therapeutic efficacy. Since the procedure may be painful, it is performed under sedation/analgesia when one or two insertions are foreseen (in lesions <3 cm), or under general anesthesia with tracheal intubation when a greater number is planned.

More detailed technical information about the procedures are available in several studies.[13–24]

Evaluation of Therapeutic Efficacy

To evaluate the therapeutic response, i.e. to determine whether the tumor has become completely necrotic or whether areas of neoplastic tissue are still present, a combination of investigations and serum assays for tumor markers is used. They are the same as those adopted during initial staging and controls. Since there are many investigations and some of them are comparable, the author prefers to routinely use only contrast-enhanced US (CEUS) (with SonoVue; Bracco, Milan, Italy) and spiral multiscan computed tomography (CT) with the biphasic technique (4–5 mL/s, 20 s and 60 s after the injection of contrast medium). Other image examinations (angiography, magnetic resonance) or biopsy are performed only in rare cases of doubt about a partial or complete response. If the areas of tissue still viable are very small, beyond the present powers of resolution, they will obviously not be recognizable on the images at the end of the treatment. However, they will be easily identified in successive examinations if they are evidenced

as zones of enhancement at CT or CEUS. The response is considered complete when the CT or CEUS scan shows the total disappearance of enhancement within the neoplastic tissue and when the same picture is confirmed at scans performed at successive controls.

The absence of enhancement means the absence of blood flow due to necrotic and fibrotic modifications. Even with such characteristics, the necrotic area occupies space and remains visible in place of the tumor, but is reduced in size to different extents. As tumor markers, alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), which are often complementary, are used. Nevertheless, their assay is useful only if they are initially high. When the imaging techniques show a complete response not followed by normalization of AFP or DCP levels, it means that neoplastic tissue not detected or not yet detectable is growing elsewhere. Moreover, an increase in levels during controls always suggests a local recurrence or the appearance of new lesions. The control with CEUS, CT, and serum assay of tumor markers is carried 1 month after treatment and then every 4–6 months.

Results

Percutaneous ethanol injection

Numerous long-term survival curves have been published. The more important studies in terms of quality and quantity were conducted in Italy and in Japan.[7,10–12] Their 5-year survival in patients with a single HCC $\leq$5 cm or with three or less nodules $\leq$3 cm ranged from 43% to 63%. The main pretreatment factors influencing survival were liver function, tumoral marker (AFP, DCP) level, and number and size of tumors. The main cause of death in Child class A patients was progression of the neoplastic disease due mainly to the appearance of new lesions, while in Child class C patients it was hepatic insufficiency, thus questioning the usefulness of treatment in these patients. The incidence of appearance of new lesions at 5 years ranged from 64% to 87%, i.e. the same rates shown after surgery. The incidence of local recurrences ranged from 4% to 17%, usually due to the persistence of microsatellites around the main tumor. A study showed that complete ablation was associated with significantly improved survival.[25]

Following these results, the European and the American Associations for the Study of the Liver included PEI among the treatments considered effective for early-stage disease.[26] Mortality related to conventional treatment is negligible because only a few anedoctal cases were reported among thousands of patients treated.[27] Major complications are rare, ranging from 1.3% to 2.4%, and are usually treated conservatively (intraperitoneal hemorrhage, cholangitis, jaundice secondary to injury of main bile ducts, liver abscess, hemobilia, arterioportal shunt, shock, segmental hepatic infarction, neoplastic seeding). With the single-session technique, where larger volumes of ethanol are administered, the mortality and the complication rates increase (0.9% and 4.5%, respectively) and other major complications can occur (transient worsening of portal hypertension with risk of hemorrhage from esophageal varices, liver decompensation, transient alcohol intoxication).[8] Studies related to the total cost of treatment reported an average of US$700–US$1000.[7,27]

Some retrospective studies comparing PEI and surgical resection showed broadly equivalent 5-year survival rates, with an approximate rate of 50% for both.[27–30] These data were recently confirmed by a randomized controlled trial (RCT) that compared patients with one or two nodules ≤ 3 cm in size, without statistical differences in recurrence rate and survival.[31]

Radiofrequency ablation

After the initial studies, RFA was immediately compared with PEI for short-term results. In all of the RCTs, RFA showed better local efficacy and required fewer treatment sessions, but presented a higher rate of adverse events.[18,20] In particular, in tumors <3 cm in size, RFA obtained complete ablation in nearly the totality of cases, while PEI obtained approximately 10% less. RFA was also able to obtain a 0.5–1.0-cm safety margin around the tumor, reducing the appearance of possible microsatellites during the follow-up. RFA results were also superior to PEI in tumors of medium and large sizes.[21] Successively, RFA was compared with PEI for long-term results; in all of the RCTs, RFA was superior to PEI with respect to local recurrence, overall survival, and

cancer-free survival.[32–34] Recently, RFA was also compared with resection. Two RCTs, which enrolled patients with a single HCC ≤ 5 cm or with three or less nodules ≤ 3 cm, concluded that overall survival was equivalent, but that RFA was less invasive because of the lower morbidity rate and was less expensive because of the shorter hospital stay.[35,36]

Studies focusing on complications registered a mortality rate ranging from 0.2% to 0.5%, and a major complication rate ranging from 2% to 4%.[37–39] Initially, some unexpected intrahepatic and extrahepatic complications related to the heat damage were reported in different centers (peritonitis due to gastrointestinal tract perforation, bile duct stenosis, biliary fistulas, pleural bile leak due to diaphragmatic injury). The risk of neoplastic seeding was $<1\%$.[40] It is anticipated that additional expertise and knowledge in regard to the use of the technique will help to reduce the complication rate.

Conclusions

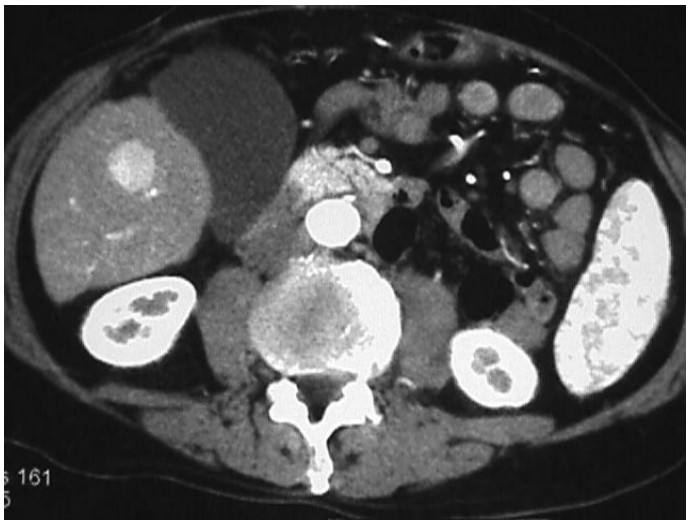
HCC usually coexists with an underlying hepatic chronic disease. According to the stage, one disease will prevail over the other. For such reason, therapies should not worsen liver function. HCC is an organ pathology, so the first nodule detected is only a prelude to others. A study on resected patients demonstrated that multicentricity is already present in 50% of early-stage HCCs and that 93% of patients with a single, minute HCC presented other nodules within 5 years.[41] Being multicentric over time, HCC needs multistep treatments. Therefore, partial resection (or PLATs) can offer a palliative cure, achieving a definitive cure only locally. In fact, according to a Japanese nationwide survey, only 1.6% of all resected patients presenting intrahepatic recurrence were reresected.[42]

Although it is understood that partial resection assures the highest possibility to completely ablate the tumor and possible satellites, different comparative studies based on historical results[27–29] and the recent RCTs comparing surgery and PLATs demonstrated roughly equivalent results.[30,31,35,36] The explanation is probably due to a balance between the advantages and disadvantages of the two therapies, the most

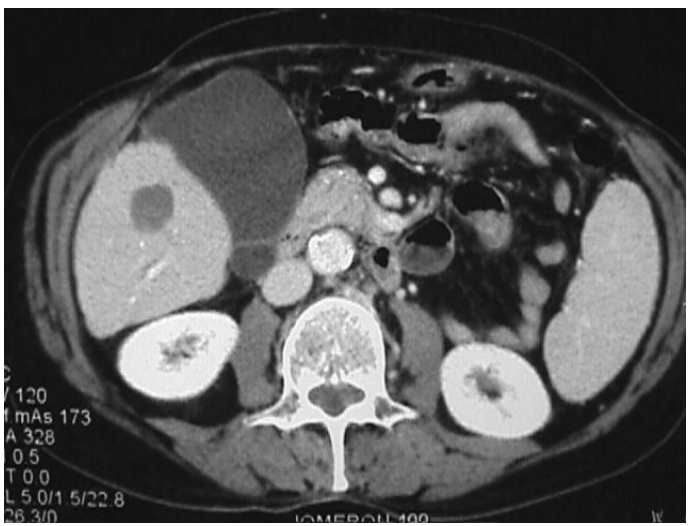
important advantages of PLATs being repeatability, no loss or damage of nonneoplastic tissue, and lower complication rate. Moreover, the overall results of both therapies were hampered by an incorrect selection of patients, some of whom were treated even though they had adverse prognostic factors for that specific treatment. For instance, the Liver Unit of Barcelona reported the usual (mean) 5-year overall survival rate reported by most studies of around 50% after resection[43]; however, when the patients were divided according to two simple adverse prognostic factors, i.e. portal hypertension and abnormal bilirubin, a rate of 74% was obtained (the best so far reported) in patients with normal values and a rate of only 25% in the worst candidates. The fact that the survival of the worst candidates was comparable with two recently reported survival rates of untreated patients (20% and 16%, respectively), even though with a more adverse profile,[44,45] questions the indication for surgery in such patients, who were probably more eligible for PLATs.

These considerations suggest that the best strategy has to be tailored according to the individual presentation of the disease. In a single operable nodule <3 cm, there is no unequivocal evidence to establish the best treatment; accordingly, each referral center follows a personal algorithm for such borderline patients. Currently, RFA is becoming the gold standard for nodules <2 cm; while for nodules between 2 cm and 3 cm, the choice is reached according to individual factors. An open question remains the choice between PEI and RFA, or other ablation procedures. In the author's department, both techniques as well as selective transarterial chemoembolization (TACE) are considered as complementary treatments, and are used according to the features of the disease (i.e. size, number, location, presence of satellites or portal thrombosis) and the response. A multifocal HCC can be treated with only one or with all of the techniques, during a single hospital stay or over the years. For instance, in a patient with four lesions, three nodules can be treated with single-session RFA and the fourth nodule with selective TACE if it is not recognizable at US examination; otherwise, the same lesion can also be treated with a combination of different techniques.

Most lesions are currently treated with RFA (Fig. 1). In multiple HCCs, when recognizable at US examination, RFA obtains greater local efficacy than whole-body or lobar TACE, without its side-effects and



(A)



(B)

Fig. 1. (A) Single small HCC before RFA. Spiral CT scan during arterial phase shows the typical hypervascularization of the nodule. (B) After RFA (single insertion under conscious sedation), the CT scan shows complete absence of contrast enhancement within the nodule, indicating complete necrosis.

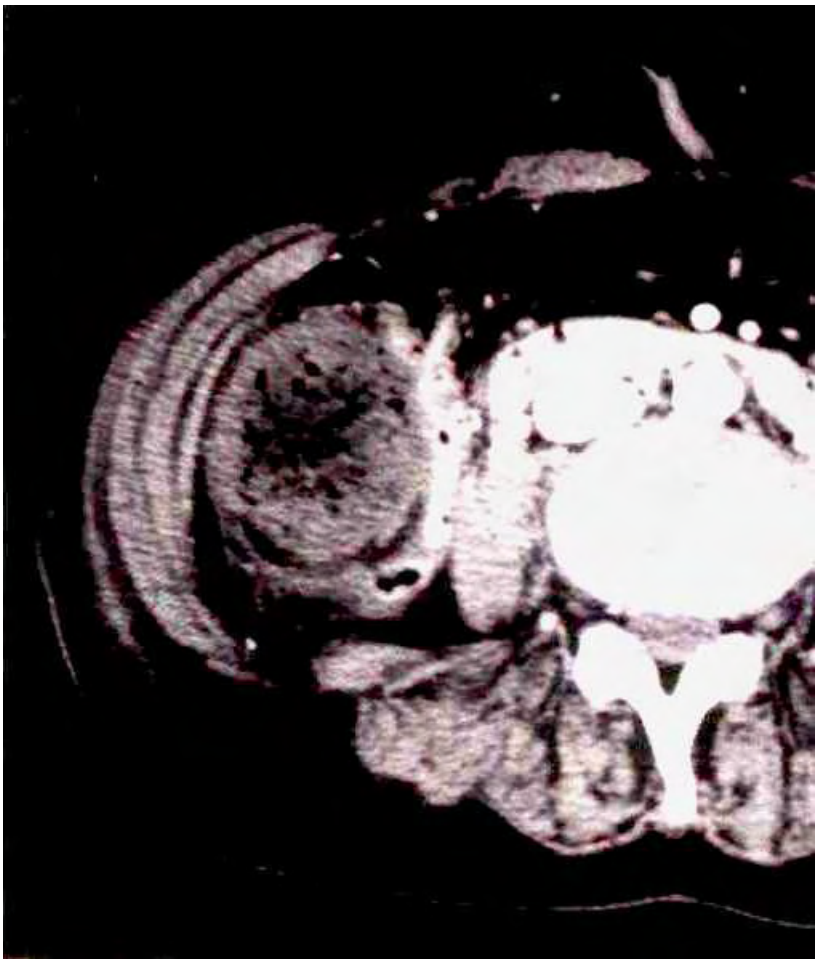


Fig. 2. Single inoperable HCC located in segment 6, surrounded by intestinal loops. Owing to the risk of perforation, one-session PEI under general anesthesia (50 mL of ethanol) was preferred to RFA. Arterial phase CT obtained the day after treatment shows no enhancement inside the tumor, suggesting complete response, and presence of gas by necrosis (normal pattern after ethanol injection, lasting for some days).

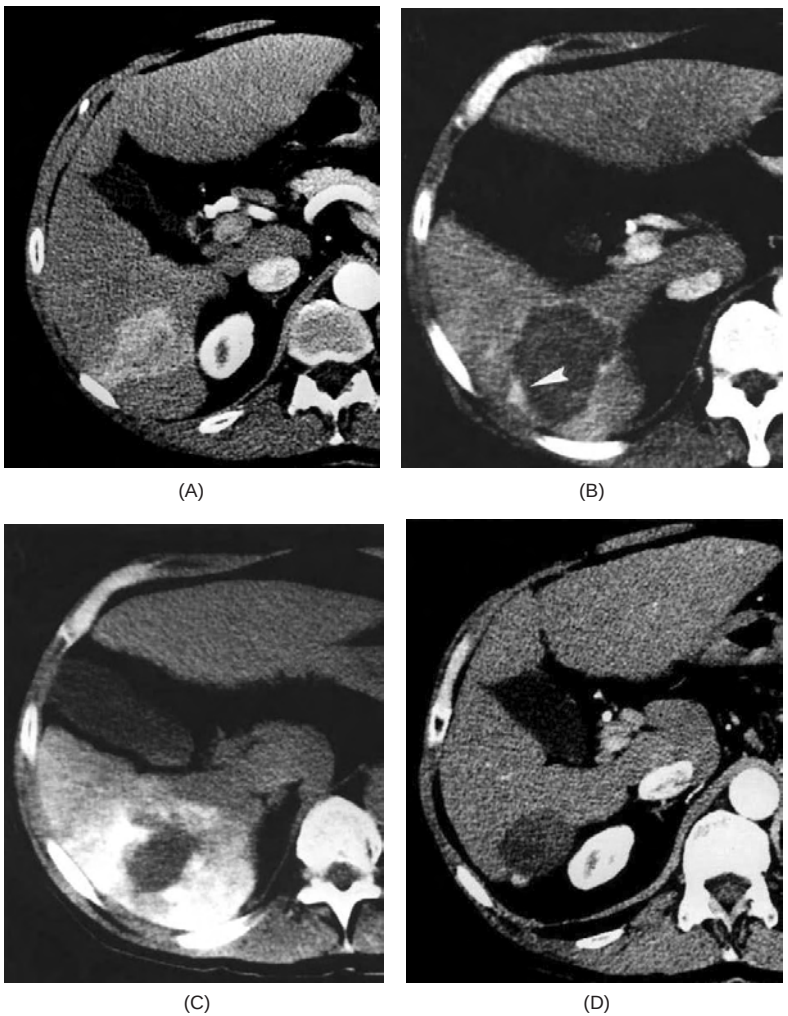


Fig. 3. (A) CT during the arterial phase shows an infiltrating HCC because of extranodular growth, before RFA. (B) CT obtained the day after treatment (5 insertions under general anesthesia) shows near-complete necrosis because of the persistence of a tiny hyperdense vital area (arrowhead). (C) Because the remnant neoplastic zone was unrecognizable at US examination, segmental TACE was performed the following day. CT scan obtained immediately after treatment shows good distribution of lipiodol inside and around the target. (D) CT scan during arterial phase performed 2 years after therapy demonstrates no enhancement inside the neoplastic area treated with RFA and persistence of complete lipiodol uptake (the same hyperdense pattern was visible on previous scans without contrast media) inside the area treated with TACE.

without impairment of liver function.[46] PEI is preferable in lesions at risk with RF (Fig. 2), i.e. those adjacent to main biliary ducts or intestinal loops (above all when fibrotic adhesions between the hepatic capsule and the intestinal wall are suspected because of the risk of perforation), in lesions difficult to treat because of the proximity to large vessels (because of the sink effect), and when a treatable portal thrombosis is present. Selective TACE is used in lesions not recognizable at US examination, in lesions not completely necrotized with the remnant vital tissue scattered or unrecognizable at US examination for additional treatment with RF or PEI (Fig. 3), and in the presence of satellite nodules after the achievement of complete necrosis of the main lesion.

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Regional Therapy

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Introduction

Without specific treatment, the prognosis for inoperable hepatocellular carcinoma (HCC) is very poor. Therefore, nonsurgical interventions have been developed. HCC is well suited to treatment with locoregional therapy because it has a tendency to stay within the liver until an advanced stage of the disease, with distant metastasis generally occurring late. This suggests that an effective local treatment will have a great impact on the course of the disease. Locoregional therapy can be further justified by the fact that patients with HCC usually die of liver failure as a result of local growth and resultant liver tissue destruction, but not as a result of extrahepatic disease.[1–7]

The rationale for regional therapy stems from the difference in the dual blood inflow supply via the portal vein and the hepatic artery between normal liver parenchyma and HCC. Normally, the portal vein is responsible for supplying most (75%–85%) of the blood to the liver, with the hepatic artery providing only a supportive role (20%–25%).

However, this balance is profoundly altered in HCC, whereby the hepatic artery practically becomes the sole supply of blood to the tumor (90%–100%). It is precisely this anatomic configuration that is being exploited in regional therapy: the hepatic artery is used as a roadway to treat the tumor, while the nontumorous liver is least affected.[1–7]

The goal of regional therapy is to cause tumor necrosis and tumor control while preserving as much functional liver tissue as possible, hopefully to prolong life. Regional therapies include transarterial embolization (TAE), transarterial chemotherapy (TAC), transarterial chemoembolization (TACE), and transarterial radioembolization (TARE). In this chapter, we will illustrate the current role of regional therapy in the management of HCC.

Transarterial Embolization (TAE)

Hepatic artery occlusion can be done by surgical ligation at laparotomy or by embolization of the feeding hepatic artery. This may induce ischemia and result in tumor regression. In a prospective randomized controlled trial (RCT) comparing surgical hepatic dearterialization with a control group receiving no treatment, no survival advantage could be demonstrated, with both groups having median survivals of less than 3 months.[8] The effect of hepatic artery ligation (HAL) is only temporary, as the arterial collateral circulations from any of the nearby arteries develop rapidly from 1 week to 4 weeks.[9]

Hepatic artery occlusion can also be carried out by embolization of the feeding hepatic artery to the tumor. It is a safer procedure and has less morbidity than HAL. The agents used for embolization are sterile absorbable gelatin sponge (Gelfoam), stainless steel coils, or polyvinyl alcohol sponge (Ivalon). The choice of embolization agent depends on the size of the artery being embolized. Stainless steel coils and Ivalon particles produce permanent occlusion of the hepatic artery, while Gelfoam produces temporary occlusion. A temporary occlusion allows subsequent intra-arterial treatment after the vessel opens up again.[10]

Two RCTs from Barcelona compared TAE with supportive treatment. Bruix *et al.*[11] investigated the results of TAE with Gelfoam particles and steel coils. Llovet *et al.*[12] conducted a three-arm study that

investigated the results of TACE, TAE with Gelfoam particles, and conservative treatment. Neither study demonstrated a survival benefit of TAE. Although TAE has failed to improve survival, it gives symptomatic control for carefully selected patients. It also remains the treatment of choice for HCC rupture.[1,10]

Transarterial Chemotherapy (TAC)

TAC is defined as the injection of chemotherapeutic agents into the hepatic artery without arterial particle embolization or emulsification of the anticancer drug with lipiodol. As HCCs mainly derive their blood supply from the hepatic artery, infusion of chemotherapeutic agents into the hepatic artery has the theoretical advantage of increasing total drug exposure to the tumor, which may in turn improve tumor cell kill. The aim of TAC is to obtain a higher concentration of cytotoxic drugs within the tumor relative to the systemic circulation, thus improving tumor cell kill and decreasing the side-effects of treatment. Drugs such as 5-FU, 5-FUDR, cisplatin, doxorubicin, and 4′-epidoxorubicin are commonly used in TAC because they have high liver extraction rates and short plasma half-lives.[13]

Various nonrandomized clinical trials suggested that TAC, as a single agent or in combination, appeared to give a better response rate than intravenous treatment. However, interpretation of the results from these studies is hampered by differences in the treatment regimen and response criteria as well as the lack of a randomized study.[14–16] There is a lack of RCTs in TAC. It is worth noting that the toxicity associated with TAC is considerable when compared with intravenous treatment.[1]

Transarterial Chemoembolization (TACE)

In recent years, TACE has replaced TAE and TAC, although there is still insufficient evidence showing that TACE is superior in therapeutic outcome. TACE involves the intra-arterial administration of some form of chemotherapy combined with arterial embolization. Treatment is usually done through the advancement of a catheter in the hepatic artery to the sectional and segmental branches, aiming to be as selective as

possible in order to induce minimal injury to the nontumorous liver. Diffuse multifocal HCC may require catheterization of the common hepatic artery for treatment.

There are at least three modalities of embolization that are commonly used to combine with TAC in order to produce the treatment of TACE:

1. Transarterial chemotherapy and lipiodolization (L-TAC);
2. Transarterial chemotherapy and particle embolization (TAC + E); and
3. Transarterial chemotherapy, lipiodolization, and particle embolization (L-TAC + E).

There has not been any standardized protocol in the choice of chemotherapeutic agent, dosage, dilution, rate of injection, and time interval between the treatments. Similarly, there is no agreement on the choice of embolizing agent, the degree of embolization, and whether the chemotherapeutic agent should be given together with or before the embolizing agent.[3,17]

A number of chemotherapeutic agents have been used, and controversy exists regarding the selection of the most appropriate drug. The most common chemotherapeutic drug used as a sole agent is doxorubicin, followed by cisplatin and epirubicin. The combinations of doxorubicin and cisplatin; doxorubicin and mitomycin; and doxorubicin, cisplatin, and mitomycin C are also common drug regimens.[17,18] RCTs failed to show significant differences in survival between doxorubicin and either epirubicin or cisplatin.[19–21] Only nonrandomized studies showed that cisplatin was more effective than doxorubicin as a single agent for TACE of HCC.[22]

Lipiodol is an iodized ethyl ester of fatty acid derived from poppy seed oil, and contains 38% of iodine by weight or 475 mg of iodine per mL. It has been used as a radiologic contrast medium for many years. Since the observation was made that lipiodol accumulates preferentially in HCC and persists for several weeks or months, it has been used as a suspension medium for chemotherapeutic agents. The exact reason why lipiodol selectively concentrates in and is retained by HCC is not fully understood. Postulations include microvascular entrapment, uptake by

the reticuloendothelial system, membrane adhesion of lipid droplets, or cellular uptake. As the chemotherapeutic agents are water-based, they have to be emulsified with lipiodol, which is an oily medium. Lipiodol is used as a drug-carrying, tumor-seeking, embolic agent in TACE.[1] Mixing lipiodol with chemotherapeutic agents is thought to increase the contact time between drugs and cancer cells.

TACE can also be carried out with particle embolization, which can be temporary by using absorbable gelatin sponge (Gelfoam) or permanent by using stainless steel coils or polyvinyl alcohol sponge (Ivalon). In addition to the different durations of occlusion by these different agents, each of these substances has a different distribution within the liver vasculature as well as a different toxicity and damage to the liver. The optimal particle or substance is still unknown.

Controversy also surrounds the method of delivery of the embolic agents. Some favor mixing the particles in slurry with the chemotherapeutic drug with or without lipiodol, whereas others prefer administration of the particles after the chemotherapeutic agent with or without the infusion or injection of lipiodol. There are data suggesting that injectable volumes of chemotherapeutic agents and long-term arterial patency were improved by embolizing the tumor-feeding vessels only after the entire dose of chemotherapy had been delivered.[23] These results may have a positive effect on the success of TACE because delayed embolization allows multiple TACE sessions through maintained arterial patency. It is generally accepted that hepatic arterial patency is important to the patient, but whether repeated TACE procedures are good is still controversial. On the one hand, it is believed that repeated and multiple treatment of TACE achieves maximal tumor response[24]; on the other hand, repeated procedures can cause progressive liver atrophy.[25] It is therefore not surprising that, in some studies, TACE was repeated at fixed time intervals until the planned number of courses was reached or death occurred[26–28]; while in other studies, repetitions were planned on the basis of tumor response and patient tolerance.[29]

In order to preserve as much functional liver tissue as possible, if technically feasible, it is recommended to carry out selective (segmental and subsegmental) treatment instead of conventional (through the main or the right/left hepatic artery) procedures. The selective approach

provides better results, both in terms of tumor response and patient tolerance.[30–32]

Patient selection for TACE

The indications and contraindications for TACE remain controversial, and it can be somewhat difficult to determine which patients will benefit most from the procedure. The reason for this difficulty stems from the fact that patients with HCC have underlying liver diseases in addition to cancer; there is no doubt that the prognosis is directly linked to the status of both. Because of the intricate relationship between tumor and liver function, traditional staging systems used in oncology (e.g. the tumor-node-metastasis [TNM] system) are irrelevant for patients with HCC. Several prognostic indexes have been developed to stratify baseline liver function and overall patient well-being,[18] including the Child–Pugh classification system,[33,34] the Okuda classification,[35] the Italian Consortium Cancer of the Liver Italian Program (CLIP),[36–38] the Barcelona Clinic Liver Cancer (BCLC) staging classification,[39] and the Chinese University Prognostic Index (CUPI).[40] There is no general consensus on which one is the most reliable (see Chapter 11).

Several predictors of survival have been studied to determine the best candidates for TACE. Patients with poor baseline liver function and large tumors were shown to benefit the least from TACE in most studies.[41–47] More specifically, tumor factors associated with good prognosis after TACE included a tumor diameter of <5 cm,[43] replacement of the liver by tumor tissue of $<50\%$,[44] and a unilobar tumor.[45] The alpha-fetoprotein (AFP) value has also been shown to be a prognostic value.[41,43–46] Llado *et al.*[44] and Takayasu *et al.*[46] showed AFP values >400 ng/mL to be a poor predictive factor. Other prognostic factors included the type of HCC, number of tumor nodules, portal vein thrombosis, presence of tumor capsule, and degree of lipiodol retention.[41–47]

Although contraindications for TACE are still not clearly defined, it is clear that patients with certain conditions should not be treated (Table 1).[3,18] Biliary obstruction does not constitute an absolute contraindication *per se*, but extra precautions must be taken to avoid

Table 1. Contraindications for TACE.

Liver failure/Insufficient liver functional reserve
Inadequate amount of residual uninvolved liver
Inadequate renal function
Extrahepatic tumors
Portal vein thrombosis
Biliary obstruction
Hepatic encephalopathy
Significant arterioshunting through tumor
Severe comorbid disease
Contraindications to angiography
Pregnancy

causing biliary necrosis of the obstructed segment(s) of the liver, which may result in abscess formation. Kim and his associates[48] suggested that the amounts of lipiodol and embolic agents used during TACE should be adjusted to reduce or prevent bile duct injury.[48] Similarly, an obstructed biliary tree should be drained, resulting in biliary decompression and often lowered bilirubin levels, thus allowing TACE to be performed safely. Portal vein thrombosis is often cited as a contraindication to TACE, but there are evidences to support the contrary (see Chapter 33).[49–52] Adjustments to the TACE protocol, however, may be necessary to minimize both the distribution of the chemoembolization material (by superselective catheterization of the hepatic artery) and the degree of embolization. Marked arteriovenous shunting from the hepatic artery to the portal or hepatic veins has also been considered as a contraindication to TACE.[3] However, TACE is still possible in these patients by first embolizing the shunt using gelatin sponge pledgets[18]; this process should occlude the shunt, but preserve the hypervascularity of the tumor. The tumors may then be treated with TACE in the usual fashion.

Complications of TACE

The most common complication of TACE is the postembolization syndrome, which consists of fever, abdominal pain, nausea, vomiting, leukocytosis, and increase in liver enzymes. It can last for a few

hours to a few days. This postembolization syndrome, which has a widely variable manifestation, is experienced after 80%–90% of TACE procedures[3,10,17,18] and is self-limiting. The syndrome is treated symptomatically and, in most patients, decreases in severity with subsequent TACE. The chemotherapeutic and embolizing agents may also cause acute cholecystitis, biliary tract necrosis, pancreatitis, and gastric erosions or ulcers if they are inadvertently injected into these organs. Infection of the necrotic tumor presenting as liver abscess can also happen.[53] An uncommon complication is bile duct injuries after TACE, presenting with subcapsular bilomas, focal strictures of the common hepatic duct or common bile duct, and diffuse mild dilatation of the intrahepatic ducts.[48] Liver failure can develop after TACE in a patient with borderline liver function before the treatment.

TACE in unresectable HCC

Nowadays, TACE is commonly used for the palliation of unresectable HCC. Results of TACE on patients with unresectable HCC must be scrutinized according to survival rather than tumor response, as prognosis strictly depends not only on the cancer progression but also on the severity of the underlying liver disease, the course of which can be accelerated by treatment.[54] Prognosis is also influenced by the nature and activity of the underlying liver disease. Therefore, it is unclear whether the results of Western trials — which mainly include alcoholic or hepatitis C virus (HCV)-infected patients — remain consistent in geographic areas where HCC is commonly associated with hepatitis B virus (HBV) infection or exposure to aflatoxin B, and vice versa. It may also be misleading to draw general conclusions on TACE without taking into account the many technical variations, combination of drugs, dose and frequency of therapy, and various other significant predictors of outcome, as all of these factors can have different degrees of efficacy and safety on the patients receiving treatment.

Many nonrandomized studies have shown significant improvement in patient survival after TACE.[46,55–66] After TACE, a significant tumor response is achieved in 17%–61.9% of patients, but a complete tumor response is rare (0%–4.8%) as viable tumor cells usually remain after

TACE.[67] Most studies on TACE reported survival rates of 60%–88% at 1 year, 30%–60% at 2 years, and 18%–50% at 3 years. Despite these encouraging results, considerable doubts on the effectiveness and safety of TACE still exist because many biases may affect the results of these nonrandomized studies.

The effect of TACE on survival has been compared with supportive care in RCTs. To date, only five RCTs have compared some form of TACE to supportive care; of these, two were reported in 2002 (Table 2).[12,26–28,68] TACE has produced modest survival advantages in two RCTs and in two meta-analyses.[12,17,68,69] It is interesting to note

Table 2. Results of randomized controlled trials of TACE vs. conservative treatment in unresectable HCC.

Study	Number of patients	1-year survival (%)	2-year survival (%)
Pelletier *et al.*[27] (1990)			
TACE (gelatin sponge, doxorubicin)	21	24	N/A
Conservative treatment	21	31	N/A
French Group study[26] (1995)			
TACE (gelatin sponge, lipiodol, cisplatin)	50	62	38
Conservative treatment	46	43.5	26
Pelletier *et al.*[28] (1998)			
TACE (gelatin sponge, lipiodol, cisplatin) + tamoxifen	37	51	24
Tamoxifen alone	36	55	24
Lo *et al.*[68] (2002)			
TACE (gelatin sponge, lipiodol, cisplatin)	40	57	31
Conservative treatment	39	32	11
Llovet *et al.*[12] (2002)			
TAE (gelatin sponge)	37	75	50
TACE (gelatin sponge, lipiodol, doxorubicin)	40	82	63
Conservative treatment	35	63	27

that of the three studies using transarterial chemotherapy, lipiodolization, and particle embolization (L-TAC + E), two showed the treatment to result in survival benefit. Of the studies using transarterial chemotherapy and particle embolization (TAC + E) or transarterial chemotherapy and lipiodolization (L-TAC), none showed the treatment to have any impact on survival. The publication of the two studies which showed TACE to be effective in prolonging the lives of patients with unresectable HCC thus re-establishes the place of TACE in the treatment of unresectable HCC.[12,68] These studies also emphasize the importance of using more strict criteria in the selection of patients for TACE before the patients can benefit from the treatment: patients should not have advanced HCC, there should be no major portal vein invasion, and the liver function should be preserved. Also, the data of these studies stress the importance of the technique employed to perform TACE as well as the timing and number of TACE procedures.

TACE is a valuable therapy with survival benefits in strictly selected patients with unresectable HCC. Further RCTs are needed to assess the best chemotherapeutic agent and the ideal retreatment schedule. It is unknown whether the survival benefits of radiofrequency ablation (RFA) or TACE are similar for patients with unresectable HCC amenable to either treatment. Thus far, only one retrospective study has shown the survival benefits of RFA or TACE to be similar for patients with unresectable HCC amenable to either treatment.[70]

Downstaging of unresectable HCC by TACE to become resectable

TACE has been shown to be able to downstage unresectable tumors to become resectable, thus providing a possible cure for patients with advanced disease.[71–73] The data in the medical literature are still limited. It is still unknown whether the outcome of salvage surgery following tumor downstaging gives a long-term survival comparable to that of resectable HCC after primary resection, but it is clear that salvage surgery following tumor downstaging is beneficial to some patients who present initially with unresectable HCC. It offers great hope to those patients who in the past had a dismal prognosis.[74,75] The role of

salvage surgery after tumor downstaging in improving disease-free and overall survival in patients with unresectable HCC should be further investigated in RCTs (see Chapter 32).

TACE as neoadjuvant therapy before curative liver resection

The high incidence of postoperative recurrence is the main reason for the bad long-term result after liver resection for HCC. Intrahepatic recurrence can represent *de novo* tumor formation in a cirrhotic liver or intrahepatic metastasis of clonally identical neoplasia. No matter how the recurrence occurs, it is generally believed that recurrences arise not because of inadequate resection, but because of pre-existing microscopic tumor foci that were undetected by imaging modalities or because of malignant cells that were disseminated during surgical manipulation. Thus, any neoadjuvant or adjuvant therapy that can decrease or delay the incidence of intrahepatic recurrence will improve the results of liver resection.

Nonrandomized case-control studies showed contradictory results.[76–88] Two RCTs using neoadjuvant TACE showed that neoadjuvant therapy had no impact on disease-free and overall survivals in one study, but decreased in overall survival when compared with a no-treatment control group in another study.[89,90] Two systematic reviews concluded that there is no evidence on the use of neoadjuvant TACE in HCC (see Chapter 32).[91,92]

Adjuvant TACE after curative liver resection

Adjuvant TACE after curative liver resection produces controversial results in nonrandomized[93,94] and randomized studies.[95–97] Three RCTs on adjuvant TACE have been undertaken. In an RCT using adjuvant L-TAC/L-TACE with adriamycin and mitomycin, the treatment group showed a significant improvement in disease-free survival and a trend towards improvement in overall survival.[95] Another RCT using L-TACE with doxorubicin and mitomycin C demonstrated a better overall survival with treatment.[96] In the third study, the addition of systemic chemotherapy to regional chemotherapy in the adjuvant setting

resulted in an adverse outcome. In this RCT using L-TAC with cisplatin and intravenous epirubicin, the treatment group had worse results than the no-treatment control group: while overall survival was the same in the two groups, significantly more patients in the treatment group developed tumor recurrence than in the control group, resulting in a significantly shorter disease-free survival in the treatment group.[97] Two systematic reviews on adjuvant therapy for HCC concluded that TACE has not been shown to improve overall survival or disease-free survival following liver resection for HCC (see Chapter 32).[91,92]

Neoadjuvant/Adjuvant TACE for liver transplantation

Theoretically, liver transplantation is better than partial hepatectomy in the treatment of HCC because liver transplantation removes the tumor and the underlying diseased liver as well as treats portal hypertension. However, given the great discrepancy between the demand for livers and the supply of livers from decreased donors, many potential recipients with HCC either die before the organ becomes available or drop out from the transplant waiting list because of tumor progression. The dropout rate can be as high as 25.0%–37.8% in 12 months. Neoadjuvant therapy has the potential to impede tumor progression and distant spread, thus allowing patients to endure the increasing waiting times for an orthotopic liver transplant. Dissemination of cancer cells is known to happen at the time of liver mobilization and explantation. TACE is the most commonly used form of neoadjuvant therapy for liver transplantation carried out for HCC.

A number of nonrandomized clinical trials have evaluated the effect of TACE alone or in combination with systemic chemotherapy prior to orthotopic liver transplantation, producing good long-term survival results.[98–103] Such good results, however, can still be because of the selection of biologically less aggressive HCCs during the wait for liver transplantation instead of the actual efficacy of TACE. Recently, more published case-control studies failed to show any benefit of neoadjuvant TACE in patient survival. The use of neoadjuvant TACE has not been tested within the context of RCTs, and thus solid evidence supporting

its practice is lacking. Currently, there is no consensus on the optimal neoadjuvant therapy before liver transplantation (see Chapter 32).

TACE for recurrent HCC after curative liver resection

There is little data on the use of TACE for recurrent HCC after curative liver resection. The available data show that the results of TACE are much worse than reresection if the tumors are still resectable.[104] The 1-, 3-, and 5-year survival rates of patients after recurrence treated with TACE ranges from 64% to 87%, 24% to 38%, and 0% to 21%, respectively.[105–107] It is uncertain whether TACE gives better or worse results when compared with local ablative therapy for patients with recurrent HCC.

TACE combined with other treatments

It has been proposed that TACE has synergistic effects with local ablative therapy in large HCC.[108] TACE has been used in combination with percutaneous ethanol injection (PEI) to treat unresectable HCC.[109] By adding PEI after TACE, the texture of the tumor parenchyma is altered and the diffusion of ethanol within tumor tissue is enhanced, thus resulting in a higher rate of complete necrosis. Nonrandomized studies demonstrated that patients who received combined TACE-PEI therapy for unresectable HCC had a good long-term survival.[110–113] Two RCTs on patients with advanced unresectable HCC showed significantly lower recurrence and better long-term survival rates with PEI plus TACE when compared with TACE alone.[114,115] TACE has been used in combination with PEI to treat small HCC with the aim of a cure.[116] An RCT on 52 patients with small HCC (one to three HCC tumor nodules, each <3 cm) showed that combination therapy with TACE-PEI was superior to PEI alone in patients with small HCC.

The effect of TACE in slowing down the blood flow in HCC, in addition to delivering high-dose chemotherapy, is also made use of by combining the treatment with RFA. Preliminary data on unresectable HCC are promising.[117,118] TACE has also been used in combination with other procedures in the palliation of unresectable HCC, including

debulking surgery, cryosurgery, and radiotherapy. No proper RCT has been carried out to evaluate the effects of these combination procedures.

Transarterial Radioembolization (TARE)

External radiotherapy has been regarded as ineffective for HCC because the radiation dose that can be delivered to the tumor is limited by the tolerance of the nontumorous liver. HCCs are relatively radioresistant, while the tolerance of the liver towards irradiation is relatively low. The tumoricidal dose required is at least 120 Gy; however, doses above 30 Gy for whole-liver irradiation may result in radiation hepatitis. The aim of TARE is to deliver the radioisotopes to the liver tumor, where it must reside for a sufficient period to deliver the scheduled dose of radiation. The amount of radiation delivered to the nontumorous liver parenchyma and other organs should be as low as possible. Based on the rationale for regional therapy, most radioactive substances injected through the hepatic artery can be delivered to the tumor, thus giving a favorable uptake ratio of tumor to normal tissue (T/N). This is called selective internal radiation (SIR).[4,6] Patients can be considered for TARE if they have an unresectable HCC but without extrahepatic disease, and if the liver function is satisfactory.

The physical characteristics of radioisotopes determine the suitability of the radioisotope in treatment of HCC. A comparison of the characteristics of the radioisotopes used in the treatment of HCC is shown in Table 3.[4,6] A radioisotope that has a higher energy and deeper penetration is better for large tumors. A greater range irradiates a greater volume of tissue, thus exhibiting a "field effect" which may compensate for any irregular distribution of the isotope within the tumor tissue. On the other hand, such a radioisotope may deposit excessive radiation to the normal liver tissue surrounding the tumor. In this aspect, a radioisotope with a lower energy, lesser penetration, and shorter range may be more suitable for treating multiple and small liver tumors. The cumulative radiation dose to the tumor and adjacent tissues is determined by the energy of the radiation, the physical half-life, and the biologic fate (biologic half-life of clearance). The therapeutic impact on the tumor may be inferred by the dose rate (dose delivered per unit time). Isotopes with

Table 3. Characteristics of the radioisotopes.

	Yttrium-90 (^{90}Y)	**Iodine-131 (^{131}I)**	**Rhenium-188 (^{188}Re)**
Physical half-life	64.2 h	8.04 h	17 h
Type of radiation	Pure β	B&γ	B&γ
β_{max} (MeV)	2.28	0.61	2.11
Cytotoxic range (mm)	11	2.4	10
Mean penetration in soft tissue (mm)	2.5	0.4	3.8
γ-ray (MeV)	—	0.364	0.155

a higher energy and a shorter effective half-life (incorporating both the physical and biological half-lives) have a higher dose rate.

The physical half-life and the type of radiation also determine the potential radiation hazards to other patients and hospital staff. Isotopes with a longer half-life need a longer period of radiation protection procedure; this usually only applies to isotopes with γ emissions. For isotopes with pure β radiation, the requirement for radiation protection is much less as the majority of the radiation can be attenuated by the patient's body. Yttrium-90 (^{90}Y) only emits β-rays with a maximum penetration of 11 mm in soft tissue. This means that the abdominal wall is thick enough to shield off all of the radiation from the ^{90}Y in the liver; only weak secondary X-rays (Bremsstrahlung radiation) can be detected outside the body. Iodine-131 (^{131}I) emits both β-rays and γ-rays. The γ component contributes about 10% of the total radiation dose. This type of radiation can penetrate through the body and allow the distribution of ^{131}I inside the liver and adjacent organs to be detected from outside the body, but at the same time acts as a radiation hazard to the hospital personnel and to the public.

Iodine-131(^{131}I)–Lipiodol

The iodine moiety of lipiodol can be changed to radioactive ^{131}I through an atom-for-atom exchange reaction. ^{131}I-lipiodol has been shown to have a significantly longer half-life in tumor than in normal tissue.

^{131}I-lipiodol emits γ radiation with an energy of 364 keV and a mean penetration of 0.4 mm. The physical half-life is 8.04 days. The radioactive ^{131}I-lipiodol is usually given slowly through an angiographic catheter that is placed in the tumor-feeding branch of the hepatic artery. Since the substance is radio-opaque, the flow of lipiodol is easily traced during injection. By scanning with a gamma camera, the distribution and kinetics of the radioactive lipiodol can be worked out. As lipiodol is degraded within the liver, a trace amount of radioactive iodine is detected in the patient's urine. The thyroid needs to be blocked by nonradioactive iodine before treatment to prevent the uptake of radioisotopes. To allow the radiation to decay to a safe level before hospital discharge, patients need to be hospitalized for approximately 10–14 days, depending on the effective half-life of the radioactive ^{131}I-lipiodol.[1,4,6]

Early studies on therapeutic ^{131}I-lipiodol showed good treatment tolerance.[119,120] Adverse reactions from treatment mainly included fever, mild abdominal pain, nausea, and elevation of liver enzymes. ^{131}I-lipiodol therapy resulted in a 17%–92% response rate for unresectable HCC.[121] Our group[122] published a cohort of 26 patients treated with ^{131}I-lipiodol, with an objective response of 52% and a median survival of 6 months.

The main limitation of ^{131}I-lipiodol is its ineffectiveness in large (>5 cm) tumors. The treatment is more effective for small, solitary, and well-encapsulated tumors, and the response rate to ^{131}I-lipiodol decreases with increasing tumor size. Transarterial therapy with ^{131}I-lipiodol was shown to be superior to systemic therapy in tumors up to 5 cm in diameter, and it may be given to patients with portal vein thrombosis. In the RCT of Raoul *et al.*,[123] the efficacy of treatment with ^{131}I-lipiodol ($n = 14$) was compared to medical support ($n = 13$) in Okuda stage I or II HCC with portal vein thrombosis. The medical support consisted of tamoxifen ($n = 5$), 5-FU intravenously ($n = 1$), and NSAIDs or corticosteroids ($n = 5$). Tolerance was excellent in patients treated with ^{131}I-lipiodol. The actuarial survival of the ^{131}I-lipiodol group was significantly better than that of the medical support group (3-, 6-, and 9-month survival rates of 71%, 48%, and 7%, respectively, vs. 10%, 0%, and 0%, respectively).

^{131}I-lipiodol compares favorably to other regional therapy procedures for palliative treatment of HCC. A multicenter RCT of Raoul *et al.*[124] showed that ^{131}I-lipiodol therapy ($n = 73$) was associated with better patient tolerance and fewer vascular complications than TACE ($n = 69$), although no survival advantage was demonstrated. The 6-month and 1-, 2-, 3-, and 4-year overall survival rates were 69%, 38%, 22%, 14%, and 10% in the ^{131}I-lipiodol group, respectively; and 66%, 42%, 22%, 3%, and 0% in the TACE group, respectively. Reduction in tumor size was similar between the two groups, with complete response in 1 and 0 patient and partial response in 15 and 16 patients in the ^{131}I-labeled lipiodol and TACE groups, respectively. In another comparative study of Bhattacharya *et al.*,[125] patients with unresectable HCC receiving L-TAC ($n = 69$) or ^{131}I-lipiodol ($n = 26$) showed comparable survival rates (6-month survival, 40% vs. 58%; 1-year survival, 25% vs. 25%) with acceptable toxicity in either modality of treatment. Tumor size at 2 months remaining static or partially diminished in the L-TAC and the ^{131}I-lipiodol groups were 55% and 68%, respectively.

Based on the available evidence, ^{131}I-lipiodol therapy is a safe and effective palliative treatment for unresectable HCC. Further RCTs are needed to evaluate its long-term results.

Neoadjuvant/Adjuvant transarterial ^{131}I-lipiodol

The high rate of recurrence after surgical resection of HCC is a major therapeutic challenge. Neoadjuvant/Adjuvant transarterial ^{131}I-lipiodol has been studied to improve the results of partial hepatectomy and liver transplantation for HCC.

A pilot prospective study showed an antitumoral effect in 50% of patients treated by transarterial ^{131}I-lipiodol followed by liver transplantation.[126] Raoul *et al.*[127] further examined the efficacy of preoperative transarterial ^{131}I-lipiodol in 34 patients with HCC, including 29 with cirrhosis. Twenty-five patients had a single hepatic tumor, and the mean tumor size was 5.2 cm (range, 2–15 cm). The patients received between one and three injections of ^{131}I-lipiodol (60 mCi per injection) before surgery. Operations included 14 liver transplants, 13 minor hepatectomies, 6 major hepatectomies, and 1 exploratory laparotomy.

No major toxic effect was observed. There was one complication after lipiodol injection due to acute ischemia of the small bowel. Three of 34 patients died within 28 days. An objective tumor response was observed in 19 of 34 patients, and a complete histological response in 8 of 34 patients. The 5-year survival rate was 48.4% (69% after transplantation and 36% in patients who underwent resection). In the absence of RCTs, it is still unknown whether there is a survival benefit through the use of neoadjuvant transarterial ^{131}I-lipiodol in patients with HCC.

Adjuvant treatment with ^{131}I-lipiodol delivered through the hepatic artery after curative liver resection was first proposed by our group.[128] In our RCT,[128] a single dose of 1850 MBq of intra-arterial ^{131}I-lipiodol given after curative resection significantly decreased the rate of recurrence and increased the disease-free and overall survivals. Subsequently, two French nonrandomized studies also demonstrated favorable results with adjuvant ^{131}I-lipiodol.[129,130]

More RCTs using more patients are necessary to confirm the value of ^{131}I-lipiodol in neoadjuvant and adjuvant therapies (see Chapter 32).

Rhenium-188–HDD/lipiodol

^{188}Re has favorable characteristics for radionuclide therapy and, considering the limited success of ^{131}I-lipiodol for the treatment of relatively large tumors, a switch toward another radionuclide with a higher-energy β emission may yield improved response rates. ^{188}Re emits a γ-ray of 155 keV with an abundancy of 15%, allowing γ camera imaging; and it has a relatively short physical half-life of 17 hours, thus limiting radiation protection problems. Additionally, the radionuclide is eluted from a ^{188}W/^{188}Re generator, which has a long useful shelf-life of several months and provides a good yield of carrier-free ^{188}Re routinely. In phase I trials, the tolerance and the preliminary response rates of ^{188}Re-HDD/lipiodol were promising.[131,132]

Yttrium-90 (^{90}Y) microspheres

^{90}Y is a pure β emitter and decays to stable zirconium-90 with a physical half-life of 64.2 hours. The average energy of beta emission is

0.935 MeV (maximum energy, 2.27 MeV), with a mean tissue penetration of 2.5 mm and a maximum penetration of 11 mm. The mean energy and mean penetration of ^{90}Y is so great that it can be used to treat larger tumors. ^{90}Y microspheres can be delivered either through an angiographic catheter during hepatic angiography or through an implantable arterial port.

There are two absolute contraindications to ^{90}Y microsphere treatment: exaggerated hepatopulmonary shunting, and reflux into the arteries that supply the gastroduodenal region.[133] The sizes of the microspheres range from 20 μm to 40 μm. Therefore, once injected into the hepatic artery, they embed in the tumor vasculature rather than pass to the venous system, as the end arterioles are <10 μm in diameter. The microspheres eventually lodge in the microvasculature of the liver and tumor, remaining until complete decay of the radioisotope. The lung is the next arteriole bed that the microspheres can embed. Arteriovenous shunts in the liver would allow free passage of the microspheres into the venous system and then to the lungs. A simulation test using technetium-99m macroaggregated albumin (^{99}Tc-MAA) is used to predict the radiation dose to the tumor and nontumorous liver before treatment[134–136] and to detect the degree of lung shunting. Tc-MAA is biodegradable and has a similar size as the ^{90}Y microsphere. By injecting a small dose of ^{99}Tc-MAA into the hepatic artery, a gamma camera can be employed to collect the count rates over the tumor, nontumorous liver, lungs, and other organs. The T/N ratio and percentage shunting of ^{99}Tc-MAA to the lungs can then be computed. Typically, if there is an excessive shunting of more than 10%–15%, the patient should not be given the treatment. Giving ^{90}Y microspheres to patients with a high lung shunting results in radiation pneumonitis.[137] The toxicity profile of ^{90}Y microsphere therapy remains low, and the treatment is generally well tolerated. The most common side-effects associated with ^{90}Y microspheres are transient elevations in liver enzymes. Other side-effects include gastrointestinal symptoms such as abdominal pain, nausea, vomiting, anorexia, and gastritis, and occasionally gastric and duodenal ulcers.

The microspheres were developed as carriers for ^{90}Y and come in many forms, which vary greatly in their physical properties.[4,6] Glass

is relatively resistant to radiation damage, is highly insoluble, and is nontoxic. Glass can be easily spheridized in uniform sizes and has minimal radionuclidic impurities. A new type of microsphere developed in the late 1980s has ^{90}Y embedded in a glass matrix from which the yttrium is unable to leak, thus avoiding the most dreaded complication of bone marrow toxicity. Studies with ^{90}Y glass microspheres in the treatment of HCC showed that, even when patients with a significant amount of activity shunted to the lungs and gastroduodenum (as assessed by ^{99m}Tc-MAA simulation) were excluded, gastroduodenal ulceration and gastritis still occurred. These complications, not predicted by the ^{99m}Tc-MAA scan, were attributed to the much higher density (3.29 g/mL) of the glass microspheres compared with the MAA particles, increasing the chances of the microspheres going to the gastroduodenum under gravity. It appears, therefore, that ^{99m}Tc-MAA does not provide a good simulation for the glass microsphere. The second type of microsphere developed utilizes ^{90}Y labeling by an ion–ion exchange reaction. These microspheres are resin-based and have a density of 1.6 g/mL, which is close to that of ^{99m}Tc-MAA particles. Thus, ^{99m}Tc-MAA gives a better simulation for the resin microspheres. The amount of ^{90}Y leaching from the resin microspheres is consistently less than 1%.

Goin *et al.*[138] found that the risk of liver toxicities in patients with unresectable HCC treated with ^{90}Y microspheres increases with increasing pretreatment total bilirubin level and liver radiation dose to a maximum of 150 Gy for a single administration. They also found that the toxicities attributed to treatment resolved over time, and none of the patients studied had confirmed radiation-induced liver disease. Consequently, doses as high as 150 Gy on a single administration and as high as 268 Gy on repeated administrations were well tolerated.

Glass-based ^{90}Y microspheres

The initial development of glass-based ^{90}Y microspheres for the treatment of HCC took place largely in Canada in the early 1990s.[139,140] Glass ^{90}Y microspheres were found to be safe. The low toxicity profile was confirmed by later studies, and the treatment was generally well

tolerated by patients. Other than a transient elevation in liver enzyme levels and mild fatigue and fever, no substantial treatment-related toxicities were observed. Gastrointestinal toxicities occurred in a limited number of patients, but these are preventable with proper knowledge of the visceral arterial anatomy.

In the retrospective series of Geschwind *et al.*,[141] patients with Okuda stage I ($n = 54$) and II ($n = 26$) HCC treated with ^{90}Y microspheres had median and 1-year survival rates of 628 days and 63% as well as 384 days and 51%, respectively. In the retrospective series of Liu *et al.*,[142] 11 patients were treated with ^{90}Y microspheres; of these, 1 patient (9%) had a complete response, 8 patients (78%) had a partial response, and 2 patients (18%) showed no response. Okuda stage II and III patients showed a median survival of 11 months and 7 months, respectively. In the cohort study by Carr,[143] 65 consecutive patients with HCC were treated with ^{90}Y microspheres. The median dose delivered was 134 Gy. Forty-two patients (64.6%) had a substantial decrease in tumor vascularity in response to therapy, and 25 patients (38.4%) had a partial response. The median survival for Okuda stage I patients ($n = 42$) was 649 days (historical comparison, 244 days); and for Okuda stage II patients ($n = 23$), 302 days (historical comparison, 64 days). All patients were followed after therapy for a minimum of 6 months. There were 42 deaths, of which 21 were from liver failure, 6 from HCC progression, and 3 from metastases.

Recently, Salem *et al.*[144] reported a cohort of 43 patients with HCC who were treated with ^{90}Y microspheres over a 4-year period. Twenty patients (47%) had an objective tumor response based on percent reduction in tumor size, and 34 patients (79%) had a tumor response when percent reduction and/or tumor necrosis was used as a composite measure of tumor response. Median survival times of 24.4 months and 12.5 months by Okuda scores I and II, respectively, were achieved. Patients had median survival times of 20.5 months and 13.8 months according to Child class A and class B/C disease, respectively. Patients classified as having diffuse disease exhibited decreased survival and reduced tumor response. There were no life-threatening adverse events related to treatment.

Resin-based ^{90}Y microspheres

Most clinical trials of the resin-based ^{90}Y microsphere treatment for HCC have been performed in Hong Kong.[145–147] We conducted phase I and II studies of 80 patients with unresectable HCC treated with ^{90}Y microspheres; the treatment was well tolerated without major complications. In all patients, the alpha-fetoprotein (AFP) level fell to 41%–0.2% of the pretreatment level. Tumor regression was dose-related. Progressive or static disease occurred in a higher proportion of patients whose tumors received <120 Gy. Survival was better in tumors receiving >120 Gy (median survival, 55.9 weeks) than in tumors receiving lower doses (median survival, 26.2 weeks). The study showed that ^{90}Y microsphere therapy is safe and that tumor response is dose-related. A tumor dose of >120 Gy is recommended.[133] We further conducted an efficacy study on 71 patients with unresectable HCC treated with resin-based ^{90}Y microspheres. There was a 50% or more reduction in tumor volume in 26.7% of patients, and 89% of patients had a significant drop in AFP level.[146] Four of 71 patients with initially unresectable HCC became resectable after treatment; histologic examination of the resected specimens revealed complete pathologic remission in two of these patients. The median survival was 9.4 months.

Based on the available clinical evidence, ^{90}Y microsphere therapy for unresectable HCC is well tolerated and appears to extend survival in a selected group of patients. Further research in this area is warranted.

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31

Systemic Chemotherapy

Thomas W. T. Leung

Hepatocellular carcinoma (HCC) is a prevalent disease in Asia and Africa, and its incidence is also increasing in Europe and North America. Systemic chemotherapy is indicated for patients with advanced HCC who are not suitable for surgery, local ablative therapy, or intra-arterial therapy; however, HCC is resistant to most conventional chemotherapies. The objective response rate of chemotherapy, either single-agent or combination, is generally low and is around 10%–30%. Therefore, more research work should be done in exploring new drugs to treat HCC, and those patients who are considered for systemic chemotherapy should enter into a prospective clinical trial. Occasionally, a small proportion (about 10%) of patients with advanced HCC respond dramatically to combination chemotherapy so that surgical resection becomes possible. Therefore, downstaging with systemic therapy is not entirely impossible for patients who initially have unresectable HCC, and such treatment remains the only chance of a cure for these patients. However, the toxicity of conventional cytotoxic treatment is substantial, especially in patients with borderline liver function. Careful selection of patients for

chemotherapy is therefore important. There is so far no evidence from large prospective randomized studies to suggest that chemotherapy prolongs survival when compared with the control, or that multiple-agent chemotherapy is better than single-agent chemotherapy. However, there is early data to suggest genetic alteration, i.e. different viral etiologies of HCC are related to chemotherapy resistance. New biological agents targeting HCC are now in clinical trials, and some have been found to prolong progressive-free survival when compared with no treatment.

Introduction

HCC is an aggressive illness and often presents at late stages, when patients become symptomatic. Although surgery can offer a chance of cure, most patients (80%) have unresectable disease at presentation and are incurable. Treatment for unresectable but localized HCC includes intra-arterial treatment (chemoembolization, selective internal radiation) and local ablative therapy (radiofrequency ablation, ethanol injection) (Fig. 1). However, a significant proportion of patients are not suitable for these treatment modalities because of extensive local disease,

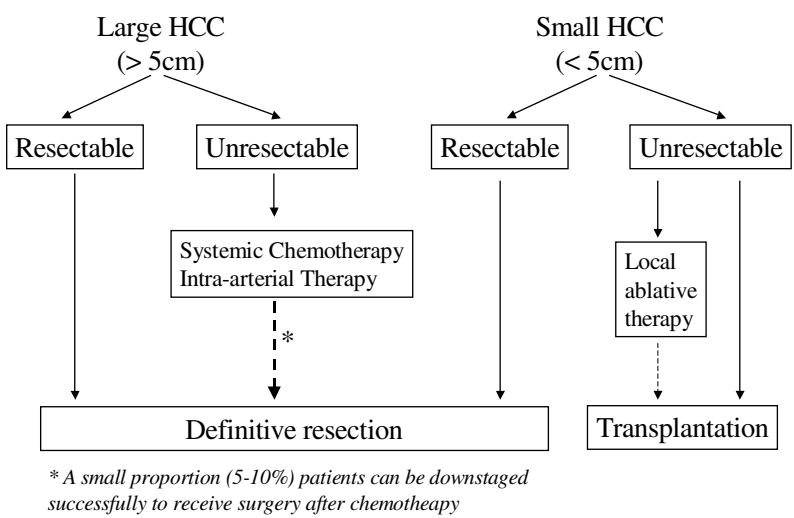


Fig. 1. Management algorithm for hepatocellular carcinoma.

presence of extrahepatic disease, or main portal vein tumor thrombosis. Patients with infiltrative or multifocal HCC are normally poor candidates for intra-arterial therapy or local ablation.

Systemic chemotherapy remains the only option of treatment for these patients, who comprise 20%–30% of HCC patients. Due to the toxicity of conventional cytotoxic treatment and given that most patients with HCC have compromised liver function due to a chronic liver disease background, the selection of patients to receive systemic treatment must be done very carefully, paying particular attention to their liver function and general condition (Karnofsky Performance Status [KPS] or Eastern Cooperative Oncology Group [ECOG] score). The indications for systemic chemotherapy are given in Table 1.

Efficacy of Systemic Chemotherapy

HCC is resistant to most conventional chemotherapeutic agents when compared with other cancers. Response rates for most single-agent cytotoxics are low, and durable remission is uncommon. Although some reports showed a response rate of up to 32%, similar results were not found with repeated studies and the response criteria were not uniform for studies carried out in the 1970s and 1980s (Table 2).

The most commonly used single agents for HCC are the anthracyclines, namely, doxorubicin and 4′-epidoxorubicin. These drugs consistently produce response rates of around 10%–15%. Complete remissions have been described, but seldom last.[1,2] Furthermore, in a

Table 1. Indications for systemic chemotherapy.

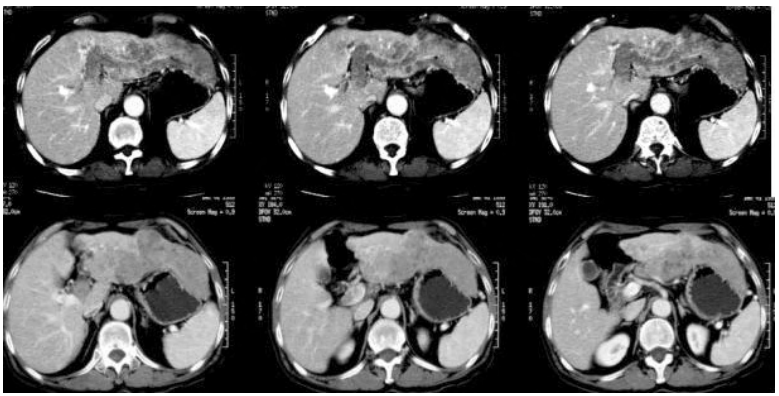
1. Extrahepatic disease
2. Localized disease not suitable for surgery, local ablation, or intra-arterial therapy
3. Main portal vein tumor thrombosis
4. Good performance status (KPS, >70%; ECOG, 1 or less)
5. Acceptable liver function
   a. Total bilirubin <30 μmol/L (or <2 × upper limit of normal)
   b. Albumin >30 g/L
   c. International normalized ratio <1.4

Table 2. Objective response rates to single-agent chemotherapy.

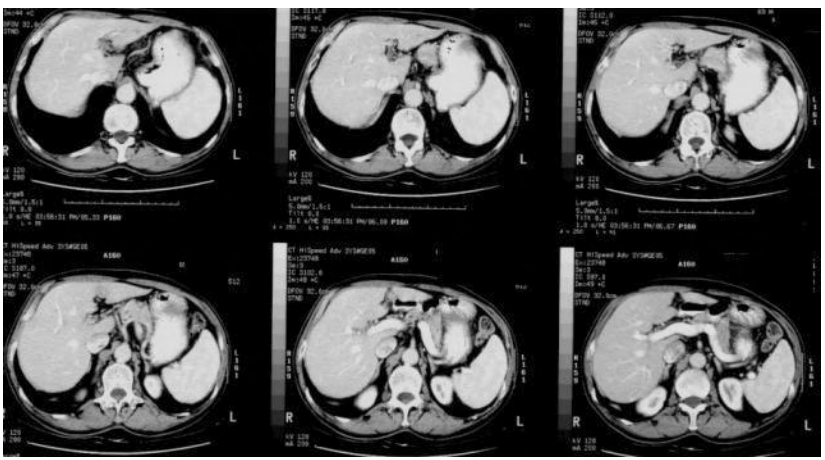
Investigators	Drug	No. of patients	Objective response rate (CR and PR) (%)
Johnson *et al.*[2] (1978)	Doxorubicin	44	32
Chlebowski *et al.*[4] (1984)	Doxorubicin	52	11
Melia *et al.*[5] (1983)	VP-16	24	13
Hochster *et al.*[6] (1985)	4′-epidoxorubicin	18	17
Dunk *et al.*[7] (1985)	Mitoxantrone	22	27
Falkson *et al.*[8] (1987)	Cisplatin	35	17
Lin *et al.*[19] (1993)	Ifosfamide	17	0
Chao *et al.*[10] (1998)	Paclitaxel	20	0
Mok *et al.*[11] (1999)	Nolatrexed	37	0
Yeo *et al.*[12] (1999)	Liposomal daunorubicin	14	0
Halm *et al.*[13] (2000)	Liposomal doxorubicin	16	0
Yang *et al.*[14] (2000)	Gemcitabine	28	18
O'Reilly *et al.*[15] (2001)	Irinotecan	14	7
Leung *et al.*[16] (2002)	T-138067	21	10
Patt *et al.*[17] (2004)	Capecitabine	37	13

CR, complete response; PR, partial response.

systematic review of five randomized trials involving doxorubicin, no significant survival effect of doxorubicin was discernable.[3] The dose-limiting toxicity of doxorubicin is mainly cardiac and bone marrow suppression. Treatment with doxorubicin is relatively contraindicated in patients with concomitant heart disease, and the dosage should be reduced if liver function is poor (total bilirubin more than two times the upper limit of normal). Response to doxorubicin can be seen after one or two courses of treatment, with a reduction in serum alpha-fetoprotein (AFP) level and tumor size. A total of six treatment cycles is usually recommended if a response is documented after two or three cycles of treatment and if the toxicity of treatment is acceptable to the patient. Occasionally, HCC can have dramatic regression with resolution of portal vein thrombosis to allow surgical resection after chemotherapy (Fig. 2).



CT scan before treatment



CT scan after 6 cycles of doxorubicin therapy

Fig. 2. CT scans of a patient before and after single-agent doxorubicin.

Recently, new agents have been found to be useful in other cancers. However, the activity of these agents in HCC is still low and the clinical benefit with single-agent treatment is doubtful. Objective response rates for single-agent chemotherapy in phase II clinical studies are given in Table 2.

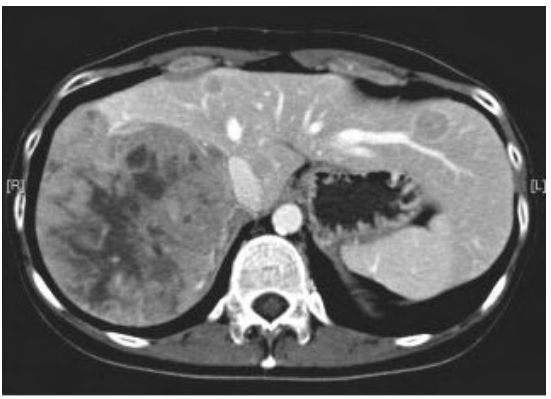
Theoretically, combining different active single agents can improve the response rate. However, combination therapy also carries with it higher toxicity. Most combination chemotherapy regimens include doxorubicin and cisplatin. Although combination chemotherapy seems to have a higher response rate, there has to date been no convincing evidence suggesting that combination chemotherapy is better than single-agent chemotherapy. For both single-agent and combination chemotherapies, the objective response is commonly partial and the duration of remission is short. It is also difficult to compare activity among different regimens because most trials have been single-armed phase II studies. Different response criteria were also used, making interpretation and comparison of results difficult. In general, even for well-selected patients, the expected objective response rates for various single or combination chemotherapies is around 15%–20%. The low response rate of most single-agent and combination chemotherapies is not likely to have a significant impact on survival. Table 3 shows the response rates of combination chemotherapy.

Among various combination chemotherapy regimens, the PIAF regimen was first reported as not just active, but also capable of achieving complete pathological remission.[26,32] It was also first reported to convert 10% of patients to an operable stage after chemotherapy.[26] The PIAF regimen is a combination chemotherapy consisting of cisplatin, interferon-alpha, doxorubicin, and 5-fluorouracil. Patt *et al.*,[32] in a case of disseminated HCC treated with PIAF, reported the resolution of lung metastases and a major response in the local tumor; this tumor was subsequently operated on and a complete pathological remission was documented. In a subsequent phase II study of PIAF, the objective response rate was 26% (all partial response) and the median survival was 8.9 months.[26] Although the response rate was not dramatically high, 9 out of 13 partial responders had their disease rendered operable after chemotherapy. Pathological examination of the resected specimens confirmed complete pathological remission in four patients. The same group has recently updated their results, and reported 15 cases (including the 9 cases reported earlier) of unresectable HCC that underwent surgical resection for the residual lesion(s) after partial response to PIAF.[33] There were 8 complete pathological remissions out

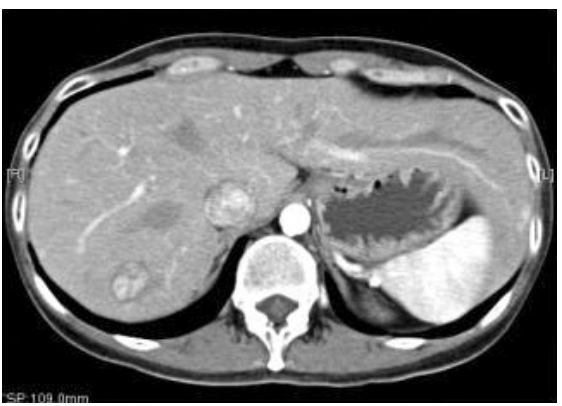
Table 3. Objective response rates for combination chemotherapy.

Investigators	Drug	No. of patients	Objective response rate (CR and PR) (%)
Al-Idrissi *et al.*[18] (1982)	Doxorubicin, 5-FU, mitomycin C	40	13
Falkson *et al.*[19] (1984)	Doxorubicin, 5-FU, MeCCNU	38	21
Ravry *et al.*[20] (1984)	Doxorubicin, bleomycin	60	16
Patt *et al.*[21] (1993)	5-FU, interferon	28	18
Porta *et al.*[22] (1995)	5-FU, leucovorin	25	28
Ji *et al.*[23] (1996)	Cisplatin, interferon α-2b	30	13.3
Bobbio-Pallavicini *et al.*[24] (1997)	4′-epidoxorubicin, etoposide	36	39
Urabe *et al.*[25] (1998)	Methotrexate, 5-FU, cisplatin, interferon α-2b	16	46.7
Leung *et al.*[26] (1999)	Cisplatin, 5-FU, doxorubicin, interferon α-2b	50	26
Ikeda *et al.*[27] (2005)	5-FU, mitoxantrone, cisplatin	51	14
Parikh *et al.*[28] (2005)	Gemcitabine, cisplatin	30	20
Park *et al.*[29] (2006)	Doxorubicin, cisplatin, capecitabine	29	24
Kim *et al.*[30] (2006)	4′-epidoxorubicin, cisplatin, UFT, leucovorin	53	17
Zhu *et al.*[31] (2006)	Gemcitabine, oxaliplatin, bevacizumab	33	20

of the 15 cases; and in the remainder, over 95% necrosis. From these reports, there is now strong evidence showing that complete pathological remission is possible after aggressive systemic combination chemotherapy alone, even for large unresectable HCC. Tumor downstaging to



CT scan before treatment



CT scan after 6 cycle of PIAF

Fig. 3. CT scans of a patient before and after PIAF.

resectable disease is also possible by systemic chemotherapy, so that clinical remission is achievable after combined chemotherapy and surgery. Figure 3 shows a patient who had successful downstaging after PIAF and achieved complete remission after surgery.

Although the new combination is effective in selected patients, the regimen is moderately toxic. There were 2 deaths out of 50 patients on PIAF, due to neutropenic sepsis.[26] Grade 3 or above leucopenia was seen in 34% of patients, and thrombocytopenia in 22%. From a multivariate analysis of 149 patients with unresectable HCC, it was found that better liver function (lower bilirubin, shorter prothrombin time, higher albumin level) and younger age are significant predictors of a response and longer survival.[34]

In Hong Kong, Yeo *et al.*[35] proceeded to perform a phase III prospective randomized study comparing single-agent doxorubicin with PIAF. All of the patients were treatment-naive with unresectable HCC. A total of 180 patients were randomized.[35] The objective response rate for PIAF was 20%; and for single-agent doxorubicin, 10%. The median survival for the PIAF group was 8.67 months; and for the doxorubicin group, 6.83 months. However, both the differences in response rate and survival were not statistically significant.[35] Patients who received PIAF also had more grade 3 and 4 bone marrow toxicity. Therefore, we cannot recommend combination chemotherapy as a standard of care at the present moment.

New Approaches in Systemic Chemotherapy

Recently, new targeted biological agents have been developed in the treatment of breast, colon, and lung cancers. HCC, being a highly vascular tumor, is theoretically suitable for antiangiogenic therapy. The first agent to be tested was thalidomide, but only modest activity was detected (although the side-effects were fewer than with cytotoxic therapy).[36] Another antiangiogenesis agent is bevacizumab. A phase I/II study using single-agent bevacizumab once every 2 weeks reported 1 out of 12 patients with a partial response and no grade III toxicity.[37] HCC also has overexpression of epidermal growth factor receptor (EGFR); erlotinib is a tyrosine kinase receptor inhibitor specific to EGFR, and was found to have a 10% response rate with acceptable toxicities (skin and diarrhea) in patients with HCC.[38] Sorafenib is an oral multikinase inhibitor that targets the Raf kinase and receptor tyrosine kinases, and is now in phase III trials for the treatment of HCC. Early data suggest that

Table 4. Objective response rates for targeted biological agents.

Investigators	Drug	No. of patients	Objective response rate (CR and PR) (%)
Patt *et al.*[36] (2005)	Thalidomide	37	5
Schwartz *et al.*[37] (2004)	Bevacizumab	12	1
Philip *et al.*[38] (2005)	Erlotinib	38	10
Abou-Alfa *et al.*[39] (2006)	Sorafenib	137	8

CR, complete response; PR, partial response.

sorafenib treatment can prolong progression-free survival in patients with advanced HCC.[39] Table 4 lists the response rates for the new biological agents.

Predicting Response to Systemic Chemotherapy

Patients with HCC are commonly associated with liver cirrhosis and compromised liver function. Side-effects from chemotherapy are expected to be significant, but the response rate is generally low. Therefore, careful selection of patients for systemic chemotherapy is important. Besides pretreatment liver function and performance status, which are both important predictors of response, there is emerging evidence to suggest that genetic alteration[40] and different viral etiologies for HCC[41] might also have an impact on chemotherapy resistance.

Conclusions

HCC remains a relatively chemotherapy-resistant tumor. Systemic chemotherapy should not be given to patients who are otherwise suitable for surgery, local ablation, or intra-arterial therapy. Careful selection of patients for systemic treatment can downstage a small proportion of patients to receive surgery after a satisfactory response. New agents that are useful in other cancers should be tested in treatment-naive HCC in a clinical trial setting.

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Neoadjuvant/Adjuvant/Chemoprevention Therapy and Tumor Downstaging

W. Y. Lau and Eric C. H. Lai

Introduction

Surgical resection with complete extirpation of tumor gives the best chance of a cure for patients with hepatocellular carcinoma (HCC). Following curative liver resection for HCC, 50%–90% of postoperative deaths are due to recurrent disease.[1–3] Intrahepatic recurrence is frequently the only site of recurrence, and it happens in 68%–96% of patients.[1–3] HCC commonly arises from chronic viral or alcoholic liver diseases, which are likely to harbor multiple and independent clones of premalignant cells. When these clones are further exposed to continuous carcinogenic insults, unicentric or multicentric carcinogenesis follows. Thus, intrahepatic recurrence can represent either *de novo* tumor formation in a cirrhotic liver or intrahepatic metastasis of a clonally identical neoplasm. No matter how the recurrence happens, it is generally believed that recurrences in the early postoperative period arise not because of inadequate resection, but because of pre-existing microscopic tumor foci that are undetected by imaging modalities[4] or because of malignant cells

that have been disseminated during surgical manipulation.[5–7] In the delayed follow-up period, *de novo* tumor formation in the liver remnant is more likely.

In order to prevent tumor recurrence after curative treatment, the eradication and/or inhibition of such clones of malignant cells is essential. Thus, any neoadjuvant or adjuvant therapy which can decrease or delay the incidence of intrahepatic recurrence, or cancer chemoprevention (defined as the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent the initial phase of carcinogenesis or the progression of premalignant lesions), will improve the results of liver resection. The objectives of neoadjuvant/adjuvant/cancer chemoprevention are to prevent tumor recurrence from the primary tumor or to reduce the incidence of a second HCC from forming, and thus, ultimately, to reduce the likelihood of death from a recurrent HCC.

Neoadjuvant therapy differs from tumor downstaging.[8] In the former, therapy is used preoperatively on resectable tumors with the aim to improve the results of curative liver resection, while the latter is used on unresectable tumors which in the past were believed to be incurable. The aims of neoadjuvant therapy are to reduce the tumor mass, thus making surgery easier, and to destroy microscopic tumor foci. It may also render the tumor less vascular or cause the uninvolved liver to hypertrophy, thus allowing a safer resection or even allowing a less extensive resection to be accomplished if the tumor shrinks in size. There is also the possibility of preventing the spread of tumor cells, as the liver is being manipulated during liver resection. However, neoadjuvant therapy has the main disadvantage of delaying the surgery; this can be detrimental if the tumor fails to respond to the therapy and continues to grow, eventually becoming incurable. There is a distinct risk of a resectable HCC becoming unresectable. Unfortunately, we cannot predict who will respond to the therapy. Neoadjuvant therapy also has the potential to affect the liver function, with a potential increased risk of liver failure after partial hepatectomy.

On the other hand, tumor downstaging is a new concept in the management of advanced and unresectable HCC. With improvements in regional and systemic therapy, some treatments that were originally aimed at palliation can downstage tumors from unresectable to become

resectable because tumors shrink in size, satellite lesions disappear, main portal vein tumor thrombi regress and disappear, and nontumorous parts of the liver hypertrophy.[8–12]

In this chapter, we will discuss the current roles of neoadjuvant, adjuvant, chemoprevention, and tumor downstaging therapy for HCC in liver resection and liver transplantation.

Neoadjuvant/Adjuvant/Chemoprevention Therapy in Liver Resection for HCC

Two systematic reviews on the role of neoadjuvant/adjuvant therapy for HCC treated with partial hepatectomy have recently been published.[13,14] Both reviews concluded that there was no evidence to suggest efficacy of the neoadjuvant/adjuvant protocols. However, more light can be shed on this area if we look at each of these clinical trials in detail. Furthermore, there are recently reported large nonrandomized trials and randomized controlled trials (RCTs) on the new modalities of treatment that have not been included in these two systematic reviews.

Neoadjuvant transarterial chemoembolization (TACE)

TACE involves the intra-arterial administration of some form of chemotherapy combined with arterial embolization.[10] There has not been any standardized protocol in the choice of chemotherapeutic agent, dosage, dilution, rate of injection, and time interval between the treatments. Similarly, there is no agreement on the choice of embolizing agent, the degree of embolization, and whether the chemotherapeutic agent should be given together with or before the embolizing agent. Since the observation was made that lipiodol, a poppy seed oil, accumulates preferentially in HCC, lipiodol has been used as a suspension medium for chemotherapeutic agents. As the chemotherapeutic agents are water-based, they have to be emulsified with lipiodol, which is an oily medium. Lipiodol is used as a drug-carrying, tumor-seeking embolic agent in TACE. TACE can also be carried out with particle embolization, which can be either temporary by using absorbable

gelatin sponge (Gelfoam) or permanent by using stainless steel coils or polyvinyl alcohol sponge (Ivalon). Thus, there are at least three modalities of embolization that are commonly used to combine with transarterial chemotherapy (TAC) in order to produce the treatment of TACE:

1. Transarterial chemotherapy and lipiodolization (L-TAC);
2. Transarterial chemotherapy and particle embolization (TAC + E); and
3. Transarterial chemotherapy, lipiodolization, and particle embolization (L-TAC + E).

The aims of TACE are to induce tumor necrosis and tumor shrinkage, while at the same time preserve as much functional liver tissue as possible. TACE was initially used as a palliative treatment for unresectable HCC. With the promising results in its palliative role, TACE was then studied as a form of neoadjuvant therapy. The place of neoadjuvant TACE on HCC remains controversial, and its effectiveness in preventing tumor recurrence and prolonging survival is not proven. The arguments against the use of neoadjuvant TACE include the following[15–20]: (1) the associated complications of preoperative TACE, such as perihepatic adhesions which render liver resection more difficult; (2) the increased risk of liver failure; (3) a delay in definitive surgery; (4) an increased difficulty in future transarterial treatment for recurrent HCC as a result of the development of collateral neoplastic feeding vessels after embolization of hepatic arteries; and (5) the partial tumor necrosis induced by neoadjuvant TACE, causing the remaining tumor cells to become less firmly attached and more likely to be dislodged into the bloodstream during hepatic resection. Nonrandomized case-control studies showed contradictory results.[15–27] In a recently published large case-control study (treatment arm, $n = 109$; control arm, $n = 126$) from Japan, the 5-year overall survival rate after hepatic resection was significantly lower in the preoperative TACE group (28.6%) than in the control group (50.6%), especially in patients without cirrhosis or with early HCC.[19]

There are only two RCTs on TACE used in the form of neoadjuvant therapy before partial hepatectomy for HCC.[20,28] Both Wu *et al.*[20] and

Yamasaki *et al.*[28] used TACE with doxorubicin (Table 1). Wu *et al.*[20] randomized 52 patients with large but resectable HCC (>10 cm), and they showed a decreased overall survival and a higher extrahepatic recurrence rate (57% vs. 23%) when compared with the control group. Yamasaki *et al.*[28] randomized 97 patients with small HCC (2–5 cm), and they showed that neoadjuvant therapy had no impact on disease-free and overall survivals when compared with the control group.

Based on the currently available clinical evidence, neoadjuvant TACE cannot be recommended for resectable HCC.

Adjuvant regional chemotherapy with or without embolization

Regional chemotherapy can be in the form of TAC or TACE. Adjuvant regional chemotherapy after curative liver resection produces controversial results in nonrandomized and randomized studies.[29–42] A number of case-control studies demonstrated less recurrence and better disease-free or overall survival in patients who received adjuvant regional chemotherapy,[29–32] and two retrospective studies showed favorable results even for resectable but advanced T-stage HCC.[33,34] One recent large case-control study (adjuvant TACE group, $n = 987$; control group, $n = 643$) from China showed that adjuvant TACE after liver resection significantly decreased the incidence of recurrence of HCC at 6 months (22.2% vs. 61.1%), but not at 12 months (78.0% vs. 74.7%) and at 18 months (88.6% vs. 80.1%).[35]

Several RCTs have been conducted on partial hepatectomy for HCC to compare adjuvant regional chemotherapy with a control group, using survival as the outcome measurement, as detailed below (Table 1).[36–40]

Adjuvant regional therapy

Izumi *et al.*[36] and Ueno *et al.*[40] demonstrated better disease-free survival, but not overall survival, for the treatment groups; although Li *et al.*[37] demonstrated better overall survival with treatment.

Table 1. Results of RCTs on neoadjuvant and adjuvant regional chemotherapy in liver resection for HCC.

Study	No. of patients	3-year overall survival (%)	3-year disease-free survival (%)
Neoadjuvant TACE			
Wu *et al.*[20] (1995)			
L-TACE (doxorubicin)	24	33	50
Control	28	60	40
Yamasaki *et al.*[28] (1996)			
L-TACE (doxorubicin)	50	91	54
Control	47	88	42
Adjuvant TACE			
Izumi *et al.*[36] (1994)			
L-TACE (doxorubicin, mitomycin C)/L-TAC	23	57	32
Control	27	53	12
Li *et al.*[37] (1995)			
L-TACE (doxorubicin, mitomycin C)	47	69.5	N/A
Control	47	35.1	N/A
Lai *et al.*[39] (1998)			
L-TAC (cisplatin) + i.v. epirubicin	30	66	18
Control	36	65	48
Adjuvant TAC			
Ono *et al.*[38] (1997)			
TAC (epirubicin) + i.v. epirubicin + oral HCFU	29	72	32
Control	27	82	42
Ueno *et al.*[40] (1999)			
TAC (cisplatin, mitomycin C)	10	72	N/A
Control	11	28	N/A
Ono *et al.*[41] (2001)			
(1) TAC with epirubicin + oral + tegafur; (2) TAC + i.v. epirubicin oral HCFU; (3) i.v. epirubicin	57	48	36.8
Control	51	74	42.2

i.v.: intravenous.

Adjuvant regional and systemic therapy

Lai *et al.*[39] and Ono *et al.*[38,41] demonstrated completely different results in their studies. In the study by Lai *et al.*,[39] 30 patients received a combination of adjuvant systemic intravenous epirubicin and L-TAC with an emulsion of iodized oil and cisplatin, while 36 patients received no adjuvant treatment. Twenty-three of 30 patients in the treatment group and 17 of 36 patients in the control group developed tumor recurrence. Patients who received adjuvant therapy had a significantly higher incidence of extrahepatic metastases (11 patients vs. 5 patients) and significantly poorer disease-free survival (1, 2, and 3-year disease-free survival rates of 50%, 36%, and 18%, respectively, vs. 69%, 53%, and 48%, respectively). They also demonstrated that the adjuvant therapy was associated with a worse overall survival, particularly during the first 2 years after operation, although the difference was not statistically significant.

In the study by Ono *et al.*,[38] the scheduled adjuvant therapy protocol could only be completed in 7.2% of patients, and severe side-effects of chemotherapy and liver failure occurred in 12.5% and 4.2% of patients, respectively. The overall and disease-free survivals were not significantly different in the treated and the control groups. In 2001, Ono *et al.*[41] reported another RCT that included a control group and three different adjuvant chemotherapy protocols in the treatment arm: (1) TAC with epirubicin + oral tegafur; (2) TAC + intravenous epirubicin + oral 1-hexylcarbamoyl-5-fluorouracil (HCFU); and (3) intravenous epirubicin. There were no significant differences in disease-free survivals among the four groups of patients; however, overall survival was significantly better in the control group. In subgroup analysis, they showed that patients with cirrhosis who received adjuvant therapy had significantly worse disease-free and overall survivals when compared to the control group. These RCTs suggest that the addition of systemic chemotherapy to regional chemotherapy in the adjuvant setting results in an adverse outcome.

Neoadjuvant plus adjuvant regional therapy

Lygidakis and Tsiliakos[42] conducted the only RCT (treatment group, $n = 42$; control group, $n = 49$) on the effect of a complex neoadjuvant plus adjuvant regional therapy regimen. The regimen included combined preoperative portal vein chemoembolization, neoadjuvant L-TAC (regional chemotherapy regimen), and adjuvant regional immunochemotherapy regimen. Their results suggested survival benefit in the treatment group. However, the operative mortality of the control group was particularly higher (13% vs. 4%), and the control group had a markedly poorer survival rate when compared with other studies on HCC (3-year survival rate, 15%). The treatment group had a similar survival result as the control group of studies reported by others (3-year survival rate, 55%).

Based on the available evidence, neoadjuvant plus adjuvant regional therapy cannot be recommended for patients who receive curative liver resection.

Adjuvant systemic chemotherapy

Since systemic chemotherapy results in no survival benefit in patients with unresectable and advanced HCC, there are very few studies on adjuvant systemic chemotherapy for HCC. In an RCT using adjuvant systemic chemotherapy with oral HCFU, the treatment improved the disease-free and overall survivals in patients with mild liver dysfunction, but no significant difference could be demonstrated in patients with moderate liver dysfunction.[43] In this study, there was a high rate (44.4%) of incomplete chemotherapy due to the severe side-effects of the therapy. Yamamoto *et al.*[43] suggested that the potential benefits of HCFU on tumor recurrence should be weighed against the risk of adverse reactions in patients with mild liver dysfunction. There has been no RCT or nonrandomized comparative study on adjuvant chemotherapy published in the last decade.

Adjuvant transarterial radioembolization (TARE)

Adjuvant treatment with ^{131}I-lipiodol delivered through the hepatic artery after curative liver resection was first proposed by the authors'

group.[44,45] The idea is to use lipiodol to carry the radioactive ^{131}I to the residual tumor foci in liver remnant after liver resection in order to kill the tumor cells. Lipiodol is an iodized ethyl ester of fatty acid derived from poppy seed oil, and contains 38% of iodine by weight or 475 mg of iodine per mL. It has been used as a radiologic contrast medium for many years. The iodine moiety of lipiodol can be changed to radioactive ^{131}I through an atom-for-atom exchange reaction. ^{131}I-lipiodol has been shown to have a significantly longer half-life in the tumor than in the normal tissue. ^{131}I-lipiodol emits gamma radiation with an energy of 364 keV and a mean penetration of 0.4 mm. The physical half-life is 8.04 days.

Between April 1992 and August 1997, we randomized 43 patients who received curative resection for HCC and recovered adequately within 6 weeks after the operation.[45] Twenty-one patients received a 1850-MBq dose of ^{131}I-lipiodol, while 22 patients received no adjuvant treatment. During a median follow-up of 34.6 months (range, 14.1–69.7 months), there were six (28.5%) recurrences among the 21 patients in the adjuvant treatment group compared with 13 (59%) in the control group. The median disease-free survival rates in the treatment and control groups were 57.2 months (range, 0.4–69.7 months) and 13.6 months (range, 2.1–68.3 months), respectively. The 3-year overall survival rates in the treatment and control groups were 86.4% and 46.3%, respectively. There was a significant increase in disease-free survival and overall survival in the treatment group when compared with the control group.

Subsequently, two French nonrandomized studies also demonstrated favorable results with adjuvant ^{131}I-lipiodol.[46,47] The single-arm prospective trial of Partensky *et al.*[46] ($n = 28$ patients) reported 3- and 5-year overall survival rates of 86% and 65%, respectively. The median time to recurrence detection was 28 months (range, 12–62 months). There was no significant adverse effect of the adjuvant therapy. The other case-control study reported by Boucher *et al.*[47] ($n = 76$ patients) demonstrated a significant difference in survival between the adjuvant ^{131}I-lipiodol group against the no-treatment group (3-year disease-free survival rate, 68.4% vs. 41.5%; 3-year overall survival rate, 91.7% vs. 49.9%). This study also supported the use of adjuvant ^{131}I-lipiodol after resection of HCC. More RCTs with more

patients are necessary to confirm the value of ^{131}I-lipiodol in adjuvant therapy.

Adjuvant immunotherapy

RCTs using adjuvant immunotherapy after liver resection for HCC have been conducted using interferon, adoptive immunotherapy, and tumor vaccine.

Interferon has multiple therapeutic mechanisms, including the direct antiviral effect, immunomodulatory effect, and direct and indirect antiproliferative effects. Ikeda *et al.*[48] randomized 20 patients to either an interferon-β group ($n = 10$) or a control group ($n = 10$) after treatment with surgery or percutaneous ethanol injection (PEI) for hepatitis C virus (HCV)-related HCC. Seven patients in the control group developed tumor recurrence, while only one patient in the treatment group developed tumor recurrence during a median observation period of 25 months. Unfortunately, the endpoint of survival was not measured in this study. Kubo *et al.*[49] randomized 30 patients to an interferon-α treatment group ($n = 15$) or a control group ($n = 15$) after liver resection for HCV-related HCC. Recurrent tumors were detected in 9 patients in the interferon-α group, and in 13 patients in the control group. The 5-year overall survival rate was significantly higher in the interferon group than in the control group (78% vs. 48%). Unfortunately, the number of patients in this study was too small. Recently, Sun *et al.*[50] randomized 236 patients into an interferon-α treatment group ($n = 118$) and a control group ($n = 118$) after resection of hepatitis B virus (HBV)-related HCC. They found that the median disease-free survival (31.2 months vs. 17.7 months) and the total number of recurrence ($n = 67$ vs. $n = 71$) were not statistically significant. However, the overall survival in the treatment group was significantly better than that in the control group (median survival, 63.8 months vs. 38.8 months). They suggested that this difference was due to the delayed and decreased severity of recurrence after interferon-α treatment, rendering secondary local ablative treatment and resection possible.

Adoptive immunotherapy involves the removal of the patient's own lymphocytes, the generation of tumoricidal immune effector cells, and the reinfusion of these effector cells into the tumor-bearing host. Takayama *et al.*[51] randomized 150 patients to receive adoptive immunotherapy ($n = 76$) or no treatment ($n = 74$) after curative liver resection for HCC. Autologous lymphocytes activated *in vitro* with recombinant interleukin-2 and antibody to CD3 were infused five times during the first 6 months after surgery. The adoptive immunotherapy group had a lower recurrence rate (45% vs. 57%) and a better disease-free survival (37% vs. 22%) than the control group after a median follow-up of 4.4 years; however, the overall survival did not differ significantly.

Cancer vaccines are an active specific immunotherapy using the patient's own tumor to elicit a long-term cell-mediated immune response, which has been studied in melanoma, renal cell carcinoma, and colon carcinoma. The vaccine containing human autologous HCC fragments essentially showed no adverse effect in a phase I/II clinical trial.[52] Peng *et al.*[53] randomized 50 patients to a vaccine group ($n = 24$) or a control group ($n = 26$) to study the effects of adjuvant autologous tumor vaccine on tumor recurrence after partial hepatectomy for HCC. The study suggested a decrease in tumor recurrence with tumor vaccine. The 1-, 2-, and 3-year recurrence rates of the treatment group were 16.7%, 29.2%, and 33.3%, respectively; while those of the control group were 30.8%, 53.8%, and 61.5%, respectively. The time to first recurrence in the treatment group was significantly longer than that in the control group. No survival data were provided in this study.

The real benefit of adjuvant immunotherapy in HCC requires further and bigger randomized trials to establish.

Chemoprevention with vitamin analog therapy after curative liver resection

Retinoid is collectively termed as vitamin A (retinol) and its derivatives. Polyprenoic acid is a synthetic acyclic retinoid that inhibits experimental hepatocarcinogenesis and induces differentiation and apoptosis of human HCC-derived cell lines. Muto *et al.*[54] randomized patients who had curative resection or PEI for HCC to receive either polyprenoic acid

($n = 44$) or placebo ($n = 45$) for 12 months. After a median follow-up of 38 months, significantly less patients treated with polyprenoic acid (12 patients or 27%) developed recurrence or new HCC when compared with placebo-treated patients (22 patients or 49%).

Vitamin K is a fat-soluble vitamin that can be either naturally produced (vitamins K_1 and K_2) or chemically synthesized (vitamin K_3). Vitamin K inhibits the proliferation of tumor cells *in vitro* at decreasing potency from vitamin K_3 to vitamin K_1, although the mechanism is not understood fully. Menatetrenone, a vitamin K_2 analog, was studied in a recent pilot RCT in 61 patients after curative liver resection or local ablative therapy, and the result suggested that menatetrenone may have a suppressive effect on recurrence of HCC and a beneficial effect on survival.[55] The 1-, 2-, and 3-year cumulative recurrence rates in the treatment group were 12.5%, 39.0%, and 64.3%, respectively; and the corresponding recurrence rates in the control group were 55.2%, 83.2%, and 91.6%, respectively. The 1-, 2-, and 3-year cumulative survival rates for the treatment group were 100%, 96.6%, and 87%, respectively; while the corresponding survival rates for the control group were 96.4%, 80.9%, and 64%, respectively.

The beneficial role of vitamin A or K analog in the chemoprevention of HCC requires further and bigger randomized trials for confirmation.

Neoadjuvant/Adjuvant Therapy in Liver Transplantation for HCC

Theoretically, liver transplantation is better than partial hepatectomy in the treatment of HCC because liver transplantation removes the tumor and the underlying diseased liver as well as treats portal hypertension.[2] For liver transplantation carried out for a solitary HCC up to 5 cm in diameter, or for no more than three tumor nodules each 3 cm or less in diameter (Milan criteria), the 4-year overall and disease-free survival rates were 85% and 92%, respectively.[56] The 5-year overall survival rates after liver transplantation were as good as 58%–69%.[57,58] However, given the great discrepancy between the demand for and the supply of livers from decreased donors, many potential recipients with HCC either die before the organ becomes available or dropout from the

transplant waiting list because of tumor progression. The dropout rate can be as high as 25%–37.8% in 12 months.[59,60] A variety of bridging therapies, such as TACE and local ablative therapy, have been developed to deal with this problem.[61] It is expected that these bridging interventions slow down tumor progression, decrease tumor cell dissemination during recipient hepatectomy, and lower the risk of postoperative recurrence, with no or very little side-effects.

Currently, there is no consensus on the optimal neoadjuvant therapy before liver transplantation. Although most people would agree that neoadjuvant therapy is useful, no definitive evidence has been produced so far on its efficacy in increasing patient survival and in decreasing tumor recurrence rates after liver transplantation. The questions of when to commence the therapy and what treatment to give remain unanswered.

Neoadjuvant TACE

TACE is the most commonly used form of neoadjuvant therapy for liver transplantation carried out for HCC. It is reassuring to note that TACE before transplantation does not increase the risk of hepatic artery complication (e.g. thrombosis) after liver transplantation.[62] For technical reasons, TACE has not been used as an adjuvant therapy following liver transplantation. A number of single-arm studies have demonstrated good long-term survival results.[63–65] Such good results, however, can still be because of the selection of biologically less aggressive HCCs during the wait for liver transplantation instead of the actual efficacy of TACE.

Recently, more published case-control studies failed to show any benefit of neoadjuvant TACE in patient survival.[66–68] In the large multicenter case-control study conducted by Decaens *et al.*[67] on 100 patients who received TACE before liver transplantation and 100 control patients who received no treatment, the overall 5-year survival was 59.4% with TACE and 59.3% without treatment. The use of neoadjuvant TACE has not been tested within the context of RCT, and thus solid evidence supporting its practice is still lacking.

Neoadjuvant local ablative therapy

Local ablative therapy is considered to be the best treatment option for patients with cirrhosis and a single, nodular-type HCC <5 cm or as many as three HCC lesions each <3 cm when surgical resection or liver transplantation is not suitable.[2,9,69] Radiofrequency ablation (RFA) has emerged as the most effective method for percutaneous treatment of early-stage HCC.[70] Recent studies have shown that RFA can achieve more effective local tumor control than PEI and with fewer treatment sessions.[71] Llovet *et al.*[72] reported that RFA for HCC was associated with a high risk of tumorous seeding of 12.5%. Tumor seeding was associated with subcapsular tumor location, poorly differentiated tumors, and a high alpha-fetoprotein (AFP) level. More recent trials on a larger number of patients showed that the tumor seeding rate after RFA was just 0.3–0.9%.[73,74] Fontana *et al.*[75] showed no patients having evidence of tumor seeding on post-RFA imaging, at liver transplantation, or in the explant.

The role of local ablative therapy before liver transplantation remains unclear. The retrospective case-control study of Johnson *et al.*[76] showed that neoadjuvant treatment before transplantation with tumor ablation was associated with a longer waiting period on the transplant list (median time, 484 days vs. 253 days). The cost-effective analysis of Llovet *et al.*[77] showed that local ablative therapy during the wait for liver transplantation increased the patients' life expectancy by 5.2–6.7 months with a marginal cost of approximately US$20 000/year of life gained in all cases, and that the treatment was cost-effective for all waiting times. Nonrandomized studies showed local ablative therapy to be a safe treatment for small HCC in patients with cirrhotic liver awaiting liver transplantation.[78–82] However, the number of published studies on local ablative therapy used as neoadjuvant therapy for liver transplantation remains small. There are neither RCTs nor well-designed comparative studies in this area.

Histological evidence in the explanted liver after liver transplantation validates RFA to be an effective treatment for small (<3 cm) HCC.[81,82] Tumor size (>3 cm) and time from treatment (>1 year) predicted a high risk of tumor persistence in the targeted nodule.[81] It is still unclear

whether local ablative therapy allows patients to wait longer for liver transplant and eventually affect the long-term outcome. The relationship between the extent of tumor necrosis after local ablative therapy and the survival outcome is also unknown.

Neoadjuvant multimodality therapy

RCTs showed that combination therapy with TACE-PEI was superior to PEI alone in the treatment of small HCC.[83,84] However, the role of multimodality therapy before liver transplantation has not been evaluated in RCT. The number of studies in this area is small, and there is also a lack of comparative studies comparing multimodality treatment with single-modality treatment before liver transplantation.[85–87]

Neoadjuvant/Adjuvant systemic chemotherapy

The rationale for neoadjuvant systemic chemotherapy is to eradicate the growth of already-established microscopic extrahepatic tumors at the time of liver transplantation and to reduce the risk of tumor seeding during manipulation of the liver during recipient hepatectomy. Two RCTs have been conducted on early and advanced T-stage HCC. These studies compared neoadjuvant and adjuvant systemic doxorubicin with no additional treatment in liver transplantation.[88,89] Both studies failed to show any benefit in the overall and disease-free survivals with treatment.

Salvage Surgery After Tumor Downstaging of Advanced HCC

In general, most surgeons would agree that partial hepatectomy for HCC should only be carried out when the surgery is curative and when the risks of operative morbidity and mortality are reasonably low. However, most patients with HCC are still diagnosed at an advanced stage; only a small proportion of patients are amenable to curative surgical resection at the time of diagnosis. The median survivals for patients with unresectable early and advanced tumors are 6–9 months and 1–2 months, respectively.[1,2]

"Salvage surgery after tumor downstaging" is a new concept in the management of advanced and unresectable HCC. HCCs that are initially unresectable may become resectable because of the disappearance of some tumor nodules, the shrinkage of a large HCC, and the enlargement of the nontumorous part of the liver. This concept is not unique for HCC; indeed, it was reported with good results in other unresectable hepatic malignancies such as hepatoblastoma, colorectal liver metastases, and undifferentiated (embryonal) liver sarcoma. However, the number of studies on HCC in the literature is small[12,20,90–94] because most clinicians do not realize the potential beneficial outcome of tumor downstaging and salvage surgery, and most patients with unresectable advanced HCC are labeled as "incurable HCC" from the very beginning.

Indication and prerequisites for salvage surgery and tumor downstaging

Obviously, patients who are not candidates for partial hepatectomy because of poor general condition or decompensated liver function are not candidates for tumor downstaging and salvage liver resection. For the other patients, the general criteria of unresectability of HCC commonly employed by surgeons include large-sized tumor with insufficient hepatic remnant after liver resection, extensive and multifocal bilobar tumors, extrahepatic spread of the disease, and tumor with main portal vein tumor thrombus/hepatic vein/inferior vena cava (IVC) involvement.

There are several prerequisites for a successful tumor downstaging and salvage surgery treatment regimen for HCC: (1) an effective treatment that can shrink the tumor in a significant proportion of patients; (2) close radiological monitoring of the tumor response to the treatment; (3) repeated assessment by a liver surgeon with a view to carry out liver resection at the right time; and (4) an aggressive surgical approach to liver resection.

Several tumor downstaging regimens such as TACE, TAC, TARE, and systemic chemoimmunotherapy have been used. However, it is still unknown which regimen is more effective. The selection of the tumor downstaging regimen depends on many factors including the general condition of the patient, the tumor stage, the liver function of the

patient, the patient's preference, and the availability of expertise. For HCC with extrahepatic involvement, regional therapy would not be useful and systemic therapy is the only option. For HCC with main portal vein thrombosis, TACE or TARE is generally considered as contraindicated.

Rationale for salvage surgery after successful tumor downstaging

In order to induce complete remission, liver resection after tumor downstaging is required even when the tumor has shown complete necrosis radiologically or when the patient's serum AFP level has returned to normal. The rationales are as follows:

1. There is a lack of good correlation between complete tumor necrosis as shown radiologically/biochemically and histopathologically. In the study reported by Fan *et al.*,[91] 10 of the 14 patients who had raised AFP levels before, but normal AFP levels after, tumor downstaging treatment were found to have histopathological evidence of viable tumor cells.
2. It has also been shown that the degree of necrosis in the tumor after downstaging therapy had no impact on the long-term survival of patients.[12]
3. The behavior of the tumor after complete tumor necrosis has been induced by the downstaging therapy and, as shown radiologically, is unknown. The residual tumor cells after tumor downstaging may be biologically more aggressive. Surgery is therefore necessary to remove these tumors before these residual tumor cells regrow, and to provide the pathological information about the tumor and its response to the tumor downstaging treatment.

Results of salvage surgery after tumor downstaging

Tumor downstaging with TACE

In a retrospective study by Majno *et al.*,[22] the impact of L-TACE on 49 patients with initially resectable or unresectable HCC who subsequently underwent liver resection or liver transplantation was studied.

Computer tomography (CT) scanning was performed 4 weeks after TACE. The overall rate of tumor downstaging after TACE was 42%. Complete tumor necrosis occurred in 50% of patients; of these patients, five patients with initially unresectable HCC received salvage liver resection after tumor downstaging. The survival of these five patients with initially unresectable HCC was not mentioned in the study.

In a retrospective study by Fan *et al.*,[91] 65 patients with unresectable HCC underwent liver resection after tumor downstaging with L-TACE. Ultrasound and CT scans were used to monitor the tumor size. Complete tumor necrosis occurred in 16.9% of patients, and the median tumor size decreased from 9.9 cm to 3.7 cm. The 5-year overall survival was 56%. The main criticism of this study is that some of the tumors might not have been initially unresectable.

In the retrospective comparative study by Tang *et al.*,[94] 1085 patients with unresectable HCC received tumor downstaging procedures including (1) a combination of hepatic artery ligation (HAL), L-TAC, and radiotherapy/radioimmunotherapy; (2) a combination of HAL and L-TAC; and (3) HAL alone or L-TAC alone. Salvage surgery on 139 (12.8%) patients resulted in a 5-year overall survival of 24.9% in the triple-treatment group, 15.2% in the double-treatment group, and 10.9% in the single-treatment group. The corresponding tumor downstaging resection rates were 34.6%, 16.2%, and 1.8%, respectively. Unfortunately, because this study was a nonrandomized study, no firm conclusion could be drawn as to which tumor downstaging regimen was better. The fact that patients who received triple therapy had a better long-term survival or a higher tumor downstaging resection rate could be explained by these patients having a better general condition, better hepatic reserve, or biologically less aggressive tumors. Other criticisms of this study are that there is no information on why the tumors were initially unresectable, and that the proportions of patients with partial or complete response are not given.

Tumor downstaging with TAC

In the retrospective study by Meric *et al.*,[92] of the 25 patients with unresectable HCC treated with TAC, 4 (16%) demonstrated partial

response. CT scan was used to restage the tumor before surgery. Two patients underwent liver resection with clear resection margins, and the other two patients were treated with RFA because of the underlying liver cirrhosis. At a median follow-up of 16 months, all four patients were alive and disease-free. In the prospective pilot study by Clavien *et al.*,[93] three of five patients underwent curative resection after successful tumor downstaging with TAC. CT scan was used to evaluate the response before chemotherapy and then every three-monthly. The 3-year survival rate was 60%.

Tumor downstaging with multimodality therapy

Sitzmann and Abrams[90] reported the first series of 14 patients with unresectable HCC who underwent salvage surgery following tumor downstaging. They used a combination of external radiotherapy and systemic chemotherapy with or without TARE/TAC. CT scan was used to evaluate the tumor volume and progress at various treatment intervals. If metastases were present initially, complete resolution as determined by CT for at least 3 months was required before consideration of resection. The exact details of the toxicity of the downstaging regimen were not mentioned in this study; however, the overall toxicity of the downstaging regimen (e.g. liver parenchymal dysfunction due to radiation) and hematological toxicity were reported to be low, and this did not preclude subsequent successful resection in any patient. The total number of patients with initially unresectable HCC who received the tumor downstaging regimen was also not mentioned. The 5-year overall survival rate after salvage surgery was 50.1%.

In the prospective study by our group,[12] 49 patients with initially unresectable HCC received salvage liver resection after tumor downstaging. The downstaging treatment consisted of systemic chemoimmunotherapy, systemic chemotherapy, TARE, or sequential therapy with both systemic and regional treatments. CT scan was done routinely before and every two-monthly after the downstaging treatments to monitor the response. Resectability of the tumor was assessed by the same liver surgeons before, during, and after the completion of the different modalities of treatment either alone or in combination. All

CT scans were assessed by the surgeons with the radiologist. Surgical resection of residual lesions was offered to patients at any stage of the treatment if surgery could potentially resect all gross lesions with a clear margin as shown radiologically. Salvage surgery resulted in 1-, 3-, and 5-year survival rates of 98%, 64%, and 57%, respectively. About 42.9% of patients had tumor recurrence after surgery. In this study, two patients had solitary residual metastatic deposits in the lung and in the omentum, respectively, although they had complete radiologic response to their primary tumors. One patient who underwent pulmonary segmentectomy survived 38.4 months; the other patient who underwent omentectomy survived 30.1 months.

It must be pointed out that in all of the above series, apart from the use of the tumor downstaging therapy, all of the other procedures that can improve tumor resectability (including preoperative portal vein embolization, two-stage hepatectomy, or combined liver resection with local ablative therapy) were not used.

Challenges of tumor downstaging

The main difficulties of tumor downstaging in HCC are as follows:

1. Only a small proportion (8%–18%) of patients respond well enough to the treatment to allow salvage liver resection.
2. The responders cannot be predicted, and the data in the medical literature are too limited to have a meaningful analysis on the prediction of the good responders.
3. There has not been a single effective tumor downstaging agent so far.
4. Recurrence after tumor downstaging and salvage surgery is common. One possible explanation is that some resistant clones of the tumor cell that escaped the cytotoxic effect of the therapies start to regrow in the liver remnant after the salvage surgery. The other explanation is that a second tumor develops in the cirrhotic liver remnant.[8]

Prognosis and survival

The reported 5-year survival rate after salvage surgery following tumor downstaging varied from 24.9% to 57% (Table 2).[8,11,12,22,90–94] The

Table 2. Studies on salvage surgery after tumor downstaging for unresectable HCC.

Study	No. of patients receiving downstaging regimen	Downstaging agent	No. of patients with salvage surgery	Patients with residual cancer cells in the specimen (%)	Survival
Sitzmann and Abrams[90] (1993)	Unknown	Combined external radiotherapy and systemic chemotherapy ± TARE/TAC	14	N/A	5-year survival, 50.1%; median survival, 57.4 months
Majno *et al.*[22] (1997)	49	L-TACE	5	50	Unknown
Fan *et al.*[91] (1998)	360	L-TACE	65	84.7	5-year survival, 56%
Meric *et al.*[92] (2000)	25	TAC	2 (the other 2 patients underwent RFA)	N/A	Alive without disease at a median follow-up of 16 months (range, 6–48 months)
Clavien *et al.*[93] (2002)	5	TAC	3	N/A	3-year survival, 60%
Lau *et al.*[12] (2004)	270	Chemoimmunotherapy; TARE with yttrium-90 microspheres; sequential therapy	49	N/A	5-year survival, 57%
Tang *et al.*[94] (2004)	1085	HAL/L-TAC alone; L-TAC + HAL; L-TAC + radioimmunotherapy/radiotherapy + HAL	139	69.7	5-year survival, 48.7%

outcome of salvage surgery following tumor downstaging can give a long-term survival which is comparable to that of resectable HCC after primary resection. Unfortunately, there are still no RCTs to support its role. One clear message is that salvage surgery following tumor downstaging offers the possibility of a cure for a proportion of patients with unresectable HCC.

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Management of Portal Vein Tumor Thrombus

W. Y. Lau, Eric C. H. Lai and Simon C. H. Yu

Introduction

Several factors contribute to the poor prognosis associated with hepatocellular carcinoma (HCC), with major vascular invasion being one of the most important ones.[1–3] When the tumor thrombus extends to involve the main portal vein, prognosis is extremely poor because (1) tumor cells may spread along the portal vein, resulting in extensive intrahepatic metastases; (2) portal vein obstruction causes further deterioration in liver function, resulting in liver failure; and (3) portal hypertension is aggravated, leading to intractable ascites and esophageal variceal bleeding. The prognosis for patients with HCC accompanied by portal vein tumor thrombus (PVTT) is generally poor, if left untreated; a median survival of 2.7–4.0 months was reported.[4,5] However, the optimal treatment for HCC with major vascular invasion remains controversial. This chapter discusses the current management of HCC with PVTT.

Diagnosis

The diagnosis of PVTT in patients with HCC is important in determining therapy and prognosis. Although portal vein thrombosis is readily detected by contrast-enhanced computed tomography (CT) scan or contrast-enhanced magnetic resonance imaging (MRI), these radiological examinations do not discriminate between tumor or blood thrombus, both of which commonly occur in cirrhosis. CT scan and MRI can suggest a malignant tumor thrombus by visualizing a diffuse thrombus enhancement due to neovascularization of the tumor thrombus in the vessels (Fig. 1).[6–8]

Color Doppler ultrasonography (USG) is a reliable way to differentiate between benign and tumor thrombi. The presence of pulsatile arterial flow in the thrombus is a highly sensitive and specific sign of a malignant portal vein thrombus.[9–12] Some investigators have resorted to USG-guided fine needle aspiration (FNA) of portal vein thrombus in order to distinguish malignant from benign thrombi; those PVTTs that fail to be diagnosed by color Doppler USG can be diagnosed early by USG-guided FNA. USG-guided FNA has been shown to be a safe, accurate, and well-tolerated diagnostic procedure.[13–17]

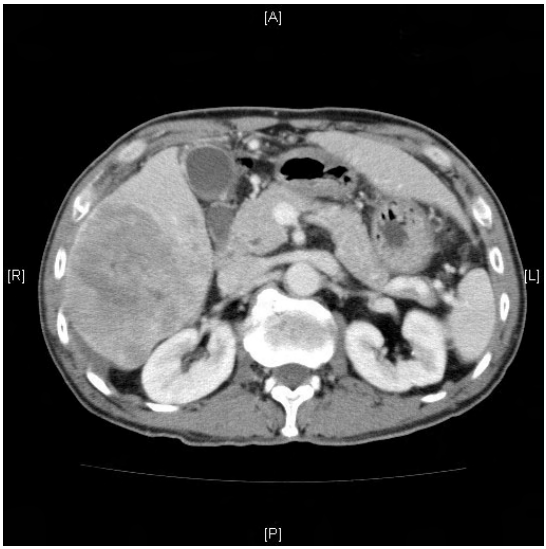
Treatment

Curative therapy

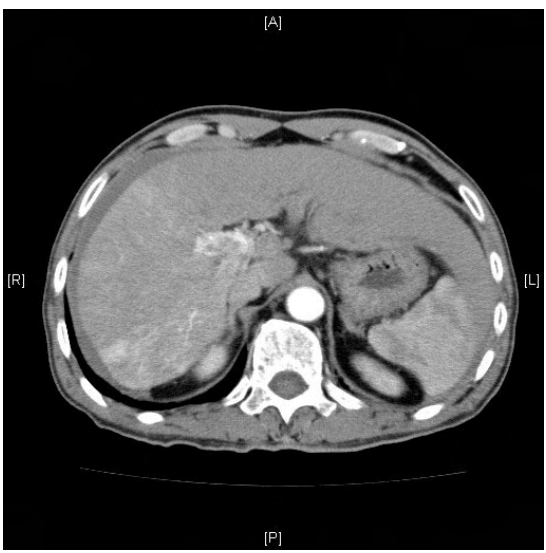
Surgical resection with complete extirpation of tumor gives the best chance of a cure for HCC. Tumor extension into the portal vein remains a contraindication to liver transplantation because of early tumor recurrence. Therefore, liver resection remains the only therapeutic option that may offer a chance of cure for HCC with PVTT.

Liver resection

The potential benefits of surgical resection of HCC with PVTT include the following: (1) portal venous pressure may decrease; (2) liver function may improve; (3) survival may be prolonged; and (4) quality of life may improve.

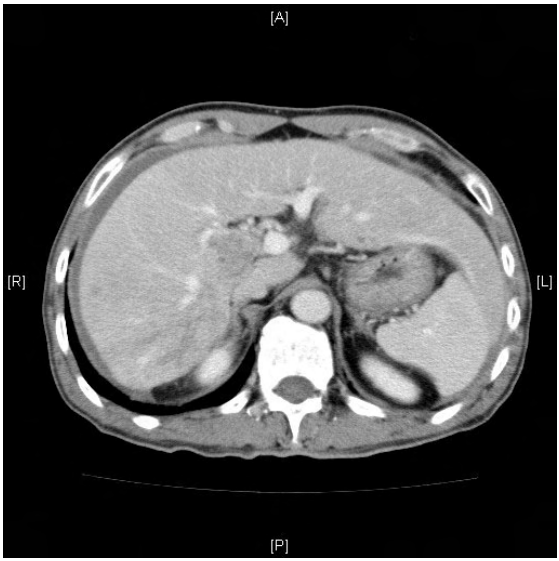


(A)



(B)

Fig. 1. (A) CT scan showing an 8-cm HCC over the right hemiliver. (B) CT scan (arterial phase) showing contrast-enhanced right main PVTT. (C) CT scan (portal venous phase) showing right main PVTT. (D) Specimen showing the corresponding right main PVTT.



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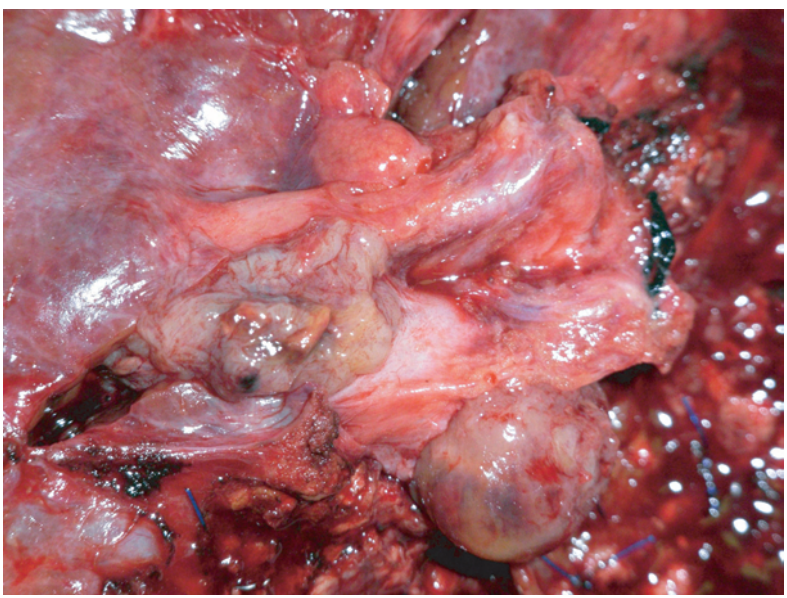

(D)

Fig. 1. (*Continued*)

The effects of the location and extent of PVTT on the long-term outcomes of surgical treatment for HCC have not been fully delineated. In the retrospective study of Chen *et al.*,[18] liver resection yielded better outcomes in patients with HCC when the PVTT was confined to the first or second branch of the main portal vein compared to when the PVTT extended into the main portal venous trunk (5-year survival, 22.7% vs. 0%, respectively; remnant liver recurrence within 1 year after surgery, 45.0% vs. 78.8%, respectively).

A patient is selected for liver resection by most surgeons when the tumor thrombus is located in the first or second branch of the main portal vein. In these patients, the tumor can be completely removed by liver resection with resection of the ipsilateral portal venous branch containing the tumor thrombus. When the tumor thrombus extends to the portal bifurcation or the main portal venous trunk, surgical resection — although technically feasible — becomes a controversial issue; in such cases, concomitant liver resection with direct removal of the tumor thrombus in the portal vein (thrombectomy) or partial portal vein resection with reconstruction has been proposed. It is still unclear whether there is any difference in outcome between thrombectomy and partial portal vein resection, as there is no comparative study on this. In studies by Chen *et al.*[18] and Konishi *et al.*,[19] liver resection with thrombectomy was performed for patients with PVTT in the main portal venous trunk (2-year survival, 20.4% and 34%, respectively; operative mortality, 2.6% and 0%, respectively); while Wu *et al.*[20] performed liver resection with partial portal venous resection for patients with PVTT in the portal venous bifurcation (2-year survival, 48%; operative mortality, 0%). However, it is logical to assume that if the tumor thrombus does not infiltrate into the portal venous wall, then thrombectomy is a viable treatment option. The long-term survival and postoperative morbidity/mortality after surgery for HCC with PVTT have not been well documented.

Table 1 shows the outcomes of liver resection for HCC with PVTT published in the last decade.[18–24] The median survival ranged from 8.9 months to 33 months, and the operative mortality ranged from 0% to 5.9%. Although these results are superior to the historical control of patients who received no operation, we should be aware that

Table 1. Results of liver resection for HCC with PVTT.

Study	No. of patients	Extent of PVTT	Median survival (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Operative mortality (%)
Chen *et al.*[18] (2006)	286/152	First branch of PV vs. main PV	18.8/10.1	58.7/39.5	22.7/5.7	18.1/0	0/2.6
Ikai *et al.*[21] (2006)	78	First branch of PV	8.9	45.7	21.7	10.9	3.8
Le Treut *et al.*[22] (2006)	20	First branch of PV/Main PV	12	50	26	17	—
Pawlik *et al.*[23] (2005)	102	First branch of PV/Main trunk of hepatic vein	11	45	17	10	5.9
Konishi *et al.*[19] (2001)	18	Main PV	—	48	—	—	0
Wu *et al.*[20] (2000)	15/97	Main PV vs. branch of PV	—	—	—	26.4/28.5	0/3
Ohkubo *et al.*[24] (2000)	47	Segmental branch of PV/First branch of PV/Main PV	33	53.9	33.2	23.9	2.1

these patients who were operated on are highly selective. At present, only a small number of studies have evaluated the prognostic factors for the treatment of HCC with PVTT.[21,23,25–28] Liver function was consistently shown to be an important prognostic factor. Tumor size was significant in some studies,[21,26,28] but not in other studies.[23]

To improve the efficacy of surgical resection for HCC with PVTT, neoadjuvant/adjuvant therapies were evaluated. Table 2 shows the results of surgical resection plus neoadjuvant/adjuvant therapy, demonstrating survival benefit with treatment added to surgery.[29–33] One study, a randomized controlled trial (RCT) from China, showed significant survival benefit with adjuvant therapy.[29] Unfortunately, because the number of studies is small and most are nonrandomized studies, no firm conclusion can be drawn. The results from nonrandomized studies cannot be relied on. Patients may have been selected to receive neoadjuvant/adjuvant therapy because they had a better general condition, better hepatic reserve, or a biologically less aggressive tumor so that there was time to give the additional treatment before recurrence was detected; as a consequence, these patients had better long-term survival. More RCTs are needed to evaluate the potential benefit of neoadjuvant/adjuvant therapy for HCC with PVTT.

With improvements in regional and systemic therapy, some treatments originally aimed at palliation can downstage tumors from unresectable to become resectable because tumors shrink in size, satellite lesions disappear, main PVTTs regress and disappear, and the nontumorous part of the liver hypertrophies.[34–38] Tumor downstaging is a new concept in the management of unresectable malignancy. The authors have reported a series of 49 patients with unresectable HCC who underwent nonsurgical treatment to downstage the disease followed by salvage surgery[38]; 7 of these 49 patients had PVTT in the main portal vein, and their 5-year survival rate was 56% after tumor downstaging and salvage surgery (see Chapter 32).

Based on the available evidence, liver resection with thrombectomy/partial resection of portal vein is justified in selected patients with HCC with PVTT. However, surgical resection for HCC with PVTT involving the portal bifurcation or the main trunk should only be carried out in highly specialized centers.

Table 2. Results of neoadjuvant/adjuvant therapy for HCC with PVTT.

Study	Type of study	Treatment arms	No. of patients	Median survival	Mean survival	Survival (%)
Li *et al.*[29] (2006)	Randomized trial	Surgery vs. surgery + adjuvant TACE vs. surgery + adjuvant TACE and PVC	112	—	—	1-, 3-, 5-year disease-free survival: 50.7, 17.8, 0 vs. 62.3, 23.7, 4.0 vs. 74.4, 46.1, 11.5, respectively
Niguma *et al.*[30] (2005)	Nonrandomized trial	Surgery vs. surgery + TAC	12	8 months vs. 58 months	—	—
Fan *et al.*[31] (2005)	Nonrandomized trial	Conservative treatment vs. TACE/PVC/HAL + TAC vs. surgery vs. surgery + adjuvant TAC/TACE/PVC	179	—	3.6 months vs. 7.3 months vs. 10.1 months vs. 15.1 months	0.5-, 1-, 2-, 3-year survival: 5.5, 0, 0, 0 vs. 34.6, 11.8, 0, 0 vs. 46.8, 22.7, 9.8, 0 vs. 55.8, 39.3, 30.4, 15.6, respectively
Minagawa *et al.*[32] (2001)	Nonrandomized trial	Conservative treatment vs. neoadjuvant TACE + surgery	45	—	0.36 years vs. 3.4 years	1-year survival: 7 vs. 82
Tanaka *et al.*[33] (1996)	Nonrandomized trial	Conservative treatment vs. surgery + adjuvant TAE	62	199.6 days vs. 900.5 days	90 days vs. 305 days	—

TACE, transarterial chemoembolization; PVC, portal vein chemotherapy; TAC, transarterial chemotherapy; HAL, hepatic artery ligation; TAE, transarterial embolization.

Palliative therapy

To improve the prognosis, various treatments have been proposed. These include locoregional therapy (transarterial chemotherapy [TAC], transarterial chemoembolization [TACE], transarterial radioembolization [TARE], and external radiotherapy), systemic therapy (chemoimmunotherapy), and combined modality of therapy (TACE plus external radiotherapy or systemic chemotherapy). There is still no universally accepted form of palliative treatment.

TAC/TACE

As HCCs derive their blood supply mainly from the hepatic artery, infusion of chemotherapeutic agents into the hepatic artery has the theoretical advantage of increasing total drug exposure to the tumor, which may in turn improve tumor cell kill.[36] Advances in the technology of implantable drug delivery systems have facilitated repeated arterial infusion of chemotherapeutic agents. TAC has been evaluated in the palliative treatment of HCC with PVTT (Table 3).[39–41] Cisplatin and 5-FU have been commonly used. The rationale is that both drugs have an antitumor effect, and cisplatin has a synergistic effect as a modulator for 5-FU; therefore, cisplatin and 5-FU, when used together, can be administrated in low doses to reduce the adverse reactions. A tumor response rate of 33%–48% and a median survival of 7.5–10.2 months were reported. Both Lai *et al.*[39] and Ando *et al.*[41] showed that responders had better median survivals than nonresponders (median survival, 15 months vs. 7.5 months, and 31.6 months vs. 5.4 months, respectively). TAC using low-dose cisplatin and 5-FU may be useful for HCC with PVTT.

The survival benefit of TACE for unresectable HCC has been shown in two RCTs from Europe and Hong Kong, and in two meta-analyses.[42–45] However, portal vein thrombosis is generally considered as a contraindication to TACE for HCC. The theoretical concern is that as the blood supply to the liver has already been compromised by portal vein thrombosis, embolization of the hepatic artery may result in hepatic infarct or acute hepatic failure. There are evidences to support

Table 3. Results of TAC for HCC with PVTT.

Study	No. of patients	Chemotherapeutic agents	Complete response (%)	Partial response (%)	Median survival (months)	1-year survival (%)	2-year survival (%)	3-year survival (%)	5-year survival (%)
Lai *et al.*[39] (2003)	18	Cisplatin, 5-FU	0	33	9.5	28	—	—	—
Itamoto *et al.*[40] (2002)	7	Cisplatin, 5-FU	14.3	28.6	7.5	14.3	—	—	—
Ando *et al.*[41] (2002)	48	Cisplatin, 5-FU	8.3	39.6	10.2	45	31	25	11

the contrary, which is likely to be due to the development of collateral circulation or portal vein recanalization. Adjustments to the TACE protocol, however, are necessary through superselective catheterization of the hepatic artery and through the degree of embolization. A median survival of 6–15 months was reported (Table 4).[46–50] Lee *et al.*[48] and Chung *et al.*[49] showed that TACE was not efficacious in the treatment of diffuse-type HCC. TACE may be a safe treatment for HCC with PVTT, provided that the patients have good hepatic function and collateral circulation. RCTs are necessary to show this conclusively.

TARE/External radiotherapy

External radiotherapy has been regarded as ineffective for HCC because the radiation dose that can be delivered to the tumor is limited by the tolerance of the nontumorous liver.[51] While HCC is relatively radioresistant and an irradiation dose of 120 Gy is required to kill the tumor, the tolerance of the nontumorous liver towards irradiation is relatively low and is approximately 30 Gy. Whole-liver irradiation beyond this limit is likely to result in radiation hepatitis (also called radiation-induced liver disease, RILD).[52] The tolerance dose for the liver depends

Table 4. Results of TACE for HCC with PVTT.

Study	No. of patients	Median survival (months)	1-year survival (%)	2-year survival (%)	3-year survival (%)	5-year survival (%)
Georgiades *et al.*[46] (2005)	32	9.5	25	—	—	—
Uraki *et al.*[47] (2004)	61	15	42	—	11	3
Lee *et al.*[48] (1997)	31	6	—	13	—	—
Chung *et al.*[49] (1995)	110	6	30	18	9	—
Katsumori *et al.*[50] (1995)	9	—	44	22	—	—

significantly on the liver volume irradiated. With technological advances in radiotherapy, three-dimensional (3D) conformal radiotherapy, proton beam radiotherapy, and TARE have been developed. These methods increase the likelihood of killing cancer cells by delivering a higher dose of radiation to the tumor, while at the same time sparing healthy tissue from excessive irradiation. The results of radiotherapy as a treatment for HCC with PVTT are shown in Table 5. A median survival of 4.9–27.6 months was reported.[53–58]

In an RCT conducted by Raoul *et al.*,[58] TARE with ^{131}I-lipiodol in HCC with PVTT significantly increased the survival rate when compared with the medical support group (3-, 6-, 9-month survivals of 71% vs. 10%, 48% vs. 0%, and 7% vs. 0%, respectively). However, de Baere *et al.*[57] showed that TARE with ^{131}I-lipiodol was associated with a poor tolerance and a low response rate in HCC with portal vein thrombosis. In 23 patients, static and progressive diseases occurred in 12 and 8 patients, respectively; while early death due to liver failure and transient symptomatic liver failure occurred in 1 patient and 9 patients, respectively. Salem *et al.*[56] showed that TARE with yttrium-90 glass microspheres was feasible and safe in HCC with PVTT involving one or both of the first-order and related segmental portal venous branches; however, this is the only study published on this treatment. Based on the available evidence, TARE cannot be recommended as a routine treatment for HCC with PVTT.

Three-dimensional conformal radiotherapy, stereotactic radiotherapy, and proton beam therapy can deliver a good radiation dose to the target HCC with PVTT when compared with conventional photon irradiation. Kim *et al.*[55] and Hata *et al.*[54] defined the clinical target volume as the macroscopic tumor volume and PVTT with certain margins. Kim *et al.*[55] reported a 45.8% objective response rate for HCC with PVTT after 3D conformal radiotherapy. A dose–response relationship existed between the radiotherapy dose and the PVTT response. The responders had a significantly higher overall survival rate than the nonresponders. Hata *et al.*[54] reported a 100% objective response rate for HCC with PVTT after proton beam therapy. The median progression-free survival rate was 2.3 years. Lin *et al.*[53] defined the clinical target volume as the PVTT only in order to analyze the recanalization rate of the thrombosed

Table 5. Results of radiotherapy for HCC with PVTT.

Study	No. of patients	Type of radiotherapy	Complete response (%)	Partial response (%)	Median survival (months)	1-year survival (%)	2-year survival (%)	5-year survival (%)
Lin *et al.*[53] (2006)	9/7	Stereotactic radiotherapy/ 3D conformal radiotherapy	0/17	75/67	6/6.7	—	—	—
Hata *et al.*[54] (2005)	12	Proton beam therapy	16.7	83.3	27.6 (progression-free median survival)	—	67% (progression-free survival)	24% (progression-free survival)
Kim *et al.*[55] (2005)	59	3D conformal radiotherapy	6.8	39	10.7/5.3 (responder/ nonresponder)	40.7/25 (responder/ nonresponder)	20.7/4.7 (responder/ nonresponder)	—
Salem *et al.*[56] (2004)	15	TARE with yttrium-90 glass microspheres	—	—	16.5	—	—	—
De Baere *et al.*[57] (1999)	24	TARE with ^{131}I-lipiodol	—	13	4.9	6	—	—
Raoul *et al.*[58] (1994)	14	TARE with ^{131}I-lipiodol	—	—	5.6	7	—	—

portal vein. Both 3D conformal radiotherapy and stereotactic radiotherapy had encouraging and comparable results in the recanalization of the thrombosed portal vein. However, of 43 patients, 29 patients received incomplete radiotherapy or did not have follow-up evaluation because they died of the disease before the scheduled appointments. For the 14 evaluable patients, the crude response rate was 79%. TACE was subsequently conducted in five patients. The median survival for the evaluable patients was 6.7 months. Preliminary studies thus showed that 3D conformal radiotherapy, stereotactic radiotherapy, and proton beam therapy are feasible for the treatment of HCC with PVTT. RCTs are needed to evaluate the true roles of these new treatments.

Chemoimmunotherapy

Chemotherapy uses drugs to kill or slow down the growth of cancer cells, while immunotherapy uses treatments to stimulate or restore the immune system to fight against the cancer. Interferon-alpha exerts its antiproliferative effect. However, monotherapy with either TAC or interferon-alpha showed low response rates and hardly demonstrated any clinical effect against HCC. The combination of the two therapeutic agents seems to have a synergistic effect. A tumor response rate of 30.5%–72.7% and a median survival of 4.4–11.8 months were reported for HCC with PVTT (Table 6).[59–63] These results provide a rationale for future RCTs.

Combination therapy

TACE, when used on advanced HCC, has limited effects on PVTT.[64–67] Local radiotherapy together with TACE has been investigated as a means to enhance tumor control. The strategy is to use radiation to treat PVTT and to use TACE to treat liver tumors. The median survival rates ranged from 5.3 months to 9.7 months (Table 7).[65–67]

Large HCCs, when treated by TACE alone, rarely achieve complete remission. A combination of systemic chemotherapy and TACE was investigated in one study. In a case-control study by Jang *et al.*,[64] systemic chemotherapy with TACE for large HCC (>10 cm) with PVTT

Table 6. Results of combination therapy of intra-arterial chemotherapy and systemic interferon-alpha for HCC with PVTT.

Study	No. of patients	Chemotherapeutic agents used in the combination	Complete response (%)	Partial response (%)	Median survival (months)	1-year survival (%)	2-year survival (%)	3-year survival (%)	5-year survival (%)
Obi *et al.*[59] (2006)	116	5-FU	16	42	6.9	34	18	—	—
Ota *et al.*[60] (2005)	55	5-FU	14.5	16	11.8	48.9	28.8	16.4	16.4
Kaneko *et al.*[61] (2002)	29	5-FU, methotrexate, cisplatin	10.3	34.5	11 (patients with CR/PR)	—	17.2	—	—
Sakon *et al.*[62] (2002)	11	5FU	27.2	45.5	—	—	—	—	—
Chung *et al.*[63] (2000)	19	cisplatin	0	33	4.4	27	—	—	—

Table 7. Results of combined therapy for HCC with PVTT.

Study	No. of patients	Treatment combination	Complete response (%)	Partial response (%)	Median survival (months)	1-year survival (%)	2-year survival (%)	3-year survival (%)
Jang *et al.*[64] (2007)	80	TACE & systemic 5-FU	—	21.3	8.7	29.8	13.4	—
Yamada *et al.*[65] (2003)	19	TACE & 3D conformal radiotherapy targeting the PVTT	—	—	7	40.6	10.2	—
Ishikura *et al.*[66] (2002)	20	TACE & external radiotherapy targeting the PVTT	0	50	5.3	25	—	—
Tazawa *et al.*[67] (2001)	24	TACE & external radiotherapy targeting the PVTT	16.7	33.3	9.7/3.8 (responder/ nonresponder)	61/19 (responder/ nonresponder)	21/9 (responder/ nonresponder)	10/0 (responder/ nonresponder)

was found to be more beneficial than conservative treatment alone (median survival, 8.7 months vs. 3.5 months, respectively) (Table 7). The combination therapy seems feasible and efficacious in patients with good hepatic functional reserve. More controlled studies are necessary to clarify the survival advantage with the combination therapy.

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Palliative Care

Winnie Yeo and Anthony T. C. Chan

Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide. Eighty percent of new cases occur in developing countries, but the incidence is rising in developed areas including the United States and Western Europe.[1] The incidence of HCC doubled during the period of 1975–1995 in the United States, and has continued to rise over the past decade.[2,3] In contrast to Asia where the disease is mainly associated with chronic hepatitis B virus (HBV) infection, in the West this has largely been attributed to chronic hepatitis C virus (HCV) infections.

For patients with HCC, surgery remains the most commonly used curative treatment to date. However, more than 80% of patients present with advanced unresectable disease. Even for those who undergo surgical resection, the recurrence rate remains high with up to 50% at 2 years.[4,5] For most patients, the underlying reasons for tumor unresectability include high incidence of coexisting advanced cirrhosis, large primary lesion, multifocal disease, invasion and thrombosis of major blood vessels, inadequate size of future hepatic remnant, or extrahepatic

metastases. For the 80% or so of patients with unresectable tumors, the prognosis is dismal with a median survival of only 4 months.[6,7]

Patients with unresectable disease could be considered for some form of locoregional therapy such as transarterial chemoembolization (TACE),[8,9] percutaneous ethanol injection (PEI),[10,11] thermal ablation,[12,13] or internal radiotherapy.[14] While some would consider local ablative therapies as a potentially curative treatment, other forms of therapy remain, by and large, to be of a palliative nature. Among these, only TACE has been shown to improve survival in randomized controlled trials; however, the patients entered were highly selected and, in one of the two randomized studies, predominantly asymptomatic patients with Child class A cirrhosis were included.[8,9] Although some form of locoregional treatment is usually offered where facilities exist, it has to be emphasized that another major limitation of these locoregional therapies is that they are only effective in patients with small tumors, which represent a minor proportion of patients with unresectable disease.[15] For the majority of patients with unresectable HCC, systemic chemotherapy and best supportive therapy (especially for patients with poor liver function, i.e. Child grade C cirrhosis) remain the main options of palliative treatment.

In a meta-analysis on systemic chemotherapy evaluating the role of regional and systemic chemotherapy, nonsurgical treatments were ineffective or minimally effective.[16] Furthermore, most published studies of systemic chemotherapy reported response rates of 0%–25%. Although combination chemotherapy has increased response rates in unresectable HCC, a recent randomized phase III study reported no improvement in survival when compared with single-agent chemotherapy.[17] Systemic chemotherapy has not been shown to prolong survival in patients with HCC.[18]

HCC commonly develops in a setting of chronic hepatitis and cirrhosis.[19] Thus, even a series as recent as from the past 2 years has reported that 20% of newly presented HCC patients could not be offered curative or palliative anticancer treatment at the time of presentation due mainly to poor hepatic function.[20] Thus, for a significant proportion of patients who present with advanced HCC and cirrhosis, best supportive therapy may be the only option available at the time

of presentation. On the other hand, for patients who initially undergo curative resection or interventional palliative therapies, upon disease relapse or progression and especially towards the terminal phase of the illness, best supportive therapy forms an important part of patient care.

Palliative care seeks to help patients achieve and maintain their maximum potential physically, psychologically, socially, and spiritually, however limited these may become as a result of disease progression. In patients with HCC, specific needs should be identified due to the special clinical characteristics of the disease. As a result of concurrent chronic liver diseases, HCC patients may manifest a variety of cirrhosis-related symptoms including ascites, variceal bleeding, peripheral edema, and hepatic encephalopathy, in addition to tumor-related symptoms, in the clinical course of the illness.[21]

In a recent study, the symptoms among 110 terminally ill HCC patients were studied. The most common symptom was pain (76%). The majority of patients suffered from abdominal pain secondary to enlarged tumor mass. One third of the patients experienced bone pain due to bone metastasis, which could be aggravated upon movement. Fatigue or weakness (73%), anorexia and vomiting (68%), peripheral edema (67%), cachexia (66%), ascites (64%), and dyspnea (44%) were also common complaints. Commonly detected laboratory abnormalities included hypoalbuminemia (85%), anemia (75%), hyponatremia (71%), hyperbilirubinemia (70%), and thrombocytopenia (37%).

Symptoms resulting from portal hypertension and liver failure frequently complicate the symptomatic management of terminal HCC patients. In the same series described above,[20] upper gastrointestinal bleeding (including variceal bleeding and peptic ulcer, 69%) was the most common complication; other complications were hepatic encephalopathy (48%), tumor rupture (14%), hepatorenal syndrome (14%), and spontaneous bacterial peritonitis (11%). In addition, delirium (57%), infections (e.g. urinary tract infections, pneumonia, and bacteremia; 40%), hypercalcemia (12%), and malignant fever (10%) were reported.

The severity of the underlying liver cirrhosis has been strongly correlated with the prognosis in HCC patients.[22,23] When compared with HCC patients with compensated liver cirrhosis or no cirrhosis, there

was a significantly higher prevalence of peripheral edema, ascites, dyspnea, upper gastrointestinal bleeding, jaundice, and thrombocytopenia in HCC patients with decompensated cirrhosis.[20] However, there was no significant difference in the occurrence of tumor-specific complications, such as hypercalcemia and tumor rupture, between patients with decompensated cirrhosis and their counterpart.

In assessing the efficacy of any form of palliative therapy, there are two aspects, namely quality of life and cost associated with care, which may be important outcome measures alongside conventional endpoints such as response rates and survival.

Two Aspects in the Assessment of Effectiveness of Palliative Care

Quality-of-life assessment

Quality-of-life (QOL) is an important aspect of palliative care treatment. QOL has been acknowledged as an important endpoint in cancer clinical trials and clinical practice, along with the traditional endpoints of tumor response rate, disease-free survival, and overall survival.[24,25]

The European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30) is a widely used questionnaire. It incorporates a range of QOL issues relevant to a broad range of cancer patients. It has been translated into many languages and is validated for many cancer types. It contains five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), a global QOL scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).[26] All scales and items of the EORTC QLQ-C30 range in score from 0 to 100. A high score for a functional or global QOL scale represents a relatively high/healthy level of functioning or global QOL, while a high score for a symptom scale or item represents more severe symptoms or problems.[27]

It is possible that baseline QOL for HCC patients may be affected by other concurrent diseases or conditions. In the context of assessing the treatment outcome of patients with cancer of the liver, pancreas,

gall bladder, or biliary ducts, addressing disease-specific issues has been acknowledged to be an important component of QOL assessment. The Functional Assessment of Cancer Therapy–Hepatobiliary questionnaire (FACT-Hep) supplements the general QOL questionnaire (FACT-G), and has been used as a tool to assess the treatment outcome for patients with hepatobiliary malignancies.[28] FACT-Hep has been put forth as a reliable and valid instrument that increases the accuracy of overall QOL assessment.[28] Specifically, for patients with HCC, with the majority of them suffering from coexisting cirrhosis, the usefulness of the QOL instrument based on the EORTC QLQ-C30 in assessing patients with HCC could be further enhanced by the addition of an assessment related to a disease-specific module in the more recently reported EORTC QLQ-HCC18 questionnaire.[29] In the latter, symptoms from chronic liver disease are taken into consideration and include abdominal distension from ascites, limb edema related to sodium and fluid retention, pruritus related to hyperbilirubinemia, and bleeding related to clotting impairment and thrombocytopenia.[29] The inclusion of a HCC-specific questionnaire into the standard QLQ C-30 assessment would potentially improve the sensitivity of QOL assessment as an outcome measure.

More recently, pretreatment QOL has been increasingly recognized as a potential prognostic factor of survival.[30] In a recent report assessing baseline pretreatment QOL in HCC patients receiving palliative systemic chemotherapy or tamoxifen, baseline QOL as measured by the EORTC QLQ-C30 was assessed alongside conventional clinical variables as a prognosticator for survival.[31] The results revealed that, in addition to conventional clinical variables, patients who scored better in the physical functioning and role functioning domains of the QOL questionnaire were associated with longer survival, while those who scored worse in the appetite score domain were associated with shorter survival. Thus, QOL assessment could be applied as a new prognosticator for survival in patients with unresectable HCC. When used along with conventional clinical factors, patient-reported baseline QOL assessment provides additional information and can be part of a more comprehensive prediction of patient prognosis. In addition, QOL assessment enables the identification of symptoms whereby interventions to improve QOL may be useful in reducing the burden of the

disease, and may also assist clinicians to recalibrate the clinical prediction of survival and optimize the use of palliative care.

Cost of palliative care

Most patients with inoperable HCC have a background history of liver cirrhosis, and advanced HCC exacerbates the severity of cirrhosis, resulting in a variety of complications in the terminal stages of the disease. In a series of terminally ill HCC patients,[20] treatments that were commonly prescribed included opiates for pain management (76% of patients), nonsteroid anti-inflammatory drugs for control of bone pain or tumor fever (29%), H_2-receptor antagonist or proton pump inhibitors to control upper gastrointestinal bleeding (72%), diuretics to control ascites (56%, with 20% undergoing abdominal paracentesis and 13% managed with pigtail drainage), and ammonia detoxication with agents such as lactulose for hepatic encephalopathy (54%). Moreover, HCC patients with decompensated cirrhosis were more likely to receive these treatments when compared with their counterparts who did not have cirrhosis or only had compensated cirrhosis.

During the course of best supportive care, patients may be transferred to an extended care facility or a hospice care facility. There have been studies assessing the cost of care for HCC patients during the last stages of their illnesses. Earlier reports conducted on HCC patients were based on the assignment of costs to specific care protocols, rather than on actual values based on observation.[32–35] Although observation-based studies provided a more accurate estimation of the cost incurred in the provision of care for these patients, they initially examined the hospital costs of end-stage liver disease and the social costs of colorectal cancer with liver metastases rather than HCC-specific costs.[36,37]

To address the specific treatment issues of HCC, an observation-based study was undertaken in Hong Kong, in which 204 HCC patients with unresectable HCC who underwent palliative therapies in a single institution that included locoregional therapies, systemic chemotherapy, and best supportive care were included.[38] The patients were prospectively tracked from first hospitalization until death for health service utilization. A societal perspective of cost was taken, including costs

of formal and informal services incurred by payers, caregivers, and patients as well as other related costs including transportation, herbal and Chinese medicines, and indirect costs of time loss for patients and caregivers.

With a median survival of 95 days and a mean observation period of 153 days, the results revealed that the number of days of observation, age, and survival were negatively related to cost; while the Child–Pugh grading system and the two interventional treatment therapies (systemic and locoregional therapies) were positively related with the cost per observed day. Patients with Child–Pugh grades A and B who received active noncurative treatment strategies incurred only moderately greater costs per day than patients with Child–Pugh grades A and B who were given best supportive care. Chemotherapy increased the cost by twofold, and increased severity of cirrhosis as measured by the Child–Pugh Index added about 50% to the cost, which reflected the additional cost incurred in symptoms for palliation of advanced-stage liver failure. Nonsurvival was shown to be correlated with doubling of the cost per case — a finding that was consistent with the presence of an expenditure "bubble" just prior to death, as noted by some earlier investigators.[39]

The mean value per person of the formal healthcare cost for HCC patients in Hong Kong was calculated to be equivalent to US$3872 (1998 values). This was lower than the three previous studies on HCC patients, which only presented estimates for the cost of HCC that were not based on direct observation,[32,33,35] but was similar to the cost calculation derived from observational data in the UK study on patients with colorectal liver metastases[33] despite the difference in treatment processes involved. The relatively modest average cost per patient with HCC in Hong Kong reflects the very short median survival and, subsequently, the limited use of inpatient care and chemotherapy in these patients relative to those with other diseases treated for extended periods.[39]

Future studies assessing the cost of care for HCC patients should be based on observational formal costs and cost-effectiveness, with the inclusion of factors such as age, severity of cirrhosis on presentation, observational period, and treatment modality within the assessment.

Conclusions

In patients with terminal cancers, those diagnosed with HCC appear to have shorter survival than non-HCC patients.[20] This may be due to the aggressive behavior of the former and the coexisting poor liver function. Therefore, for HCC patients with advanced disease, the provision of care for terminal phases of the illness should be anticipated relatively earlier than for patients with other incurable diseases.

Concurrent assessment of the psychological symptoms of patients, such as depression, anxiety, or altered mental condition, should be included. Mental condition is usually difficult to assess because of impaired liver function and hepatic encephalopathy. Physicians must take into consideration factors such as the existence of cirrhosis, hepatic functional reserve, degree of portal hypertension and its complications, and short survival time when managing the progression of disease in HCC patients.

As palliative care comprises active total care of patients' families and the patients themselves, a multidisciplinary approach with close liaison among the physicians and the nurses in a general hospital setting with palliative care and hospice team staff should be established. Since there is a potential for overlap of roles between various teams, coordination is an important part of teamwork. Palliative care should respond to the physical, psychological, social, and spiritual needs of the patients and their families, and should extend if necessary to support in bereavement.

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Management of Specific Complications

Eric C. H. Lai and W. Y. Lau

Introduction

Hepatocellular carcinoma (HCC) commonly presents with local symptoms if the tumor reaches a size of 10 cm and beyond. These consist of right upper quadrant pain or discomfort, or a mass may be felt by the patient. General symptoms of malignancy consisting of weight loss, anorexia, and malaise follow as the tumor becomes advanced. Patients with HCC can also present with specific complications, including spontaneous rupture, jaundice, variceal hemorrhage, and paraneoplastic syndrome.[1] These complications can only be managed properly with the appropriate background in knowledge. In this chapter, we will illustrate these four specific complications of HCC in detail.

Spontaneous Rupture

Spontaneous rupture of HCC occurs in 3%–15% of patients with HCC.[2] Ruptured HCC with intraperitoneal hemorrhage is a life-threatening complication, and is associated with a high in-hospital mortality rate of 25%–75%.[2–5] The mechanism of spontaneous rupture is still not exactly known. Proposed mechanisms include minor trauma, rapid growth of the tumor and necrosis, splitting of the overlying nontumorous liver parenchyma, tumor erosion of a vessel, increased intratumoral pressure due to the occlusion of the hepatic venous outflow by tumor thrombus or invasion, coagulopathy, and vascular dysfunction due to the degeneration of elastin and degradation of type IV collagen.[6–11]

Approximately 66%–100% of cases of spontaneous rupture of HCC present as an acute event with sudden onset of abdominal pain. Hypovolemic shock is present in 33%–90% of patients. Physical examination shows signs of peritonitis, stigmata of chronic liver disease, and abdominal distension and signs of peritoneal irritation as a consequence of hemoperitoneum. Ultrasonography (USG) and computed tomography (CT) scan of the abdomen are useful in demonstrating the presence of hemoperitoneum and liver tumor. CT scan also has the advantage of showing the patency of the portal vein. Active extravasations can only be seen occasionally on contrast CT scan or angiography in patients with active bleeding from the tumor. Sometimes, if the diagnosis is not recognized, the diagnosis is made only during an emergency exploratory laparotomy for peritonitis. In the minority of patients with slow oozing of blood into the peritoneal cavity, the patient can present with increasing abdominal distension over a period of a few days as well as symptoms and signs of anemia.

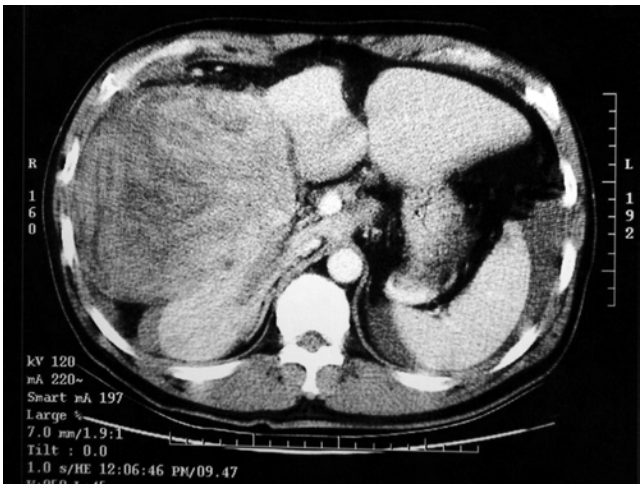
The goal of management at the acute stage is to attain hemostasis and to preserve as much functioning liver parenchyma as possible. The open surgical method was the mainstay of treatment for hemostasis in the past. Various surgical procedures including perihepatic packing, suture plication of bleeding tumor, injection of absolute alcohol, hepatic artery ligation (HAL), and liver resection were reported to be effective in hemostasis. However, open surgical procedures were associated with a

high in-hospital mortality rate, and these hemostatic procedures should nowadays be considered only when ruptured HCC is diagnosed during an exploratory laparotomy for a mistaken diagnosis of peritonitis.

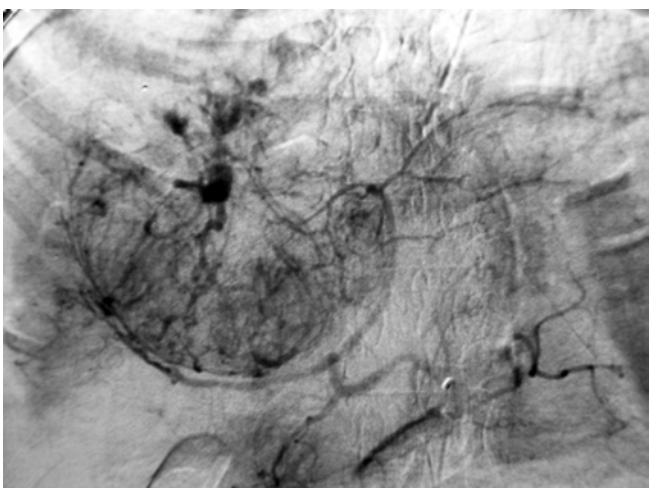
The role of transarterial embolization (TAE) in the management of ruptured HCC has become increasingly important in the last 20 years (Figs. 1 and 2). TAE has been shown to be highly effective in achieving hemostasis, even in patients with massive hemoperitoneum. TAE for hemostasis has a high success rate of 53%–100% and a lower 30-day mortality rate (0%–37%) than open surgical hemostasis. The advantages of TAE over surgery are that hemostasis can be achieved by both proximal and distal occlusion of the feeding vessels, and major surgery can be avoided in a poor-risk patient. With the use of the angiographic technique, the location of the tumor, the active bleeding site, and the patency of portal vein can be assessed. The agents used for embolization are sterile absorbable gelatin sponge (Gelfoam), stainless steel coils, or polyvinyl alcohol sponge (Ivalon). The choice of embolization agent depends on the site and size of the artery being embolized. Stainless steel coils and Ivalon particles can produce permanent occlusion of the hepatic artery, while Gelfoam can only produce temporary occlusion. Gelfoam embolization has the advantage of recanalization of the embolized artery after a few weeks, thus providing an opportunity for further regional therapy.

TAE is generally considered as a contraindication in patients with total occlusion of the main portal vein by tumor thrombus because of the high risk of hepatic infarction. The most common complication of TAE is the postembolization syndrome (26%–85%), which consists of fever, abdominal pain, nausea, and liver enzyme elevation. The syndrome usually subsides within 1–2 weeks. The major life-threatening complication is liver failure (12%–33%), which is the most common cause of death after TAE for spontaneous rupture of HCC. The prognosis for spontaneous rupture of HCC in the acute phase is determined by the serum bilirubin level, hemodynamic state on admission, and prerupture disease state.[2]

It is unknown whether routine TAE for patients with spontaneous rupture of HCC, including those without evidence of continuous bleeding, is beneficial or not. Leung *et al.*[3] conducted a nonrandomized

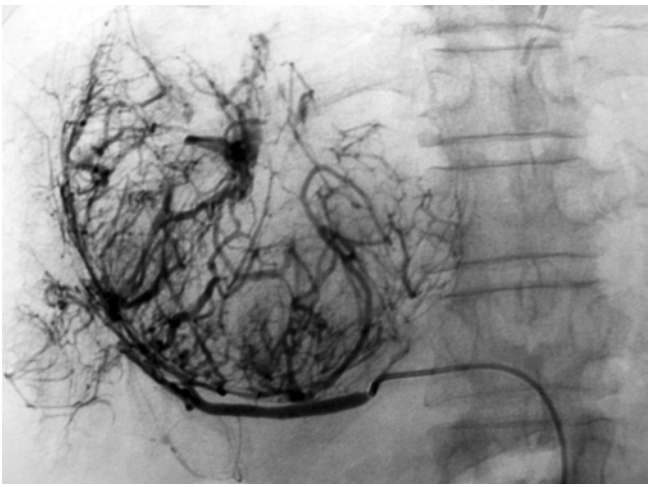


(A)



(B)

Fig. 1. (A) Contrast CT scan showing a ruptured 10-cm HCC at the right hemiliver and hemoperitoneum. (B,C) Angiograms showing the hypervascular tumor at the right hemiliver. (D) Postembolization angiogram showing marked reduction of arterial flow to the HCC after TAE with stainless steel coils.



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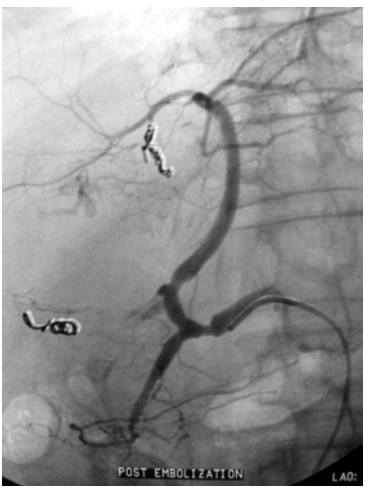
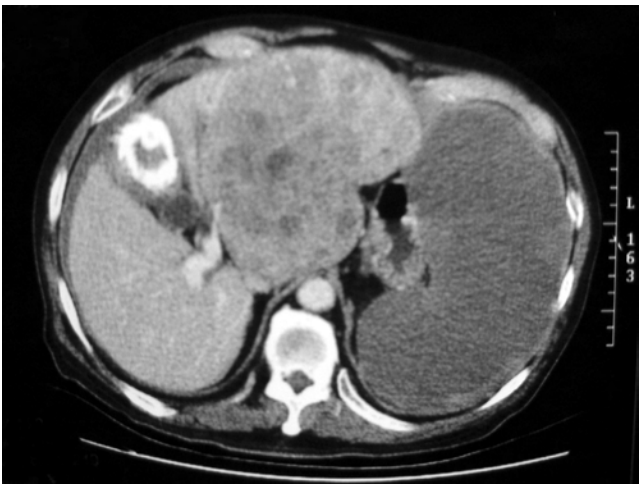


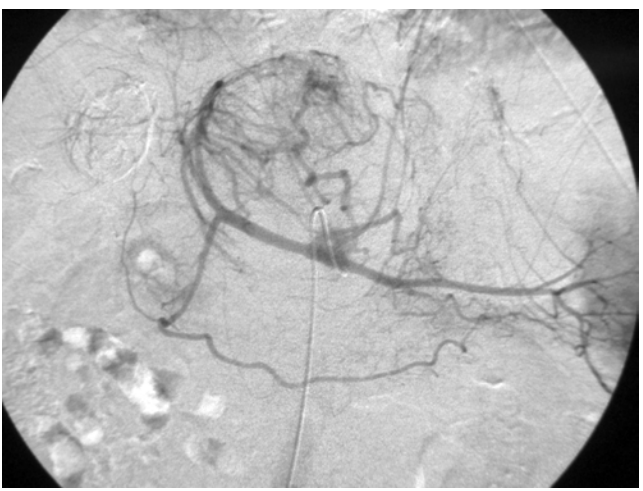
(D)

Fig. 1. (*Continued*)

comparative study on a group of patients who received a conservative approach in treatment using selective hemostatic intervention, and compared it with a historical group of patients who were managed with an aggressive approach in treatment using hemostatic interventions

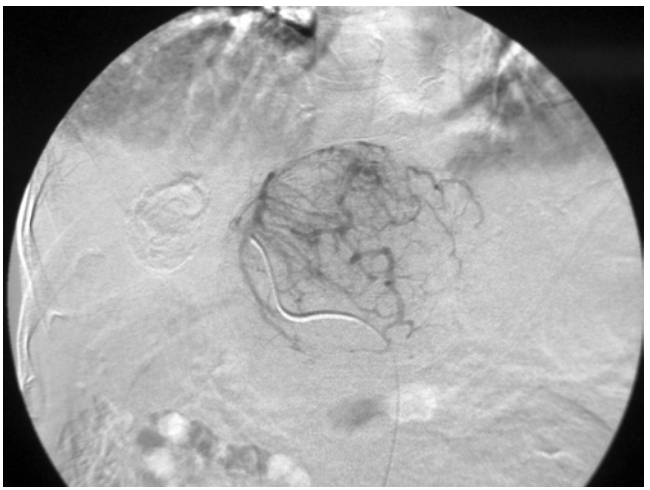


(A)



(B)

Fig. 2. (A) Contrast CT scan showing a ruptured 12-cm HCC at the left hemiliver with hemoperitoneum. (B,C) Angiograms showing the hypervascular tumor at the left hemiliver. (D) Postembolization angiogram showing marked reduction of arterial flow to the HCC after TAE with Gelfoam.



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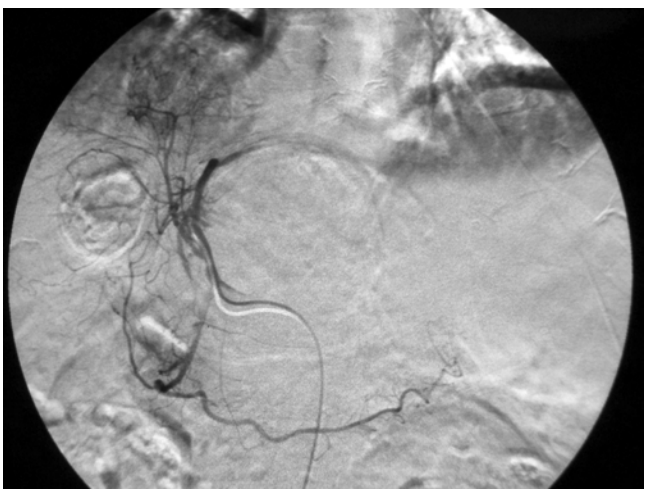

(D)

Fig. 2. (*Continued*)

nonselectively. In the conservative approach arm, patients were closely monitored and their coagulopathies were corrected; if there was any evidence of continuous bleeding, hemostatic intervention was performed. In the aggressive approach arm, hemostatic intervention was performed

routinely unless the patients were moribund. This study showed that selective intervention was more cost-effective and gave a lower in-hospital mortality and a better survival than the aggressive approach.[3]

After patients have recovered from the acute phase of bleeding, definitive treatment should be considered after reassessment. Staged liver resection is the preferred definitive treatment after the patient and the liver have recovered from the bleeding episode. Staged liver resection has a higher resection rate (21%–56% vs. 13%–31%) and a lower in-hospital mortality rate (0%–9% vs. 17%–100%) when compared to one-staged liver resection. Staged liver resection after spontaneous rupture of HCC was reported to have a 5-year survival rate of 15%–21%. One-stage liver resection is associated with a poor outcome because the tumor stage and the liver functional reserve are unclear at the time of the emergency situation. Furthermore, the presence of hemorrhagic shock renders the liver function poorer than usual. The presence of coagulopathy in a patient with compromised liver function further increases the surgical risk. One-stage emergency liver resection should be reserved for patients with a small and easily accessible tumor with a background of a noncirrhotic or mildly cirrhotic liver.

Although it is still unclear whether the long-term prognosis of curative liver resection for HCC with previous rupture is comparable to that for HCC without rupture, one clear message from the medical literature is that long-term survival is achievable in selected patients with ruptured HCC by liver resection. Figure 3 illustrates the algorithm of management of spontaneous rupture of HCC.

Jaundice

Jaundice occurs in 5%–44% of patients with HCC. The different causes of jaundice in HCC determine the therapeutic approach and the prognosis. Based on the pathophysiology, jaundice in HCC can be classified into two types: hepatocellular type and icteric type.[12]

Over 90% of cases of jaundice in HCC belong to the hepatocellular type. This is a result of hepatic parenchymal insufficiency due to the underlying liver cirrhosis and extensive hepatic parenchymal infiltration by the tumor. The prognosis is extremely poor. In Lau *et al.*'s[13] series of

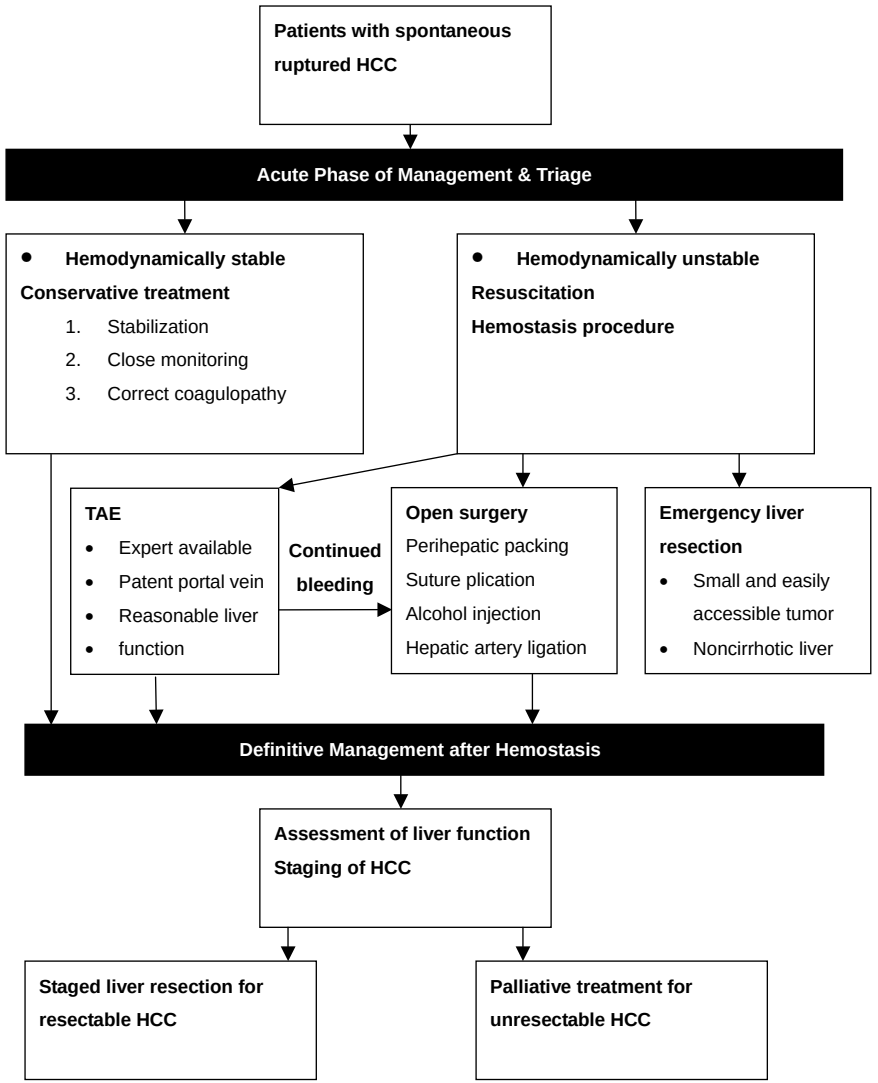

Fig. 3. Management of patients with spontaneous rupture of HCC.

481 patients with the hepatocellular type of jaundice, 90% of them died within 10 weeks of their first clinical presentation. The management is mainly supportive medical treatment after the exclusion of reversible precipitating factors such as drugs, alcohol, and hepatitis reactivation.

For HCC patients presenting with jaundice, USG is used as the first-line investigatory tool to differentiate between the hepatocellular type and the icteric type of jaundice. If there is any evidence of biliary obstruction, a cholangiography using either endoscopic retrograde cholangiopancreatogram (ERCP)/percutaneous transhepatic cholangiography (PTC) or magnetic resonance cholangiopancreatography (MRCP) should follow USG to further delineate the cause, level, and extent of biliary obstruction.

About 0.5%–13% of cases of jaundice in HCC belong to the icteric type. It is also named as icteric-type hepatoma or cholestatic type of HCC.[14,15] Icteric-type HCC was initially thought to be attributed to one of the following mechanisms:

1. A tumor erodes into a branch of the biliary tree and grows distally until it fills up the entire extrahepatic biliary tree to form a biliary tumor thrombus in the extrahepatic bile ducts.
2. A necrotic free-floating fragment of the tumor separates from the biliary tumor thrombus and migrates distally to obstruct the common bile duct. Fragments of the tumor in the bile duct — as described by Edmonson and Steiner[16] — are usually fragile, fleshy, and gray-white, and have the appearance of chicken fat.
3. Sometimes, bleeding from the biliary tumor thrombus partially or completely fills up the biliary tree with blood clots, which obstruct the biliary system.

With a better understanding of icteric-type HCC, a new classification bearing therapeutic and prognostic implications is needed. Recently, Lau and colleagues[1,12,17,18] proposed a modified classification of icteric-type HCC based on the combination of the anatomic level of biliary obstruction, cholangiographic appearances, and etiological causes (Fig. 4). This classification is important because, firstly, patients with extrahepatic biliary obstruction secondary to HCC have a higher curative resection rate and a better survival than those patients with intrahepatic biliary obstruction. Furthermore, a significant proportion of patients with type 1 intraluminal obstruction caused by a biliary tumor thrombus or a tumor fragment and type 2 hemobilia can be cured, while

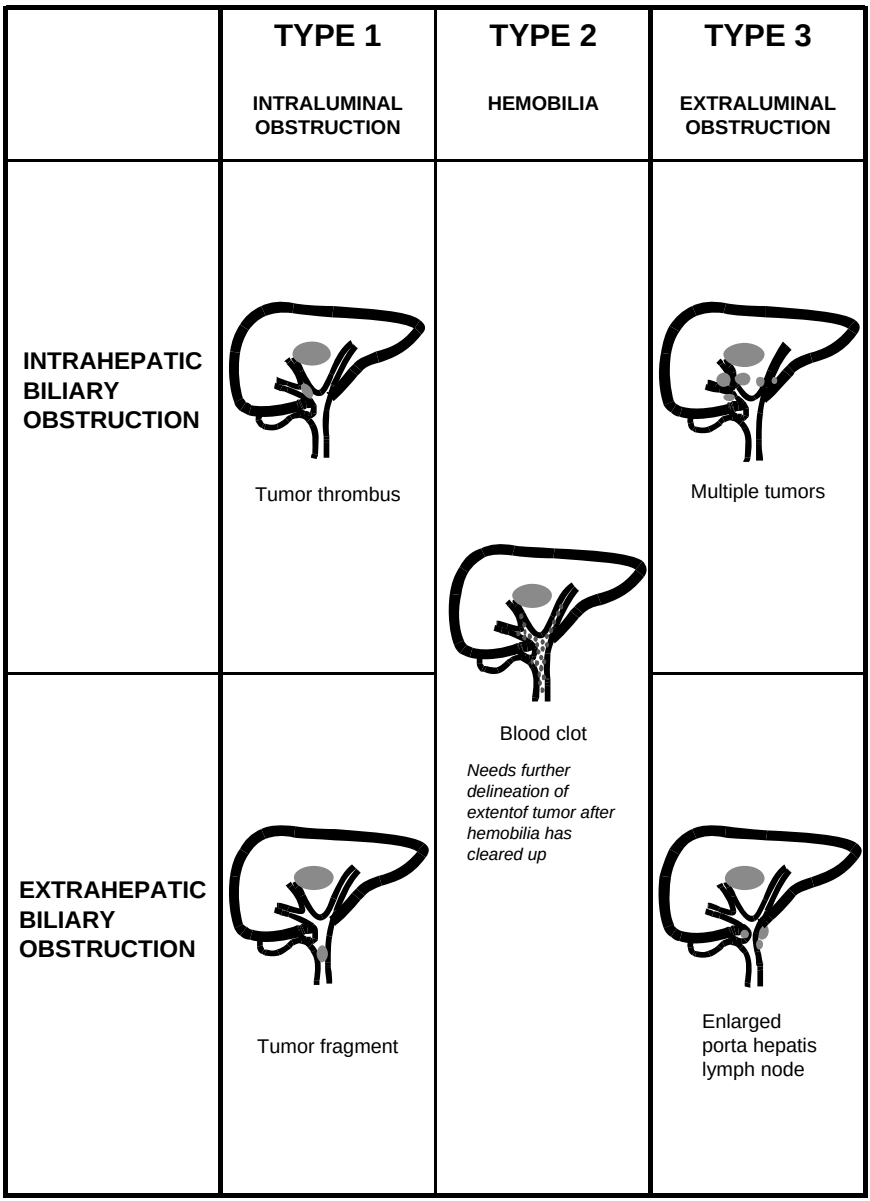

Fig. 4. Classification of icteric-type HCC (Lau *et al.*[1,12,17,18]).

those patients with type 3 extraluminal obstruction caused by tumor invasion/encasement or malignant porta hepatis lymph nodes have an incurable disease with poor prognosis.

In type 1 obstruction, the tumor, having invaded into a peripheral bile duct, grows into and along the hepatic duct until the confluence of the right and left hepatic ducts, causing partial or complete biliary obstruction. Further extension of the biliary tumor cast into the common hepatic and bile ducts causes complete obstruction of the biliary system. On cholangiography, tumor thrombus in the biliary tree gives an intraluminal filling defect that resembles a cork in the neck of a bottle, named the "Cork sign" (Fig. 5).[18,19] Occasionally, the tumor cast is within one of the main hepatic ducts, a fact which in itself would not lead to obstructive jaundice; however, tumor fragments shed from this tumor cast can drop into the common bile duct, causing biliary obstruction. The filling defects are similar to those seen in choledocholithiasis on cholangiography, but the edges of the filling defects secondary to tumor fragments are irregular and less well defined than

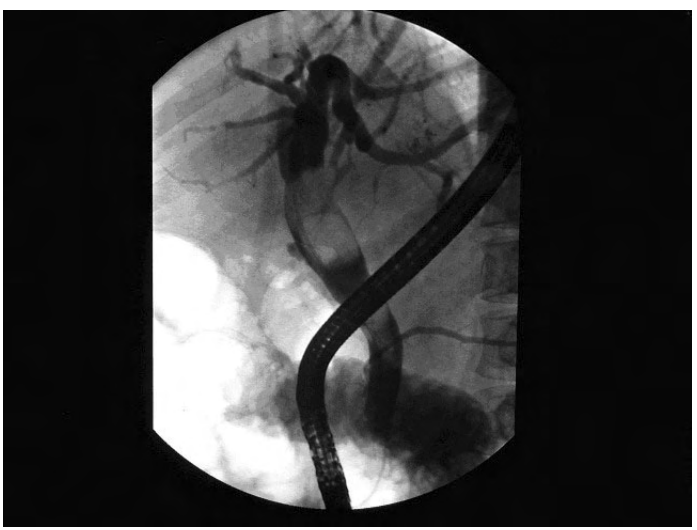

Fig. 5. Cholangiography showing tumor thrombus in the biliary tree ("Cork sign"). "Soft-tissue case 52. Presentation" — Reprinted from *CJS* August 2003; **46**(4), page(s) 301–302, by permission of the publisher. © 2003 Canadian Medical Association.

those of stones. In type 2 obstruction, hemobilia gives the cholangiographic features of fluffy intraluminal filling defects and the blood clots can obscure the underlying intraluminal tumor. In type 3 obstruction, extraluminal obstruction due to tumor invasion/encasement of the hepatic ducts or malignant porta hepatis lymph nodes gives rise to the radiological features of localized strictures with proximal biliary tree dilatation.[1,18]

The management of icteric-type HCC is divided into three phases: (1) stabilization of patients, including biliary tree decompression and hemostasis; (2) assessment for curative treatment; and (3) definitive treatment in the form of liver resection and biliary-enteric anastomosis if the tumor is resectable. In patients with significant jaundice, the biliary tree should first be decompressed by endoscopic internal drainage or external percutaneous transhepatic biliary drainage; we prefer the latter, as the drain can be easily blocked by blood clots and tumor fragments if it is not flushed from time to time with normal saline. If there is profuse hemobilia, selective hepatic angiography and embolization should be carried out to stop the bleeding, as these thrombi are supplied by arterial branches from the hepatic artery. After stabilization, if the tumor is resectable and the patient is fit for liver resection, the HCC should be resected *en bloc* with the involved biliary tree. If the biliary tumor thrombus does not infiltrate into the bile duct wall, thrombectomy through a choledochotomy is also an option for cure. Icteric-type HCCs have a better prognosis with liver resection than those without resection. The reported 5-year survival after curative resection varied from 6.7% to 45%. For patients with unresectable icteric-type HCC, palliative biliary drainage should be carried out to improve the quality of survival. If the liver function improves, some form of palliative treatment, such as transarterial chemoembolization (TACE) or transarterial radioembolization (TARE), can be considered.[13,17–21]

In conclusion, the prognosis of patients with HCC who present with hepatocellular-type jaundice is dismal. It is important to identify the small group of patients who have icteric-type HCC because, with proper treatment, good palliation and occasional cure are possible.

Esophageal Variceal Hemorrhage

Esophageal variceal bleeding can be a manifestation of HCC. In the management of patients with esophageal variceal bleeding, the possibility of HCC with portal vein thrombosis should be considered, especially in geographical regions where HCC is prevalent. The actual incidence of HCC presenting with esophageal variceal bleeding remains unclear; the reported incidence ranged from 1% to 8%.[22–26] Overall, these patients have a very poor prognosis, with a median survival ranging from 1.5 months to 3.5 months.[23–27] The mechanisms of esophageal variceal bleeding can be due to either the underlying liver cirrhosis with portal hypertension or the presence of tumor thrombi within the portal venous system, leading to portal venous obstruction and aggravation of portal hypertension. In addition, the existence of a hepatic portal venous shunt within the HCC allows direct transmission of arterial pressure to the splanchnic venous system.[28] This increased pressure not only causes and aggravates variceal rupture, but also perpetuates variceal bleeding. Endoscopic variceal ligation is considered as the most effective treatment in controlling esophageal variceal bleeding, and decreases the rate of recurrent variceal bleeding in those patients without HCC. However, esophageal variceal bleeding in HCC is characterized by a high rate of recurrent bleeding and a high failure rate of hemostasis. With the limited survival of this group of patients with advanced HCC, the survival benefit of endoscopic variceal ligation is still unclear.

In the nonrandomized comparative study of Chen *et al.*[26] on patients with bleeding esophageal varices and concomitant HCC, endoscopic variceal ligation ($n = 16$) was compared with conservative treatment ($n = 23$). Endoscopic variceal ligation significantly reduced the risk of fatal bleeding (44% vs. 70%) and the number of patients who died at the index hemorrhage (11% vs. 52%). In the absence of portal vein thrombosis, endoscopic variceal ligation significantly reduced the rebleeding rate (17% vs. 50%) and the mortality rate (0% vs. 100%).

In the randomized study of Chen *et al.*,[27] patients with unresectable HCC and acute esophageal variceal bleeding underwent emergency endoscopic variceal ligation. After hemostasis, patients were randomized to either the maintenance esophageal variceal ligation group ($n = 54$)

or the esophageal variceal ligation as necessary group (demand ligation) ($n = 55$). One or more subsequent esophageal variceal ligation sessions could be performed in 30 patients only (55.6%) in the maintenance group (actual maintenance ligation). The survival and recurrent bleeding rates were similar in both groups. A subgroup analysis of patients with Child–Pugh class A and B hepatic reserve showed that maintenance ligation ($n = 24$) reduced the rate of recurrent bleeding when compared with demand ligation ($n = 25$). The authors concluded that maintenance ligation was feasible in patients with unresectable HCC and variceal hemorrhage if these patients had good hepatic reserves. Maintenance ligation might lower the rate of recurrent bleeding in this subgroup of patients.

Paraneoplastic Syndromes

Patients with HCC presenting with paraneoplastic syndromes usually have a large tumor volume and a high serum alpha-fetoprotein (AFP) level. The most common and important paraneoplastic syndromes are hypoglycemia (4.6%–27.7%), erythrocytosis (1%–12%), hypercalcemia (5.3%–40%), and hypercholesterolemia (11%–38%).[29–32] Other rare syndromes include prophyria cutanea tarda, virilization and feminization syndromes, carcinoid syndrome, hypertrophic osteoarthropathy, hyperthyroidism, and osteoporosis.[1] These syndromes may be present long before any local effects of the tumor are apparent, and it can mislead and delay the diagnosis of HCC. Awareness of the unusual presentations of HCC is relevant in high-incidence areas in order to increase the chances of early treatment and improvement of survival.

Hypoglycemia

Hypoglycemia is a well-known paraneoplastic manifestation of HCC that usually occurs in the terminal stages of the disease. McFadzean and Yeung[33] described two different forms of hypoglycemia in patients with HCC. Type A hypoglycemia is characterized by mild-to-moderate–degree hypoglycemia, progressive cachexia, and rapid tumor growth in

the terminal stage of the disease. The hypoglycemia is readily corrected. The mechanism of hypoglycemia in these patients is attributed to the progressive demand for glucose by the tumor coupled with a progressive reduction in glucose supply, partly due to tumor encroachment of the residual liver parenchyma and partly due to undernutrition.

Type B hypoglycemia is characterized by marked hypoglycemia, no cachexia, and slow tumor growth in the early course of the disease. It is difficult to control. The mechanism for type B hypoglycemia is thought to be related to the oversecretion of big insulin-like growth factor II (IGF-II), leading to the suppression of growth hormone.[34,35] As a consequence, the formation of a growth hormone (GH)-dependent 150-kD IGF–binding protein complex, which normally carries 70%–80% of total serum IGF-II and largely restricts its bioavailability, is impaired. Impaired formation of the 150-kD complex leads to a shift of IGF-II to a 50-kD IGF–binding protein complex, resulting in a 30-fold shorter serum half-life of IGF-II, increased turnover, and enhanced bioavailability.

Erythrocytosis

Ectopic production of erythropoietin by the tumor has been suggested as a cause of erythrocytosis, which leads to polycythemia with a high hemoglobin level. Light microscopic immunohistochemistry showed that erythropoietin was definitely present in the cytoplasm of HCC cells, but not in normal hepatocytes around the carcinoma lesion or in other nonparenchymal cells such as vascular endothelial cells and Kupffer cells.[36] In electron microscopic immunohistochemistry, reaction products for erythropoietin were revealed in the cisternae of the endoplasmic reticulum in the carcinoma cells, suggesting the production of erythropoietin by these cells. Northern blot analysis as well as reverse transcriptase and polymerase chain reaction (RT-PCR) of erythropoietin mRNA extracted from a surgical specimen also indicated high expression of erythropoietin mRNA in the tumor tissue.[37] The erythrocytosis improved and the high serum erythropoietin level decreased after resection of the tumor.[38]

Hypercalcemia

The pathophysiology of hypercalcemia in malignancy can be classified into three subtypes: (1) tumors with bone metastases; (2) hematological malignancies; and (3) tumors without bone metastases.[39] The majority of patients with HCC with hypercalcemia do not have bone metastases. Parathyroid hormone–related protein (PTHrP) is the primary mediator of calcium, which stimulates increased bone resorption by osteoclasts.

Hypercholesterolemia

The mechanism of hypercholesterolemia in HCC is still unclear. The suggested mechanisms include the production of cholinesterase in tumor cells and the absent or defective receptors for chylomicron remnants on the surface of tumor cells.[40,41]

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36

Management of Acute Liver Failure

A. R. Nitin Rao

Introduction

Liver failure can be either acute (in the absence of a pre-existing liver disease) or acute on chronic (in the presence of a pre-existing liver disease). Liver failure is an entity that causes multiorgan failure and cerebral edema, and carries a high mortality. Survival rates as quoted in the medical literature range from 72% to 30%–35% for patients aged between 10 years and 40 years,[1] and 10% for patients less than 10 years of age or greater than 40 years.[2] This is equivalent to an estimated 2000 deaths a year attributed to acute liver failure (ALF) in the United States. The higher the stage of encephalopathy reached, the worse the prognosis.

Liver transplantation continues to be the only definitive treatment for liver failure, although only 20% of patients waiting for a liver transplantation actually receive a transplant,[3] with nearly 2000 candidates for liver transplantation dying while on the waiting list.[4] There are several other modalities of therapy — including hepatocyte transplantation,

extracorporeal liver perfusion, and artificial/bioartificial liver dialysis — that are promising and need to be considered in the management of acute liver failure. These modalities can support and rest the liver while it regenerates and the patient recovers fully, or can be used as a bridge for liver transplantation.

Definition

An International Association for the Study of the Liver (IASL) subcommittee[5] has defined acute liver failure (ALF) as the time of onset of encephalopathy from the time of jaundice to be less than 4 weeks, and subacute liver failure (SLF) as the time of onset of encephalopathy from the time of jaundice to be 4–24 weeks. Previously, Bernuau *et al.*[6] classified liver failure as fulminant hepatic failure (jaundice to onset of encephalopathy; $\leq$2 weeks) or subfulminant hepatic failure (jaundice to onset of encephalopathy; 2–12 weeks). O'Grady *et al.*[7] of King's College, London, defined hyperacute liver failure (jaundice to onset of encephalopathy; <7 days), acute liver failure (jaundice to onset of encephalopathy; 1–4 weeks), and subacute liver failure (jaundice to onset of encephalopathy; 5–12 weeks). The IASL suggests desisting the use of terms such as fulminant hepatitis and fulminant hepatic failure. The IASL definition of ALF is used in this chapter.

Etiology

Acetaminophen overdose is a leading cause of ALF in the United Kingdom; it also carries a high incidence in the USA,[8] but the incidence appears to be falling. Worldwide, infections with hepatitis viruses are the main cause of ALF. Among the hepatitic viruses, hepatitis B and/or D is the most frequent cause. Hepatitis C as the sole cause of ALF is frequently reported in Japan.[9] Hepatitis A and E are commonly seen as causes of ALF in Asia and Africa, with ALF being more common in pregnancy particularly in the third trimester. There have been several reports of hepatitis G as a cause of ALF, but it still needs to be proved as the sole cause of ALF.[10]

Table 1. Etiology of acute liver failure.

Category	Cause
Infective	Viral hepatitis A, B, B+D, C, E Non–A-E hepatitis Cytomegalovirus, Epstein–Barr virus, adenovirus, herpes simplex virus Tuberculosis, bacterial septicemia
Drugs/Toxins	Acetaminophen, halothane, isoniazid, sodium valproate, phenytoin, ketoconazole, ecstasy Amanita phalloides (mushrooms)
Metabolic	Acute fatty liver of pregnancy, HELLP syndrome Wilson's disease, Reye's syndrome
Vascular/Ischemic	Budd–Chiari syndrome Ischemic hepatitis, heat stroke
Infiltrative	Leukemia, lymphoma
Herbal supplements	LipoKinetix, kava, chaparral, ma huang
Postsurgical	Primary nonfunction post–liver transplantation Post–extensive liver resection in a compromised liver

As shown in Table 1, several drugs and toxins can cause ALF, with acetaminophen being the leading toxin commonly used for suicidal or parasuicidal intent or in accidental overdose. Death attributable to the ingestion of acetaminophen is usually associated with doses of 15–25 g.[11] Herbal supplements are also known to cause liver failure, with the result that the Food and Drug Administration (FDA) removed LipoKinetix from the market in November 2001 and has issued warnings against the use of Kava and Chaparral.[12] With herbal supplements becoming commonly used, it should become part of the assessment to inquire for the use of any of these supplements from patients with ALF.

Primary nonfunction of the liver after liver transplantation and liver failure after major liver resection in a compromised liver carry a high mortality, although these are not traditionally considered as causes of ALF as they do not present with the toxic liver syndrome. After liver resection, a liver mass of 20%–30% of a normal liver is required to prevent the development of liver failure, which can be fatal.[13] The

chances of post–liver resection liver failure is higher in patients with deranged liver function, prior liver diseases, and extensive resection with a small liver remnant. No specific etiology was found in a substantial proportion of ALF cases after full investigations, and these cases were categorized as either caused by a viral (non–A-E) hepatitis infection or ALF of unknown etiology.[14]

Patients with malignancy- or Wilson's disease–induced ALF rarely survive. The highest survival figures are in patients with hepatitis A– or acetaminophen-induced toxicity, followed by intermediate outcomes in those with hepatitis B or D infections, and the poorest outcome with drug-induced (except acetaminophen) or cryptogenic ALF.[15]

Management

The high mortality and morbidity of patients with ALF is due to cerebral edema, infections, renal failure, hepatic encephalopathy, pulmonary and cardiac dysfunction, coagulopathy, and metabolic abnormalities,[16] with the main cause of mortality being cerebral edema. These patients should be managed in an intensive care setting, preferably in centers with facilities for liver transplantation. Patients should be nursed with minimal stimulation in a quiet environment, with low surrounding noise and dim lights, with as minimal endotracheal suction in intubated patients as necessary, and with elevation of the patient's head at 20°–30°. Grade III or IV patients usually need intubation to maintain oxygen saturation.

Specific treatments for patients who present with or are suspected of having acetaminophen-induced ALF include prompt treatment with *N*-acetylcysteine[17] even pending confirmation of its concentration in blood, preferably within 8 hours of drug ingestion as it is less efficacious after that time. Intravenous carnitine should be administered for valproate-induced hepatotoxicity with mitochondrial injury.[18] Termination of pregnancy with delivery of the fetus should be performed in acute fatty liver of pregnancy, and a recent study showed the benefit of lamivudine treatment in patients with fulminant hepatitis B.[19]

Persistence of arterial hyperammonemia is associated with profound changes in the cerebral concentration of glutamine and alanine. The

elevation of brain glutamine concentration is correlated to the intracranial pressure (ICP) in patients with fulminant hepatic failure.[20] ICP monitoring in patients with acute liver failure is a protocol used in several centers and carries a complication rate of 20%,[21] mainly intracranial bleeding; however, in the absence of ICP monitoring, intracranial hypertension is treated less aggressively. ICP is usually measured invasively by ventricular, subdural, or intraparenchymal transducers. Recently, attempts have been made to measure ICP noninvasively either by using transcranial ultrasound to measure blood flow or by imaging the optic nerve using ultrasound to measure the optic nerve sheath diameter.[22] Making patients of acute liver failure hypothermic[23] (32°C–33°C) has been shown to induce significant reduction in ICP and mean arterial pressure, and to increase cerebral perfusion pressure with a significant reduction in arterial ammonia concentration and brain metabolism. In a randomized controlled trial, the infusion of hypertonic saline (30%)[24] significantly reduced ICP. Mannitol infusion is another modality that can be used to reduce cerebral edema.

Renal failure is frequent in ALF. Renal replacement therapy with continuous venovenous hemofiltration (CVVH) is recommended.[25] A greater removal of ammonia is achieved when CVVH dialysis (CVVH-D) is used.

Bacterial infections are commonly seen in up to 80% of patients.[26] The infections were associated with bacteremia in 20%–25% of patients. Fungal infections were also commonly seen in 33% of patients.[27] Prophylactic antibiotic administration has been shown to be of no benefit. However, the managing clinician should have a high index of suspicion for infections and the threshold for starting antibiotics should be low.

Respiratory failure, which may need to be managed with mechanical ventilation, is frequently seen in patients with ALF.

Cardiac failure develops due to a hyperdynamic circulation, peripheral vasodilatation, and central volume depletion, leading to hypotension which requires vasopressor therapy.[8]

Coagulopathy is a prominent feature of ALF. Fresh frozen plasma (FFP) administration should be avoided in these patients, as the infusion of FFP has no effect on patient survival and it affects the coagulation profile, which is used to monitor the patient's need for liver transplantation.

FFPs should be infused prior to invasive procedures in order to correct the coagulopathy.

When hypoglycemia develops, it needs to be managed with dextrose infusion. It is important to avoid giving too much glucose to cause hyperglycemia. Hyponatremia, hypokalemia, hypophosphatemia, and metabolic acidosis are the other metabolic abnormalities that may develop and need to be corrected.

Enteral nutrition continues to be the best means to provide nutritional support.

Hepatocyte Transplantation

Hepatocytes for transplantation are obtained by collagenase digestion of livers not suitable for a whole-organ liver transplantation. These hepatocytes can be used immediately, but they are more usually maintained in *ex vivo* culture for several days and then used. Hepatocytes are anchorage-dependent for survival. Freshly extracted cells have the highest chance of engraftment,[28] and only 20%–30% of infused cells in ideal conditions engraft into the liver parenchyma. Human hepatoma cells, immortalized hepatocytes, fetal liver cells, and stem cells have also been used.[29] The usual routes of transplantation are intraportal injection for lodging in the liver, splenic artery injection for lodging in the spleen (red pulp), and intraperitoneal injection usually after the encapsulation of hepatocytes to protect against the host immune response.

Habibullah *et al.*[30] showed an apparent improvement in survival in seven patients with grade III encephalopathy treated with infusion of fetal hepatocytes as compared to 50% survival in the control group. No benefit was seen in patients with a higher grade of encephalopathy. Bilir *et al.*[31] described a patient with grade IV encephalopathy who survived a full 52 days after a single hepatocyte infusion. Strom *et al.*[32] carried out a prospective controlled trial of transplanting isolated fresh and cryopreserved human hepatocytes through the splenic artery as a bridge to liver transplantation. Three of five patients with grade IV encephalopathy and multisystem organ failure were successfully bridged to liver transplantation in the treated group compared to no survivors in the control group. A patient with acute fatty liver of pregnancy in

grade IV hepatic encephalopathy who received peritoneal hepatocyte transplantation with 3×10^8 fetal hepatocytes 24 hours after delivery and who recovered completely within 7 days has been reported.[33]

Hepatectomy Prior to Transplantation

Ringe *et al.*[34] suggested using total hepatectomy in patients with toxic hepatic syndrome resulting from fulminant hepatic failure and primary graft nonfunction to stabilize the patient. Such a policy can only be carried out when there is a surety of a liver graft being available for liver transplantation in time. A patient can survive an anhepatic time of usually less than 24 hours.

Extracorporeal Liver Perfusion

Extracorporeal liver perfusion (ECLP) (Fig. 1) was first performed using human cadaveric livers by Sen *et al.*,[35] and one of five patients treated recovered completely. About 270 patients worldwide have received ECLP using human, pig, baboon, calf, and monkey livers with an overall survival rate of 26%.[15] Recently, there has been renewed interest to use ECLP as a bridge in the wait for a suitable organ for liver transplantation,[36–38] with good results.

Liver Dialysis (Liver Support)

Liver dialysis (Fig. 2) involves the use of either artificial liver (AL) support, where no hepatocytes are used in the system to remove toxic molecules only, or bioartificial liver (BAL) support, where hepatocytes are used in a bioreactor to remove toxic molecules and to replace the liver function by these hepatocytes. The common bioreactors in BAL consist of a dialysis cartridge with the hepatocytes anchored intracapillarily or extracapillarily, through which the perfusate (whole blood or plasma) flows through. The molecular weight cut-off of these cartridges ranges from 70 kD to 150 kD. Charcoal filters are generally used in the system (AL or BAL), as they adsorb a large number of toxic molecules (Table 2);

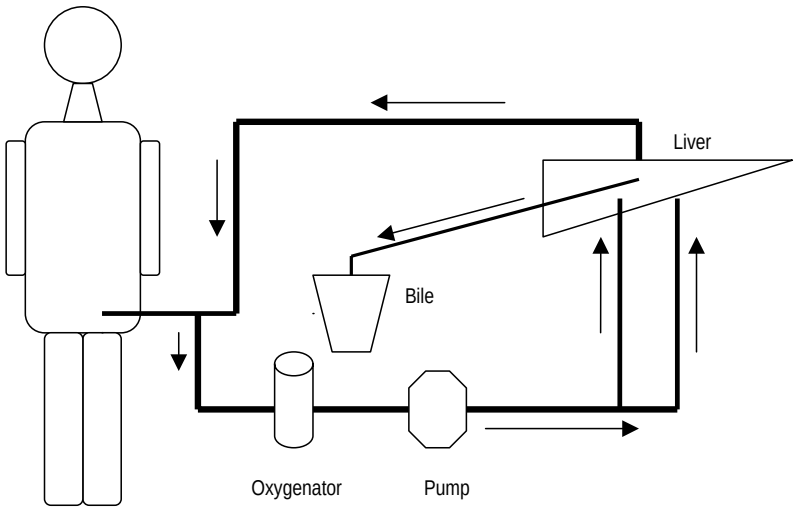

Fig. 1. Schematic diagram of extracorporeal liver perfusion.

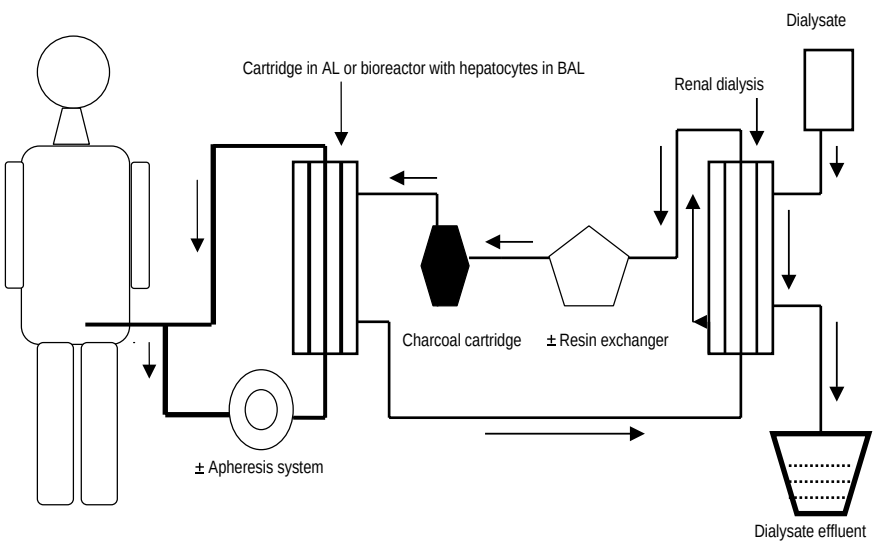

Fig. 2. Schematic diagram of a general AL or BAL, with various possible combinations generally seen.

Table 2. Molecules adsorbed by charcoal filter.

Urea	Cytokines	Phenol
Creatinine	Salicylates	Mercaptans
Lactate	Barbiturates	Catecholamines
Uric acid	Bile acids	Organic acids
Endotoxins	Aromatic amino acids	Ammonia (not effectively)

other sorbents used are synthetic resins and anion exchange resins. The hepatocytes used in BAL are primary human–, primary porcine–, or human liver tumor–based cell lines. These treatments are sometimes associated with adverse events,[39] the most important ones being bleeding (thrombocytopenia-associated), hypotension, fever, sepsis, allergic shock, and disseminated intravascular coagulopathy.

Artificial Liver Support

Artificial liver support for the failing liver has progressed over the years from hemodialysis, hemofiltration, exchange transfusion, plasmapheresis, and hemoperfusion. A randomized controlled trial on patients with fulminant hepatic failure treated with charcoal hemoperfusion[40] showed no survival benefits. This has led to newer AL systems, with the molecular adsorbent recycling system (MARS) being the most studied one.

MARS is the most commonly used AL, with an experience of use in over 3000 patients. It consists of an albumin-coated cartridge and the patient's blood is dialyzed against an albumin solution across the cartridge, leading to removal of albumin-bound toxins. It also contains a charcoal cartridge and an anion exchanger in the system, with facilities for renal dialysis of the albumin solution in the system. In a randomized trial of MARS on 13 patients with type I hepatorenal syndrome,[41] a survival benefit was shown compared to the control group. Posthepatectomy liver failure following extensive liver resection in a compromised liver carried a grave prognosis with a mortality of above 80%. In a case series with MARS treatment on such patients, out of five patients treated, there was one survival.[42] Chui *et al.*[43] showed significant biochemical and neurological improvement in ALF patients

treated with MARS, but there was no long-term survivor with posthepatectomy liver failure surviving for 28 days. A meta-analysis of the four randomized controlled trials of MARS treatment for ALF and acute-on-chronic liver failure showed no significant reduction in mortality as compared to standard medical therapy.[44]

Prometheus is a newer extracorporeal liver support device[45] that facilitates the combined removal of both albumin-bound and water-soluble toxins based upon the method of fractionated plasma separation and adsorption (FRSA). In a comparative study with the MARS systems,[46] it showed greater clearance of all measured protein and water-soluble markers including urea and bilirubin. A trial on 11 patients with acute-on-chronic liver failure showed improvements in ammonia, bilirubin, creatinine, and blood pH levels.[47]

The newer ALs being developed and tested are (1) selective plasma filtration, which includes the new plasma filtration therapy[48] for hepatic failure tested in preclinical studies on pigs that showed reduction of ammonia, aromatic amino acids (AAAs), IL6, TNFα, and C3a; (2) the sorbent suspension reaction (SSR), which makes use of powdered charcoal[49] to increase charcoal adsorption; and (3) the fluidized bed adsorbent system, which uses microscopic beads (magnetic microparticles) made up of hydrophobic neutral resin and an anion exchange resin-based detoxification system.[50]

BioLogic-DT, also known as the liver dialysis unit, is a unit that combines hemodialysis, charcoal column, and resin cartridges. It was used in a prospective controlled multicenter trial[51] on 56 ALF and acute-on-chronic liver failure (ACLF) patients; significant improvements were seen in liver function and bridging for transplantation in ACLF patients, whereas no significant benefit was seen in ALF patients as compared to the control group.

Bioartificial Liver (BAL) Support

Primary porcine hepatocytes are the most commonly used hepatocytes in bioreactors of the BAL system. Also used are primary human hepatocytes (the first choice, but limited by its availability) and human hepatoblastoma (HepG2–C3a) cell lines. There has also been a

suggestion for the use of goat[52] hepatocytes to overcome the problem of porcine endogenous retrovirus (PERV) infections. PERV is carried in the pig germline, and all recipients of porcine tissues or organs are exposed to the virus. The number of hepatocytes used in the bioreactors is usually equivalent to less than 5% of the normal human liver. Rao *et al.*[53] have shown viral and gene transfer across the bioreactor membranes, carrying the potential for xenosis with the use of xenogenic hepatocytes in BAL. Although human complement is postulated to protect humans from animal retroviral zoonoses, infection of human cells with retroviruses has been shown.[54] Infection of human cells by porcine retroviruses *in vitro* has been shown; but no such infection *in vivo*[55] has been shown in patients treated with various porcine cells for a multitude of ailments, even though microchimerism has been shown in these cells for over 8 years — a positive scenario towards the use of such cells. To reduce the risks of infection, these animals should ideally be obtained from a gnotobiotic environment (free of all associated microbial flora, except for those nonpathogens purposefully introduced for the biologic requirement of the animal). In reality, these animals are obtained from specific pathogen-free sources which are closed, microbiologically well defined, and controlled colonies, with the animals being tested for specific pathogens.

A phase I trial[56] with the Academic Medical Center, Amsterdam–developed AMC-BAL on seven patients with ALF showed full recovery in one patient without the need for transplantation, while the remaining six patients were bridged to liver transplantation.

The Modular Extracorporeal Liver Support (MELS) system developed in Berlin was used in a phase I trial[57] on eight patients with ALF, and successfully bridged all of the patients to liver transplantation. The MELS bioreactor presently holds 250–500 g of primary porcine or human hepatocytes.

The Excorp Bioartificial Liver Support System (BLSS) — which consists of a blood pump, a heat exchanger, an oxygenator, and a hollow fiber bioreactor with 70–100 g of porcine hepatocytes — has been tested only in one patient with liver failure.[58]

Sheil *et al.*[59] reported the use of the only BAL that has a continuous culture of porcine hepatocytes in the circuit on three ALF patients.

Of these, one patient with Wilson's disease was successfully bridged to transplantation.

Demetriou *et al.*[60] — in a prospective, randomized trial using their HepatAssist liver support system, which incorporates porcine hepatocytes (seven billion), plasmapheresis system, charcoal column, and oxygenator, on 171 patients with fulminant/subfulminant hepatic failure and primary nonfunctioning liver following liver transplantation — failed to show a survival benefit in the liver support group as compared with the control group. Samuel *et al.*[61] treated 10 ALF patients with HepatAssist 2000 (five billion porcine hepatocytes), and showed significant neurological improvement in all patients with 2 patient deaths and 8 survivals after liver transplantation, thus showing the system's efficacy as a tool for bridging patients to transplantation.

The Extracorporeal Liver Assist Device (ELAD) system developed by Sussmann and colleagues[62] — with the bioreactor having 100–400 g of human hepatoblastoma cell line (C3A) cells and a plasmapheresis system — was used to treat 24 patients with ALF in a randomized controlled trial, but showed no survival advantage. Another randomized controlled phase I trial[63] using the ELAD system showed a significant benefit as a bridge to liver transplantation. A modified version of the ELAD[64] with 400 g of hepatocytes (C3A) was successfully used to bridge five patients with fulminant hepatic failure to liver transplantation, with four patients surviving the 30-day endpoint of the study.

A hepatocyte spheroid (supposedly more viable with better cell performance)-based BAL, the hybrid artificial liver support system (HALSS),[65] with a plasma separator was tested on 10 patients with severe liver failure, showing improvements in hepatic encephalopathy and liver function.

Liver Transplantation

Presently, liver transplantation continues to be the best definitive therapy for ALF, with liver transplant units around the world having about 10%–15% of their liver transplants done for ALF patients. The minimal criteria to list patients with fulminant hepatic failure (FHF) regardless of etiology is the onset of stage 2 hepatic encephalopathy in a patient

who meets the definition of FHF.[66] It is to be noted that several of the patients who meet this criteria will recover while some deteriorate very precipitiously; hence, a continuous assessment of these patients is required in terms of suitability and requirement of transplantation. O'Grady *et al.*[7] from King's College, London, and Bernuau *et al.*[6,67] from the Hospital Beaujon, France, have come up with a set of criteria (Table 3) based on minimal investigations for transplantation that can be used as guidelines for the referral of patients to a liver transplant center.

Farmer *et al.*[68] — in their series of 204 liver transplants (LTs) for FHF — reported patient survival at 1 and 5 years after LT of 72.5% and 66.9%, respectively, and an overall operative mortality of 1.5% with a median time from listing to LT of 2 days. In view of the shortage of cadaveric donors in an emergency (a common scenario in the East), the use of living donors for LT has been resorted to. Uemoto *et al.*[69] from Japan reported 34 patients who received 36 living donor liver transplants (LDLTs) with the use of the lateral segment or the right or left hemiliver. The 1- and 3-year patient survivals were both 59%. Patients who received auxiliary partial orthotopic liver transplantation (APOLT) had poor results. These authors suggested a minimal graft-to-recipient weight ratio (GRWR) for a successful LDLT for FHF to

Table 3. Criteria for liver transplantation in ALF.

King's College criteria (O'Grady *et al.*[7])	*Acetaminophen-induced FHF* Arterial pH of less than 7.3 or concurrent presence of creatinine >300 μmol/L, grade III/IV encephalopathy, prothrombin time (PT) >100 s *Non–acetaminophen-induced FHF* PT >100 s or presence of any 3 of these: PT >50 s; bilirubin >300 μmol/L; age <10 yrs or >40 yrs; time to encephalopathy from jaundice >7 days; non-A–, non-B–, or drug/halothane-induced FHF
Hospital Beaujon criteria (Bernuau *et al.*[67])	*Non–acetaminophen-induced FHF* Age <30 yrs + factor V <20%, or age >30 yrs + factor V <30%

be 0.8%, and a relatively safe value to be 1%. Chenard-Neu *et al.*[70] reported 30 patients from different centers with FHF who received APOLT with an overall survival rate of 63%, and 68% of the survivors were completely off immunosuppressive medications after their original liver disease recovered. Split liver transplantation is another modality that has been used to increase the number of organs for transplantation; however, it has been shown to give inferior results in urgent (ALF) as compared to nonurgent patients.[71]

Xenotransplantation (four performed to date using chimpanzee, baboon, and pig liver) is an option in ALF patients in the situation of unavailability of a donor liver. Although the issues of hyperacute rejection seem to be resolved, xenograft rejection cannot be prevented without significant immunosuppression and toxic side-effects.[72] In view of the huge risks of viral infection, this treatment modality has currently been shelved worldwide.

Conclusions

The liver is an organ with a multitude of functions including synthesis, storage, elimination, detoxification, homeostasis, biotransformation, metabolism, and immunologic functions; therefore, its functions are complex to replicate as compared to the heart, lung, or kidney. We are still far away from an ideal liver support device; but with the development of a new device, we are probably moving towards the ideal.

Intensive care management of ALF patients, preferably in liver transplant centers, is the current treatment standard. Liver transplantation continues to be the definitive treatment for ALF patients (some authors believe it to be the gold standard) not managable either by medical means or by liver dialysis.

Although the only meta-analysis[39] of all randomized controlled trials of artificial and bioartificial support systems for acute and acute-on-chronic liver failure showed a reduction in mortality in patients with acute-on-chronic liver failure as compared to standard medical therapy, there was no survival benefit in acute liver failure. However, these devices have been shown in randomized controlled studies to have a place in the management of ALF patients, as they improve the patient's

biochemical and neurological status and can be used as a bridge for liver transplantation.

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Extracorporeal Energy Therapy

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Introduction

Hepatocellular carcinoma (HCC) is well suited to treatment with locoregional therapy because it has a tendency to stay within the liver until an advanced stage of the disease, with distant metastasis generally occurring late. Patients with HCC usually die of liver failure as a result of local growth and resultant liver tissue destruction, but not as a result of extrahepatic disease.[1–7] This suggests that an effective local treatment will have a great impact on the course of the disease. Percutaneous local ablative therapy and transarterial regional therapy are less invasive alternatives to surgery, but still require percutaneous insertion of an instrument or arterial puncture/embolization. Extracorporeal energy therapy is a truly noninvasive local-regional therapy for patients with HCC.

This chapter illustrates the development and the current role of local therapies for HCC using four kinds of extracorporeal energy sources:

(1) high-intensity focused ultrasound (HIFU); (2) conformal radiotherapy; (3) stereotactic radiotherapy; and (4) proton beam therapy.

High-Intensity Focused Ultrasound (HIFU)

HIFU is a highly precise, noninvasive procedure that uses a high-intensity, focused extracorporeal source of ultrasound to induce complete coagulative necrosis of a specific target tissue, without requiring surgical exposure or insertion of instruments into the lesion. The ultrasound energy passes harmlessly through the overlying tissues en route to a tightly focused target area. An important difference between HIFU and many other forms of focused energy, such as radiotherapy or radiosurgery, is that the passage of ultrasound energy through the intervening tissues has no apparent cumulative effect on those tissues. Other advantages of HIFU are that it does not exclude other treatment options and is repeatable.

The interest in the development of HIFU technology is because of its potential applications as a noninvasive therapy. HIFU treatment for uterine fibroids was approved by the U.S. Food and Drug Administration (FDA) in 2004. Clinical trials are underway to evaluate the treatment of cancerous tumors in the prostate, kidney, breast, liver, pancreas, bone, and brain. Although HIFU treatment of localized prostate cancer is currently an approved therapy in some countries, cancer treatments are still in the investigatory phases in most countries at this moment. HIFU is also being investigated as a potential method of hemostasis.[8]

Clinical applications of HIFU treatment have only come in recent years. However, the first work to consider the potential applications of HIFU was published in 1942 by Lynn *et al.*[9] Important early work was performed in the 1950s and 1960s by William and Francis Fry at the University of Illinois, culminating in clinical treatments of Parkinson's disease.[10–12] Unfortunately, practical and technological limitations hampered progress in the research of HIFU therapy. In the last two decades, the development of HIFU therapy has been greatly enhanced through the development of high-power ultrasound arrays and noninvasive monitoring methods.[13–16]

The mechanisms of tissue destruction with HIFU are related to hyperthermia and cavitation.[17,18] During HIFU treatment, ultrasound waves are focused as one would use a magnifying glass to focus sunlight. Ultrasound waves are generated by piezoelectric elements and are focused by spherical arrangement, acoustic lens, or paraboloid reflectors. Different organs are accessible for HIFU, but are limited by the need for an optimal wide acoustic window; these organs include the liver, kidney, prostate, breast, and brain. There are also limitations to the clinical application of HIFU, and to the planning and actual delivery of treatment. HIFU cannot be directed through air-filled viscera such as the lung and bowel or through other obstacles such as bone, which can absorb or reflect an ultrasound beam.

Ultrasound is coupled by degassed and deionized water between the source and the patient's skin in order to allow good ultrasonic transmission. Because of the comparable acoustic properties of water and tissue, the ultrasound should penetrate the intervening tissues with minimal absorption and reflection. The power density of the converging ultrasound increases as it approaches the focal point. The rapid rate of energy deposition at the target tissue far exceeds the rate of heat dissipation, resulting in a rapid rise in temperature. The focused ultrasound energy is directed at a small volume of the lesion, raising its temperature high enough to cause thermal ablation without impacting other tissues. Heat destroys tissue through coagulative necrosis, which is irreversible if the temperature reaches 60°C–100°C. Converging high-intensity ultrasound energy waves generates tremendous energy, which rapidly increases in the focal spot driving temperatures >65°C in less than 1 second. The tissue is destroyed within 3 seconds and the energy is turned off. Pulses of energy are repeated at a different point until the entire volume of the lesion is treated. The ability to focus and accurately target a lesion with HIFU by using real-time ultrasonography (USG) or magnetic resonance imaging (MRI) guidance allows precise ablation of lesions of any shape without damage to the surrounding structures. The combination of MRI and HIFU — magnetic resonance–guided focused ultrasound (MRgFUS) — enables improved visualization of tumor morphology and more precise thermal dose control. The whole procedure takes 1–3 hours, depending on the size of the lesion.

Areas of coagulative necrosis have been shown at histopathologic examination to have a spatially sharp demarcation between regions of normal and necrotic tissues.[19,20] Outside of the boundary, the treatment area was almost normal; in the treated area, all tumor cells appeared irreversibly dead in the form of nuclear pyknosis, debris, or dissolution. The blood sinusoids were collapsed with endothelial cell damage. Electronic microscopic examination showed distorted tumor cells with severe destruction of cell organelles and nuclei. The cytoplasm was irregularly vesiculated, and the membranes of the organelles were broken. Cell membrane and nuclear membrane disintegration as well as nucleus disruption were generally observed.[19,21]

The potential value of HIFU as a noninvasive local treatment for HCC has also attracted considerable interest. In the early 1990s, a large number of animal studies were carried out.[22–28] In the last decade, basic research and clinical works carried out in China further suggested that HIFU has a great potential in the treatment of HCC.[29–36] In the prospective study of Wu *et al.*,[33] 55 patients with HCC in cirrhotic liver (tumor diameter, 4–14 cm; mean diameter, 8.14 cm) received HIFU therapy and the median number of HIFU sessions was 1.69. The overall survival rates at 6, 12, and 18 months were 86.1%, 61.5%, and 35.3%, respectively. There were no severe side-effects. In the study of Yi *et al.*,[34] 46 patients with unresectable HCC had a 1-year survival of 50.84% after HIFU therapy. Another prospective nonrandomized comparative trial of Wu *et al.*[35] also demonstrated survival advantage to the combination of HIFU and transarterial chemoembolization (TACE) ($n = 24$) compared with TACE alone ($n = 26$) in patients with unresectable HCC (median survival, 11.3 months vs. 4 months, respectively; 1-year survival, 42.9% vs. 0%, respectively). Li *et al.*[36] showed that HIFU was useful in the relief of symptoms related to HCC (86.6%), such as pain, poor appetite, and weight loss; and that alpha-fetoprotein (AFP) was lowered by >50% in 65.3% of patients. An early phase II study investigating the safety and feasibility of HIFU in the treatment of liver and kidney tumors was performed at the Churchill Hospital in Oxford, England; HIFU treatment in the Western population was both safe and feasible, and the adverse event profile was favorable.[37,38]

The main side-effects of HIFU are minor skin burn, edema, thickening, pigmentation, and transient pain. However, the medical literature

reporting on the short-term outcome, efficacy, and safety of HIFU for HCC still comprises a relatively small number of patients. Randomized controlled trials (RCTs) are necessary to evaluate the long-term efficacy of HIFU treatment for HCC.

Conformal Radiotherapy

External radiotherapy has been regarded as ineffective for HCC because the dose of radiation that can be delivered to the tumor is limited by the tolerance of the nontumorous liver. While HCCs are relatively radioresistant and an irradiation dose of 120 Gy is required to kill the tumor, the tolerance of the liver towards irradiation is relatively low.[5,39] The tolerance of the normal whole liver to external irradiation is approximately 30 Gy[5,39,40]; whole-liver irradiation beyond this limit is likely to result in radiation hepatitis (also called radiation-induced liver disease, RILD). Estimates of the liver doses associated with a 5% risk of RILD for uniform irradiation of one third, two thirds, and the whole liver are 90 Gy, 47 Gy, and 31 Gy, respectively.[41–43] The mean liver doses associated with a 5% risk of classic RILD for primary and metastatic liver cancers are 28 Gy and 32 Gy, respectively, in 2 Gy per fraction.[43] RILD has a high mortality rate of nearly 50%. It develops about 2 weeks to 4 months after hepatic irradiation. The presentations include painful hepatomegaly and anicteric ascites. The alkaline phosphastase is markedly elevated, and its elevation is out of proportion to the increases in bilirubin and transaminases. Although the exact radiation tolerance of a cirrhotic liver is not known, it is speculated that the cirrhotic liver can tolerate less irradiation than normal liver. In the analysis of patients with HCC after conformal radiotherapy by Cheng *et al.*,[44] patients who were hepatitis B carriers or had Child–Pugh B cirrhosis presented with a statistically significantly greater susceptibility to RILD.

In order to increase the effective doses to the tumors in the liver, attempts have been made to use conformal radiotherapy. Conformal radiotherapy refers to a method of treatment delivery that incorporates rigid immobilization as well as three-dimensional computer planning and treatment systems to produce a high-dose area of radiation that conforms to the shape of the target. The aim is to deliver a tumoricidal

radiation dose to the tumor while keeping the dose to the nontumorous liver parenchyma below its radiation tolerance limit, thus decreasing the toxic side-effects while improving the treatment results. The dose prescription is guided by a dose–volume histogram, and the goal is to deliver the maximum possible dose to the tumor within a prescribed normal tissue complication probability. The availability of the three-dimensional treatment planning based on the dose–volume histogram concept allows high-dose irradiation to the tumors and permits quantification of the nontumorous liver to radiation, thus making the treatment safer. The use of three-dimensional conformal techniques has made partial liver irradiation possible to doses in the 70–80-Gy range with conventional fractionation.[45]

The outcome of patients with unresectable HCC, who had either failed or were unsuitable for TACE, treated with three-dimensional conformal radiotherapy has been evaluated in single-arm studies.[46–48] The tumor response rate — complete response (CR) + partial response (PR) — was 54%–61%, and the median survival was 15–19 months.[46–48] Mornex *et al.*[49] conducted a prospective phase II study including patients with unresectable small HCC (one nodule $\leq$5 cm or two nodules $\leq$3 cm) and Child–Pugh class A/B disease ($n = 25$). High-dose three-dimensional conformal radiotherapy (66 Gy, 2 Gy/fraction) was given. The CR and PR were 80% and 12%, respectively. About 41% of patients had grade 3/4 radiation-related toxicities. Studies also showed that conformal radiotherapy when combined with TACE attained varying degrees of objective responses from 18% to 90.5% and median survivals of 17–37 months.[50–52]

Portal vein invasion/thrombosis is an extremely poor prognostic factor for advanced HCC because it is associated with a high probability of extensive tumor spread and an elevation of portal venous pressure.[53,54] Portal vein thrombosis is often considered to be a contraindication to TACE. Kim *et al.*[53] showed a tumor response rate of 45.8% and a median survival of 10.7 months in 59 patients with unresectable HCC and thrombosis in the main or first branch of the portal vein after conformal radiotherapy to both the primary tumor and the portal vein tumor thrombus (PVTT). A dose–response relationship was demonstrated to exist in the PVTT. Conformal radiotherapy when given to

the PVTT (but not to the primary tumor) recanalized the portal vein, making it possible for the patients to subsequently receive TACE. In the prospective study of Lin *et al.*,[55] conformal radiotherapy recanalized portal vein thrombosis with a response rate of approximately 83% in patients who completed the treatment (a daily dose of 1.8 Gy, 5 fractions per week, given to a total dose of 45 Gy); however, due to the aggressive disease nature, only 33% of patients completed the radiotherapy regimen and could be evaluated in that study. In the prospective study of Yamada *et al.*,[56] 19 patients with unresectable HCC and tumor thrombosis in the first branch of the portal vein received conformal radiotherapy to the portal vein thrombus and TACE. The 1- and 2-year survivals were 40.6% and 10.2%, respectively. The median survival time was 7.0 months. An objective response was observed in 57.9%. Recanalization of the first portal branches was not observed; however, protrusion of the PVTT into the main portal trunk decreased in all cases (see Chapter 33).

In the absence of RCTs, it is still unknown whether there is a survival benefit with the use of conformal radiotherapy for HCC. Further trials are needed to compare conformal radiotherapy with the other treatments.

Stereotactic Radiotherapy

Stereotactic radiotherapy is an evolving cancer treatment method in which concepts and techniques previously developed for brain tumor radiosurgery are adapted to treat extracranial tumors. It is a treatment method for delivering a high dose of radiation to the target by using either a single dose or a small number of fractions with a high degree of precision within the body. This allows high-dose irradiation to be focused on the target with relatively less irradiation of normal tissues. The extension of these approaches to extracranial sites required significant technical advances in tumor imaging to guide radiation administration, patient immobilization, and conformal radiation delivery techniques.[57,58]

There are not much data on the efficacy of this treatment in HCC. Choi *et al.*[57] evaluated the feasibility and treatment outcomes of

fractionated stereotactic radiotherapy for 20 patients with HCC (mean size, 3.8 cm); the 1-year and 2-year survival rates were 70.0% and 43.1%, respectively (median, 20 months). Phase I/II trial results for unresectable HCC are yet to be determined.

Proton Beam Therapy

Proton beam therapy is a form of external beam radiation therapy that uses protons rather than photons (X-rays). The main advantage of protons over photons is related to the way their energies are released.[59] Compared with X-ray therapy, a proton beam delivers an extremely low amount of radiation until it reaches the targeted site. Protons are part of the center of the atom, the atomic nucleus, and carry a positive electrical charge. The positive charge and large mass of the proton (1800 times greater mass than an electron) make it easier to control its placement within the patient, thus allowing higher doses of radiation to the tumor region while largely sparing normal tissues. Energized protons slow down as they pass through tissues, displaying minimal lateral scatter and depositing most of their energy at the end of their paths. They then release a peak of energy at their target point — the cancer. This point is called the Bragg peak: the region of maximum energy deposition of a heavy particle as it travels into matter. Basically, the protons release their energy when they stop rather than when they are traveling through tissues.

The available evidence showed proton beam therapy to be safe and tolerable with an excellent primary tumor control rate. In the phase II trial of Bush *et al.*,[60] 34 patients received irradiation doses of 63 cobalt Gray equivalents in 15 fractions over 3 weeks; the 2-year local tumor control rate and survival rate were 75% and 55%, respectively. In another phase II clinical trial of Kawashima *et al.*,[61] 30 patients received doses of 76 cobalt Gray equivalents in 20 fractions over 5 weeks. The 2-year survival was 66%; after a median follow-up of 31 months, only one patient experienced recurrence of the primary tumor. Chiba *et al.*[62] reported 162 patients treated with a median total dose of 72 Gy in 16 fractions over 29 days. Approximately 85% developed another HCC in the liver within 5 years after therapy. They underwent TACE/TAE,

percutaneous ethanol injection (PEI), proton beam therapy, systemic chemotherapy, or no treatment for the newly developed HCC. The 5-year local tumor control rate and survival rate were 86.9% and 23.5%, respectively. Hata *et al.*[63] reported 21 patients treated with a median dose of 73 Gy in a median of 18 fractions. The objective response rate was 81%; the 5-year local tumor control rate was 93%; and the 2- and 5-year overall survival rates were 62% and 33%, respectively.

The survival benefit of proton beam therapy for patients with HCC is not known. RCTs are needed to evaluate its long-term efficacy. Unfortunately, the availability of proton beam therapy is limited to a few centers in the world and it is very expensive.

Conclusions

HIFU, conformal radiotherapy, stereotactic radiotherapy, and proton beam therapy seem to be feasible options in the treatment of HCC, with a favorable side-effect profile. This makes them viable alternatives for patients who are not candidates for other treatments. At this stage, these treatments should only be offered to patients in a research setting. Further controlled trials are required to define the precise indications and long-term results of these treatments. These noninvasive locoregional therapies can be considered as one of the therapies for clinical use only when the results from RCTs are available.

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