Recommended Reading | LIVER, PART III

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The *SRGS* Recommended Reading List is a carefully selected summary of current, classic, and seminal articles for further study. All of the articles below are cited in the order they appear in the literature review; they also appear in the reference list (43–47).

Full-text reprints of these articles are included in certain formats of *SRGS*.

1. **Hepatocellular carcinoma…54-63**

   El-Serag HB

   This article supplies a clearly written, detailed review of the pathophysiology, diagnosis and management of hepatocellular carcinoma.

2. **Screening for Viral Hepatitis and Hepatocellular Cancer…64-72**

   Cameron AM

   This is article is a thorough review of screening approaches for hepatitis and hepatocellular carcinoma.

3. **Hepatocellular carcinoma: current management and perspectives for the future…73-89**

   Rahbari NN, Mehrabi A, Mollberg NM, Muller SA, Koch M, Buchler MW, Weitz J

   This report provides perspective on the present and future management alternatives for hepatocellular carcinoma.

4. **Salvage Versus Primary Liver Transplantation for Early Hepatocellular Carcinoma: Do Both Strategies Yield Similar Outcomes?…90-98**

   Bhangui P, Allard MA, Vibert E, et al.

   This study reports data comparing outcomes of primary versus salvage liver transplantation for patients with early-stage hepatocellular carcinoma. The data analysis showed an advantage for primary transplantation.

5. **Defining long-term outcomes with living donor liver transplantation in North America…99-109**

   Olthoff KM, Smith AR, Abecassis M, et al.

   Olthoff and coauthors provide an analysis of outcomes and patient selection criteria for living donor liver transplantation.

6. **Preoperative Cholangitis and Future Liver Remnant Volume Determine the Risk of Liver Failure in Patients Undergoing Resection for Hilar Cholangiocarcinoma…110-120**

   Ribero D, Zimmitti G, Aloia TA, et al.

   Ribero and coauthors provide data supporting an important association between preoperative cholangitis and liver remnant volume with outcomes of surgical resection of hilar cholangiocarcinoma.

CURRENT CONCEPTS

Hepatocellular Carcinoma

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Each year, hepatocellular carcinoma is diagnosed in more than half a million people worldwide, including approximately 20,000 new cases in the United States.[1,2] Liver cancer is the fifth most common cancer in men and the seventh in women. Most of the burden of disease (85%) is borne in developing countries, with the highest incidence rates reported in regions where infection with hepatitis B virus (HBV) is endemic: Southeast Asia and sub-Saharan Africa (Fig. 1).[3] Hepatocellular carcinoma rarely occurs before the age of 40 years and reaches a peak at approximately 70 years of age. Rates of liver cancer among men are two to four times as high as the rates among women. Hepatocellular carcinoma related to infection with hepatitis C virus (HCV) has become the fastest-rising cause of cancer-related death in the United States, and during the past two decades, the incidence of hepatocellular carcinoma in the United States has tripled while the 5-year survival rate has remained below 12%[2] (Fig. 2). The greatest proportional increase in cases of hepatocellular carcinoma has been seen among Hispanics and whites between 45 and 60 years of age.[4]

RISK FACTORS

Major risk factors for hepatocellular carcinoma include infection with HBV or HCV, alcoholic liver disease, and most probably nonalcoholic fatty liver disease. Less common causes include hereditary hemochromatosis, alpha$_1$-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, and Wilson's disease. The distribution of these risk factors among patients with hepatocellular carcinoma is highly variable, depending on geographic region and race or ethnic group.[5] Most of these risk factors lead to the formation and progression of cirrhosis, which is present in 80 to 90% of patients with hepatocellular carcinoma. The 5-year cumulative risk for the development of hepatocellular carcinoma in patients with cirrhosis ranges between 5% and 30%, depending on the cause (with the highest risk among those infected with HCV), region or ethnic group (17% in the United States and 30% in Japan), and stage of cirrhosis (with the highest risk among patients with decompensated disease).[6]

Worldwide, chronic HBV infection accounts for approximately 50% of all cases of hepatocellular carcinoma and virtually all childhood cases. In endemic areas in Asia and Africa, where HBV infection is transmitted from mother to newborn, up to 90% of infected persons have a chronic course, with frequent integration of HBV into host DNA. Although HBV can cause hepatocellular carcinoma in the absence of cirrhosis, the majority (70 to 80%) of patients with HBV-related hepatocellular carcinoma have cirrhosis. The risk of hepatocellular carcinoma among persons with chronic HBV infection (those who are positive for the hepatitis B surface antigen [HBsAg]) is further increased if they are male or elderly, have been infected for a long time, have a family history of hepatocellular carcinoma, have been exposed to the mycotoxin aflatoxin, have used alcohol or tobacco, are coinfected with HCV or hepatitis delta virus, have high levels of HBV hepatocellular replication (as indicated

Figure 1. Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.
The incidence rates shown (numbers of cases per 100,000 persons) pertain to both sexes and all ages. Adapted from the World Health Organization.[3]

by high levels of HBV DNA),[7] or are infected with HBV genotype C.[8] HBV DNA can also be detected in persons who are HBsAg-negative, but the association with risk of hepatocellular carcinoma is unclear in these cases.

The estimated risk of hepatocellular carcinoma is 15 to 20 times as high among persons infected with HCV as it is among those who are not infected, with most of the excess risk limited to those with advanced hepatic fibrosis or cirrhosis.[9] HCV infection occurred in large numbers of young adults in Japan in the 1920s, in southern Europe in the 1940s, and in North America in the 1960s and 1970s (with the cases in North America resulting from the sharing of contaminated needles by users of injection drugs and from blood transfusions).[10] Markers of HCV infection are found in 80 to 90% of patients with hepatocellular carcinoma in Japan, 44 to 66% in Italy, and 30 to 50% in the United States.[5] It has been projected that cases of HCV-related hepatocellular carcinoma will continue to increase in the United States over the next two to three decades. Risk factors for hepatocellular carcinoma among persons infected with HCV include an older age at the time of infection, male sex, coinfection with the human immunodeficiency virus or HBV, and probably diabetes or obesity.[11-13] Prolonged, heavy use of alcohol (defined as daily ingestion of 40 to 60 g of alcohol, with a standard drink containing 13.7 g, or 0.6 oz) is a well-established risk factor for hepatocellular carcinoma both independently (with the risk increased by a factor of 1.5 to 2.0) and in combination with HCV infection and, to a lesser extent, with HBV infection.[9]

In several studies conducted in Western countries, 30 to 40% of patients with hepatocellular carcinoma did not have chronic infection with HBV or HCV, suggesting the presence of other causes of disease. Some of these patients were more likely to have had clinical or biochemical features of fatty liver disease (obesity) or the metabolic syndrome (e.g., type 2 diabetes). In population-based cohort studies in the United States, Scandinavia, Taiwan, and Japan,[12-14] hepatocellular carcinoma was 1.5 to 2.0 times as likely to develop in obese persons as in those who were not obese. Several case–control studies and a few cohort studies have shown that, on average, hepatocellular carcinoma is twice as likely to develop in persons with type 2 diabetes as compared with those who do not have diabetes.[15,16] Nonalcoholic fatty liver disease, which is present in up to 90% of all obese persons and up to 70% of persons with

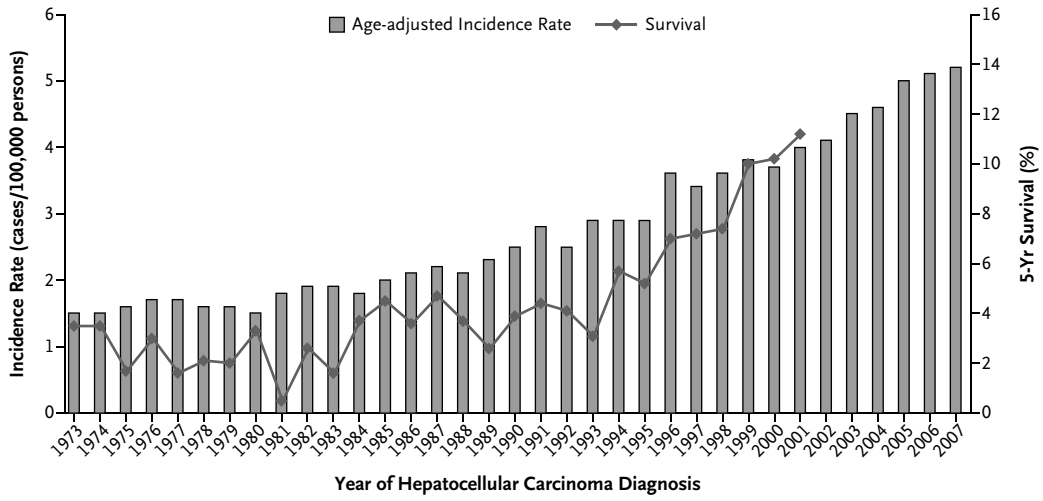

Figure 2. Age-Adjusted Incidence and 5-Year Survival Rates for Patients with Hepatocellular Carcinoma in the United States, 1973–2007.

type 2 diabetes, has been proposed as a possible risk factor for hepatocellular carcinoma.[17] Because of the paucity of data showing a direct association between progression of fatty liver disease and hepatocellular carcinoma, currently available estimates of risk are unclear. However, given the very high prevalence of the metabolic syndrome in the United States, even small increases in risk related to obesity or diabetes could translate into a large number of cases of hepatocellular carcinoma.

Several case–control and cohort studies conducted in Japan and southern Europe have shown that coffee drinking is associated with a reduced risk of hepatocellular carcinoma.[18] The mechanisms for this possible protective effect have not been established. Coffee drinking has also been associated with reduced insulin levels and a reduced risk of type 2 diabetes.[19]

PREVENTION

HBV VACCINATION

A safe and effective HBV vaccine is available and should be given to all newborns and persons without immunity who are at high risk for infection. National HBV vaccination programs have dramatically reduced the prevalence of HBV infection, and there has been a concomitant decrease in the incidence of hepatocellular carcinoma. In Taiwan, for example, the first universal HBV vaccination program for newborns began 20 years ago, with infants of mothers at high risk for HBV infection (HBsAg-positive) receiving both the vaccine and an injection of hepatitis B immune globulin. Since the program began, the incidence of hepatocellular carcinoma in children between 6 and 14 years of age has fallen by 65 to 75%.[20]

ANTIVIRAL TREATMENT

There is moderately strong evidence that antiviral therapy that controls HBV infection in HBsAg-positive patients and that eradicates HCV in patients with viremia substantially reduces but does not eliminate the risk of hepatocellular carcinoma in patients with viral hepatitis. In one large, rigorous, Chinese study, patients with chronic HBV infection who also had cirrhosis or advanced fibrosis were randomly assigned to receive 100 mg of lamivudine per day or placebo for up to 5 years; the incidence of hepatocellular carcinoma was significantly reduced in the lamivudine group as compared with the placebo group (3.9% vs. 7.4%; hazard ratio, 0.49; $P=0.047$).[21] Lower-quality evidence, from nonrandomized trials and observational studies, suggests that there is a reduction in the risk of disease with either interferon or lamivudine.[22]

The results of one randomized, controlled study and several nonrandomized studies involving patients who were infected with HCV but did not have cirrhosis indicated that among those treated with interferon-based therapy who had a sustained

viral response, the risk of hepatocellular carcinoma was reduced by 57 to 75%.[23,24] Another study showed that among patients with HCV infection who did have cirrhosis and did not have a sustained response to antiviral therapy, the risk of hepatocellular carcinoma was not significantly reduced with maintenance interferon therapy.[25]

SURVEILLANCE

Practice guidelines from the American Association for the Study of Liver Diseases recommend surveillance for patients at high risk for hepatocellular carcinoma.[26] Collectively, the strength of the evidence supporting the efficacy of surveillance in high-risk groups is modest. One randomized, controlled trial of nearly 19,000 HBV-infected patients in China showed that surveillance consisting of measurement of serum alpha-fetoprotein levels and ultrasonographic imaging every 6 months was associated with a 37% reduction in mortality related to hepatocellular carcinoma.[27] However, another randomized, controlled trial involving HBV-positive patients in China showed that surveillance was not beneficial.[28] There are no data from randomized trials of surveillance in patients with HCV or in patients with cirrhosis. Several nonrandomized trials and observational studies have shown a survival benefit in patients with small hepatocellular tumors, but these studies had unavoidable biases.[29,30]

I recommend ultrasonography of the liver combined with measurement of serum alpha-fetoprotein levels every 6 to 12 months as surveillance for hepatocellular carcinoma in patients with cirrhosis or advanced hepatic fibrosis, irrespective of the cause. Both are also useful in surveillance of HBV carriers with or without cirrhosis if they are Africans older than 20 years of age or Asians older than 40 years of age or if they have a family history of hepatocellular carcinoma. Because hepatocellular carcinoma is rare in HCV-infected patients with mild or no hepatic fibrosis, surveillance is not recommended for this group. With a cutoff point of 20 ng per milliliter, serum levels of alpha-fetoprotein have low sensitivity (25 to 65%) for the detection of hepatocellular carcinoma and are therefore considered inadequate as the sole means of surveillance. Ultrasonography has a sensitivity of approximately 65% and a specificity of more than 90% for early detection.[31] The calls for abandoning the monitoring of alpha-fetoprotein levels may be premature,[32] especially given the already low rates of surveillance of hepatocellular carcinoma in community practice. In North American studies, the combined measurement of alpha-fetoprotein and other biomarkers, such as des-gamma-carboxyprothrombin or lectin-bound alpha-fetoprotein, was shown to provide only a limited additional benefit as compared with the measurement of alpha-fetoprotein alone and thus cannot be recommended.[30,33,34]

Computed tomography (CT) and magnetic resonance imaging (MRI) are not generally recommended for hepatocellular carcinoma surveillance (as distinct from diagnosis and staging); their sensitivity, specificity, and positive and negative predictive values for this purpose are unknown, and their use is associated with high cost as well as possible harm (e.g., radiation, allergic reaction to contrast medium, nephrotoxicity with CT, and nephrogenic fibrosing dermopathy from the use of gadolinium with MRI in patients with renal insufficiency).

DIAGNOSIS

The diagnosis of hepatocellular carcinoma can increasingly be made with the use of noninvasive imaging tests, especially at specialized centers. In patients with cirrhosis and a focal hepatic mass larger than 2 cm in diameter, the diagnosis can be confidently established on the basis of the presence of typical imaging features showing areas of early arterial enhancement and delayed washout (less enhancement than the rest of the liver) in the venous or delayed phase of four-phase multidetector CT (the four phases are unenhanced, arterial, venous, and delayed) or in dynamic contrast-enhanced MRI (Fig. 3). These radiologic changes are related to increased vascularity in the hepatocellular carcinoma, supplied by the hepatic artery. For lesions 1 to 2 cm in diameter, concordant findings from CT and MRI are recommended in order to diagnose hepatocellular carcinoma with confidence. In these patients, an alpha-fetoprotein level of 400 ng per milliliter or higher is also highly predictive of hepatocellular carcinoma.

Image-guided biopsy should be considered for focal hepatic masses with atypical imaging features or discrepant findings on CT and MRI, or for lesions detected in the absence of cirrhosis. A negative biopsy result, although reassuring, does not rule out malignant disease; the nodule should be further studied at intervals of 3 to 6 months until it disappears, grows larger, or displays char-

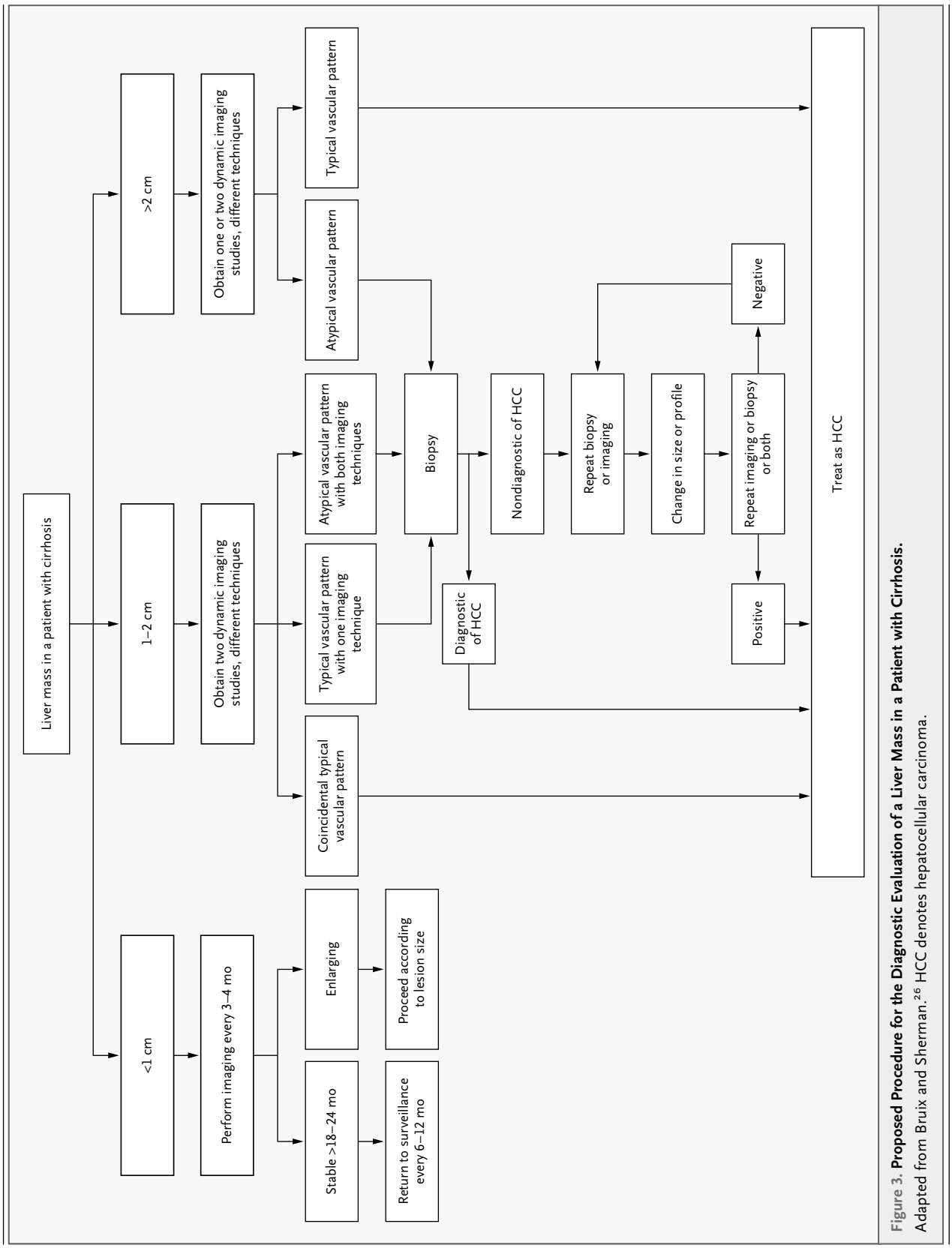

Figure 3. Proposed Procedure for the Diagnostic Evaluation of a Liver Mass in a Patient with Cirrhosis.
Adapted from Bruix and Sherman.[26] HCC denotes hepatocellular carcinoma.

acteristics that are diagnostic of hepatocellular carcinoma.[26] The risk of tumor seeding along the needle track after biopsy in patients with suspected hepatocellular carcinoma is low (2.7%).[35] Accurate assessment of liver nodules measuring less than 1 cm is difficult, whether imaging alone or imaging and biopsy are performed; these lesions are probably best monitored with the use of ultrasonography at intervals of 3 to 6 months for 1 to 2 years.

TREATMENT

STAGING-GUIDED TREATMENT

There are several potentially curative or palliative approaches to the treatment of hepatocellular carcinoma.[36] The choice of treatment is driven by the cancer stage, the resources available, and the level of practitioner expertise. Since only a few randomized, controlled trials have compared these approaches, most recommendations for staging-guided treatment rely on the findings of observational studies or expert opinion. Numerous staging systems for hepatocellular carcinoma have been developed, and they have been validated to varying degrees. Barcelona Clinic Liver Cancer (BCLC) staging has been proposed as the standard means of assessing the prognosis for patients with hepatocellular carcinoma. The BCLC staging system is a useful assessment tool that incorporates data on the patient's performance status, number and size of nodules, cancer symptoms, and liver function as determined by the Child–Pugh classification system.[37] The Child–Pugh scoring system uses five clinical measures of liver disease. Each measure is assigned a score of 1 to 3 points, with 3 points indicating the most severe derangement. Scores on the five measures are then summed to determine the overall severity of disease, with a sum of 5 or 6 points indicating class A disease, 7 to 9 points class B, and 10 to 15 points class C, or the most severe disease. (For additional details on the Child–Pugh scoring system, see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Although genomic analysis has been used to identify possible prognostic biomarkers,[38] the results require validation. High serum and tissue levels of vascular endothelial growth factor are significantly associated with poor survival,[39] but the usefulness of this biomarker in clinical practice is unclear.

Very-early-stage hepatocellular carcinoma is currently difficult to diagnose, since it requires presentation with a single, asymptomatic lesion measuring less than 2 cm in diameter, with no vascular or distant metastases (Fig. 4). Surgical resection in these cases is associated with an overall survival rate of 90%. For patients presenting with early-stage hepatocellular carcinoma who have some preserved liver function (falling within class A or B of the Child–Pugh system) with a solitary hepatocellular-carcinoma nodule measuring less than 5 cm in diameter or no more than three nodules, each measuring less than 3 cm in diameter, the choice of therapy is dictated by the severity of the liver dysfunction, the extent of portal hypertension, and the patient's status with respect to coexisting conditions. Surgical resection should be considered for patients with solitary tumors and no portal hypertension. Otherwise, the most appropriate treatment for patients with early-stage hepatocellular carcinoma is liver transplantation, which is associated with a 5-year survival rate of up to 75%. If transplantation is not possible, local ablation is the next best option.

Patients with compensated cirrhosis, no symptoms related to hepatocellular carcinoma, and no vascular invasion but with large or multifocal lesions are considered to have intermediate-stage hepatocellular carcinoma. In these patients, transarterial chemoembolization (TACE) improves the 2-year survival rate by 20 to 25% as compared with more conservative therapy.

Patients with mild cancer-related symptoms, vascular invasion, or extrahepatic spread are considered to have advanced-stage disease and are not suitable candidates for radical therapies. TACE has increased the survival rate among well-selected candidates, but the primary treatment option for patients with this stage of disease is the oral chemotherapeutic agent sorafenib. Patients with terminal-stage disease present with cancer symptoms related to liver failure, vascular involvement, or extrahepatic spread. The 1-year survival rate for such patients is less than 10%, and they do not benefit from the treatments mentioned above.[36] (A chart that provides an overview of disease stages and recommended treatments is provided in the Supplementary Appendix.)

SURGICAL RESECTION

Surgical resection is the treatment of choice in patients without cirrhosis who are in the very early stage of hepatocellular carcinoma. For patients

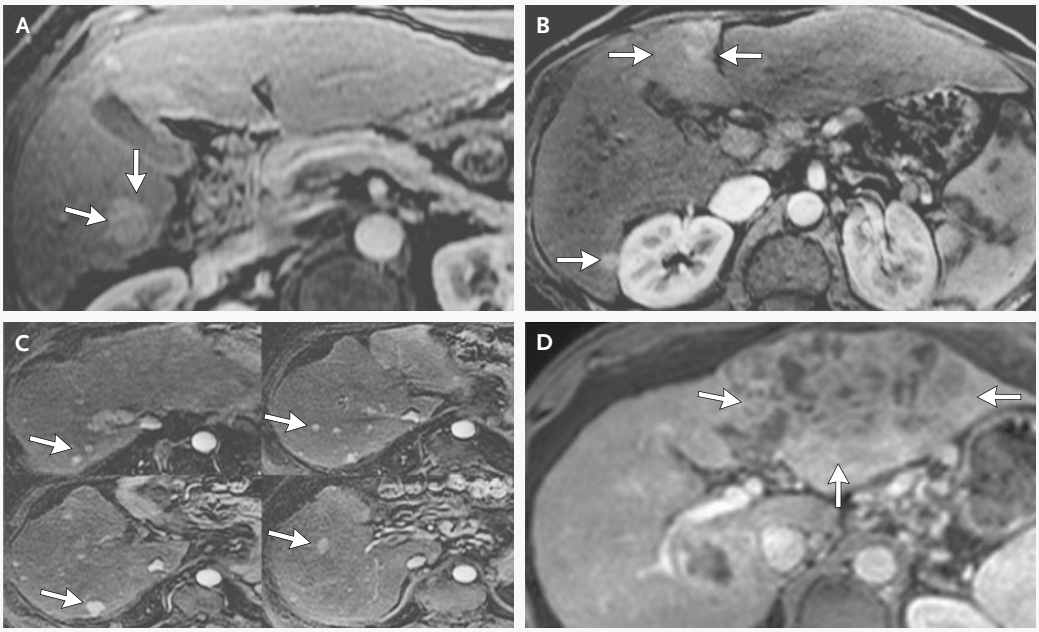

Figure 4. MRI Studies Showing the Effects of Hepatocellular Carcinoma at Different Stages of the Disease.
All MRI studies were performed with the use of intravenous contrast material and show areas of enhancement typically found in patients with hepatocellular carcinoma. Panel A shows a single mass measuring 1.7 cm in diameter (arrows), indicating very-early-stage hepatocellular carcinoma (defined as a single lesion measuring less than 2 cm in diameter). Panel B shows two lesions, measuring 2.4 and 1.2 cm in diameter (arrows), indicating early-stage hepatocellular carcinoma (defined as fewer than three nodules, each measuring less than 3 cm in diameter). Panel C shows multiple hepatocellular-carcinoma nodules (arrows) in a patient with Child–Pugh class B cirrhosis, indicating intermediate-stage disease. Panel D shows a large mass (more than 10 cm in diameter) and ascites (arrows), indicating advanced-stage hepatocellular carcinoma.

with cirrhosis, resection produces the best results when the tumor is small (<3 cm in diameter), portal hypertension (a hepatic venous pressure gradient >10 mm Hg) is absent, and the total bilirubin level is normal (≤1 mg per deciliter [≤17.1 μmol per liter]).[40,41] The 5-year risk of recurrence of hepatocellular carcinoma after resection is as high as 70% because the underlying chronic liver disease continues to put the patient at risk for the development of new hepatocellular carcinoma. In the United States, less than 5% of patients are candidates for hepatic resection. This approach is much more common in Asian countries, where there are greater numbers of young people with HBV-related hepatocellular carcinoma and no or minimal cirrhosis.

LIVER TRANSPLANTATION

Among patients with hepatocellular carcinoma who have underlying cirrhosis, orthotopic liver transplantation in selected candidates is the treatment option associated with the lowest risk of tumor recurrence. Other treatment options carry a higher long-term risk of recurrence because they have no effect on chronic liver disease, which is the major driving factor in the development of hepatocellular carcinoma. However, because of the scarcity of organs available for transplantation within an optimal time frame, strict criteria are used to limit transplantation to patients with hepatocellular carcinoma who are likely to have excellent outcomes.

Patients with hepatocellular carcinoma who meet the Milan criteria for orthotopic liver transplantation (essentially, a solitary nodule measuring less than 5 cm in diameter or three nodules, each measuring less than 3 cm) have an expected 4-year overall survival rate of 85% and a recurrence-free survival rate of 92%.[42] In the United States, experience in clinical practice supports the effectiveness of orthotopic liver transplantation in patients meeting the Milan criteria as adopted by the United Network for Organ Sharing (UNOS).[43]

The primary criteria used by UNOS to prioritize the allocation of livers available for transplantation are the Model for End-Stage Liver Disease (MELD) criteria (Table 2 in the Supplementary Appendix). The MELD criteria are based on a scoring system that uses the values for total bilirubin level, creatinine level, and international normalized ratio to assess the severity of chronic liver disease. However, these criteria were not developed to predict the risk of death among patients with chronic liver disease who also have hepatocellular carcinoma. Therefore, patients with hepatocellular carcinoma who have been placed on the list for liver transplantation are eligible for additional MELD points. The number of patients with hepatocellular carcinoma who have received transplants has increased considerably since the adoption of the MELD criteria in 2001.

Criteria developed at the University of San Francisco (UCSF) have been put forward to expand eligibility for liver transplantation among patients with hepatocellular carcinoma beyond that allowed by the Milan criteria. To meet the UCSF criteria for orthotopic liver transplantation, a patient must have a solitary hepatocellular carcinoma measuring up to 6.5 cm in diameter or up to three lesions, each measuring no more than 4.5 cm in diameter, with a total combined measurement of less than 8 cm.[44] Although several observational studies of intermediate quality have shown no significant differences in survival rates among patients deemed eligible for transplantation according to the Milan criteria as compared with those deemed eligible according to the UCSF criteria, the UNOS has not adopted the UCSF criteria because of the limited availability of organs. When a patient does not meet either the Milan or the UCSF criteria for transplantation, some institutions provide treatment with TACE or radiofrequency ablation, with the goal of downstaging the condition to improve the patient's eligibility for transplantation. This strategy has met with variable success and remains an area of investigation.[45] (Table 2 in the Supplementary Appendix provides detailed information on the MELD, Milan, and UCSF criteria.)

LOCAL ABLATION

Radiofrequency ablation has become the most frequently used form of local ablation therapy. It is the best treatment alternative for patients with early-stage hepatocellular carcinoma who are not eligible for surgical resection or transplantation. Several recent randomized trials of adequate quality have shown radiofrequency ablation to be more effective than the once-conventional method of ethanol injection in treating patients with small hepatocellular tumors (2 to 3 cm in diameter), with lower rates of local recurrence and higher rates of overall and disease-free survival.[46] Short-term outcomes are excellent, with overall survival rates of 100% and 98% at 1 and 2 years, respectively, but long-term outcomes are consistent with the noncurative nature of radiofrequency ablation, with 5-year recurrence rates as high as 70%. The results of two randomized, controlled trials comparing radiofrequency ablation and surgical resection showed no significant differences in overall or recurrence-free survival; as expected, radiofrequency ablation was associated with lower rates of complications and hospitalization.[47,48]

TRANSARTERIAL CHEMOEMBOLIZATION AND RADIOEMBOLIZATION

TACE has been shown to improve survival among patients with preserved liver function, particularly those with Child–Pugh class A cirrhosis who do not have extrahepatic metastases, vascular invasion, or prominent cancer-related symptoms. A meta-analysis of randomized, controlled trials assessing the use of arterial embolization, chemoembolization, or both as primary palliative treatment for hepatocellular carcinoma showed that these procedures were associated with an improved 2-year survival rate as compared with conservative treatment.[49] TACE is also used as a neoadjuvant therapy or as a means of downstaging a patient's condition before liver transplantation, but whether these approaches provide a survival benefit is unclear. A postembolization syndrome of fever and abdominal pain related to hepatic ischemia occurs in up to 50% of patients treated with TACE. Embolization should not be performed without the use of a chemotherapeutic agent; there are few data to guide the choice of the chemotherapeutic agent or the retreatment schedule, which in practice ranges from 2 to 5 sessions. In recent randomized, controlled trials,[50,51] the use of a drug-eluting bead that releases the drug in a controlled fashion during TACE has been shown to be associated with a reduction in both hepatic and systemic side effects and with an increase in local tumor response.

Radioembolization with yttrium-90 microspheres has recently been used as palliative treatment for patients with Child–Pugh class A cirrhosis and intermediate-stage hepatocellular carcinoma.[52] However, there have been no con-

trolled trials comparing yttrium-90 radioembolization with TACE or with other types of treatment.

TARGETED MOLECULAR THERAPY

Until recently, no systemic chemotherapy was shown to be consistently efficacious in treating hepatocellular carcinoma. Sorafenib is a small-molecule multikinase inhibitor that is administered orally and has antiproliferative and antiangiogenic properties. In recent randomized, controlled trials, it has been associated with a 37% increase in overall survival (equivalent to a gain of 2 to 3 months of life), as compared with placebo, in patients with advanced hepatocellular carcinoma and compensated cirrhosis.[53] Rash on the hands and feet, diarrhea, and fatigue are the most commonly reported side effects. The relative success with sorafenib has prompted increased interest in evaluating its use alone or in combination with other treatments (e.g., TACE) during other stages of disease and the development and testing of other targeted molecular medications. Other small molecules, such as brivanib and erlotinib, and monoclonal antibodies, such as bevacizumab and cetuximab, are currently being studied in patients with hepatocellular carcinoma.

TRANSLATING EFFICACY INTO EFFECTIVENESS

Despite encouraging reports on clinical trials and studies from referral centers regarding the efficacy of antiviral therapy for infection with HBV or HCV and of the surveillance and treatment of hepatocellular carcinoma, their effectiveness in clinical practice is low. The proportions of patients receiving these interventions and the outcomes are considerably lower in community-based studies than in those from referral centers. For example, in one U.S. population-based study, only 29% of patients who had a diagnosis of hepatocellular carcinoma had undergone annual surveillance in the 3 years before receiving the diagnosis,[54] and in another study, only 13% of patients with HCV-related cirrhosis who were at risk for hepatocellular carcinoma underwent surveillance.[55] Similar studies showed low utilization of transplantation,[56] resection, and TACE.[56] Obstacles to effective care include the difficulty of implementing surveillance that requires repeated assessments over relatively short periods and strategies ensuring prompt recall, the complicated diagnostic evaluation, and the limited availability and high cost of potentially curative therapy. In addition to the development of new biomarkers and drugs, several steps must be taken to improve the outcomes for patients with hepatocellular carcinoma. These include increasing the number of patients who receive a diagnosis in the early or very-early stages of disease through the testing and implementation of surveillance programs, provision of the optimal therapy for individual patients (e.g., drug and alcohol rehabilitation), use of validated staging systems, and perhaps most important, improvement of access to specialized multidisciplinary care.

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Disclosure forms provided by the author are available at NEJM.org.

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Screening for Viral Hepatitis and Hepatocellular Cancer

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KEYWORDS

• Screening • Surveillance • Hepatitis B virus • Hepatitis C virus
• Hepatocellular carcinoma

KEY POINTS

- Accurate tests for at-risk populations are available for hepatitis B virus, hepatitis C virus (HCV), and hepatocellular carcinoma (HCC).
- Effective treatments for all three diseases exist if diagnosed early.
- New antivirals are making a significant impact on HCV.
- Liver transplant is curative for early HCC and is prioritized by the United Network for Organ Sharing in the United States.

Screening and surveillance for deadly disease only makes sense if:

1. There are identifiable populations at risk for the condition.
2. There are sensitive and specific low-cost tests available for the condition.
3. There are effective treatments for the condition on diagnosis that result in decreased mortality.

Hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, and hepatocellular carcinoma (HCC) are each important clinical conditions that meet all of these criteria and therefore have screening recommendations that are standard of care.

SCREENING FOR HEPATITIS B VIRUS INFECTION

HBV infection is a global health problem with an estimated 350 million persons chronically infected.[1] In the United States there are estimated to be more than 1 million carriers (defined as positive for HBV surface antigen for more than 6 months).[2–4] HBV carriers in the United States or abroad are at risk for developing cirrhosis, hepatic decompensation, and HCC (25% lifetime risk of serious sequelae).[5–7] Because

effective medicines are available for HBV treatment, the following guidelines exist from the American Association for the Study of Liver Diseases (AASLD) to direct screening.

HBV is transmitted by perinatal transmission, percutaneous and sexual exposure, as well as by close personal contact.[3] In countries like the United States where vaccination of most infants and adolescents is the rule, the risk of transmission in schools or day care is low.

The tests used to screen for HBV infection include hepatitis B surface antigen (HBsAg) and anti–hepatitis B surface antibodies (anti-HBs). Alternatively hepatitis B core antibody can be used for screening as long as positive tests are followed by HBsAg and anti-HBs to determine infection versus prior exposure and immunity.

The following should be screened for HBV status (**Box 1**): persons born in endemic areas (eg, Asia, Africa, South Pacific Islands, Middle East); those born in the United States who were not vaccinated and are children of parents from an endemic area; patients with chronically increased liver function tests of unclear cause; immunosuppressed patients; men who have sex with men, have multiple partners, or a history of sexually transmitted diseases; inmates of correctional facilities; those who have ever used injection drugs; dialysis patients; those infected with HCV or human immunodeficiency virus (HIV); pregnant women; and household contacts of someone with HBV.

Box 1
Groups at high risk for HBV who should be screened

Patients from areas of endemic HBV:

- Asia
- Africa
- South Pacific Islands
- Middle East
- Mediterranean: Spain and Malta
- Indigenous arctic populations: Canada, Greenland, Alaska
- South America
- Eastern Europe
- Caribbean
- Central America

Others recommended for screening:

- US born, unvaccinated, with parents from endemic areas
- Household contacts of those with HBV
- Intravenous drug users
- Sexual contacts of those with HBV, those with multiple sexual partners, history of sexually transmitted diseases
- Inmates of correctional facilities
- Individuals with increased aminotransferase levels, HCV, human immunodeficiency virus (HIV), or cirrhosis
- Pregnant women
- Patients on hemodialysis

Organ donors, live or deceased, are tested for HBV as well. Anyone tested for HBV who is seronegative should be vaccinated.

SCREENING FOR HEPATITIS C VIRUS INFECTION

HCV infects 1% of the US population: 3 million people, less than half of whom know they are infected.[8] Because highly effective directly acting antivirals are now available for hepatitis C (ie, sofosbuvir, semipravir, ledipasvir) and liver disease is usually slowly progressive, there is a long period for detection and treatment.[9] High-risk groups who are most likely to benefit from screening have been identified. HCV transmission occurs inefficiently and usually only by direct exposure to blood (eg, via sharing of intravenous drug needles, which accounts for 60% of HCV in the United States). Blood transfusion before 1992 is the second most common route of exposure and other less common routes include maternal fetal transmission; transfer via medical device, such as endoscope; sexual intercourse, although usually only in the case of HIV-coinfected gay men; long-term hemodialysis; or needle-stick injuries in the health care setting.[10]

Testing for HCV infection is accomplished by screening for antibodies against viral proteins (anti-HCV) followed by nucleic acid testing using a polymerase chain reaction (PCR)–based test for viral RNA (reverse transcription PCR [RT-PCR]). HCV antibodies are usually not detected during the first 2 months following infection but are almost always detected by 6 months. These antibodies usually do not neutralize the virus, and do not provide immunity against subsequent viral infections. HCV antibodies may be lost several years after spontaneous clearance of virus, which occurs in approximately 20% of cases. Current screening serologic tests include electroimmunoassay and chemiluminescence immunoassay. These tests are delayed in their positivity, as described earlier; can show false-positives; do not distinguish between acute or chronic infection; and do not allow measurement of response to treatment.

Nucleic acid testing for HCV is straightforward: both genotype and quantitative viral load can be determined. RT-PCR HCV tests may remain negative for up to weeks after an exposure but are positive thereafter. Viral load (and its disappearance) is now used to determine efficacy of antiviral therapy.

Class I evidence exists for testing the following groups for HCV infection (**Box 2**): people with high-risk behavior (injection or intranasal drug use, historic or current), those with high-risk exposure (long-term hemodialysis [ever]); getting a tattoo in an unregulated setting; health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood; children born to women infected with HCV; prior recipients of transfusions or organ transplants, including persons who were notified that they received blood from a donor who later tested positive for HCV infection, received a transfusion of blood or blood components, or underwent an organ transplant before July 1992; those who received clotting factor concentrates produced before 1987; or persons who were ever incarcerated. Others for whom there is strong evidence for testing include those infected with HIV, those with unexplained liver disease or increase of liver function tests, and solid organ donors, deceased or living.

In addition, 1-time HCV testing is now recommended for any persons born between 1945 and 1965, regardless of risk status.

Annual HCV testing is recommended for persons who inject drugs and for HIV-seropositive men who have unprotected sex with men. Periodic testing should be also offered to other persons with ongoing risk factors for exposure to HCV.

Box 2
Persons who should get tested for HCV

- Those with high-risk behaviors
  - Injection drug use
  - Intranasal illicit drug use
- Those with high-risk exposures
  - Hemodialysis
  - Unprofessional tattoo
  - Health care worker with needle-stick exposure
  - Children born to HCV-positive women
  - Recipients of blood transfusion or solid organ transplant before 1992
  - Incarceration, prior or present
- Other
  - HIV infection
  - Chronic liver disease or increase of serum aminotransferase levels
  - Solid organ donors, deceased or living

DIAGNOSING OTHER VIRAL HEPATITIDES

Hepatitis A

Hepatitis A infection almost universally results in an acute, self-limited illness and can produce either icteric or anicteric syndromes. The incubation period is 28 days. The anicteric prodrome lasts from 2 days to 3 weeks and typically consists of fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain. The diagnosis may be missed in cases that do not progress to jaundice. In cases in which jaundice becomes manifest, it persists for 1 to 6 weeks. Transaminase levels are typically more than 1000 IU/mL and serum bilirubin (>10 mg/dL) and alkaline phosphatase values are increased as well. Serum immunoglobulin (Ig) M antibodies are detected in 95% of patients and are the gold standard of diagnosis. IgG antibody levels become increased as jaundice subsides and may persist for years.

Hepatitis D

The hepatitis D virus (HDV), or delta agent, is an incomplete RNA virus that requires the concomitant presence of HBV for viral assembly and propagation. The only enzymatic activity of HDV is a ribozyme that autocleaves circular RNA and makes it linear. The HDV genome is a 1680-nucleotide, single-stranded circular RNA. Eight genotypes have been proposed. A single HDV antigen is encoded, it is a structural component of the virion, and a lipoprotein envelope is provided by HBV.

It is estimated that HDV is found in approximately 5% of HBV carriers. Because of its dependence on HBV, HDV always occurs in association with HBV infection. Transmission is similar to that of HBV, via parenteral or sexual exposure to blood or body fluids. HDV hepatitis occurs only in HBsAg-positive patients.

Acute infection is diagnosed by the presence of anti-HDV IgM. Anti-HBcore IgM distinguishes coinfection from superinfection. The diagnosis in patients with chronic liver disease is made by the presence of HBsAg and antibodies against HDV in the serum and is confirmed by the presence of HDV antigen in the liver or HDV RNA in the serum.

Hepatitis E

Hepatitis E virus (HEV) is a nonenveloped single-stranded RNA virus. It is 30 nm in diameter and is most similar to other viruses of the Caliciviridae family. There are thought to be 4 genotypes.

Hepatitis E is enterically transmitted (waterborne hepatitis or enterically transmitted non-A, non-B hepatitis) and is epidemiologically similar to hepatitis A virus. Infection has been prominently observed in Asia, Africa, the Middle East, and Central America. In addition, vertical transmission from mother to child has been documented and can be a source of perinatal morbidity and mortality. HEV generally causes a self-limited acute infection, although chronic infection has been described in organ transplant recipients. The incubation period usually lasts 3 to 8 weeks, and most individuals recover without chronic findings after a transient cholestatic episode. However, young adults and women in late stages of pregnancy may develop fulminant hepatitis E. Mortality from HEV is 0.5% to 4% in the general population but up to 20% in pregnant women. Diagnosis is aided by detection of serum or fecal genomes during the acute phase. In addition, anti-HEV IgM or IgG can be shown in follow-up.

Cytomegalovirus

Cytomegalovirus (CMV) is a member of the Beta Herpes Viridae family. It is usually associated with mild hepatitis but occasionally causes acute liver failure. Transmission can be intrauterine, perinatal, or postnatal; through intimate contact of infected fluids such as blood, saliva, or urine, or through transplanted organs. Infection is lifelong because of the latency of the virus and can be detected in up to 70% of individuals in US cities. Organ injury can occur as a result of primary infection or because of reactivation of latent infection. In the neonatal period, congenital infection can be severe and fatal. In immunocompetent adults, liver dysfunction tends to be found in association with CMV mononucleosis. In immunosuppressed adults, infection leads to liver dysfunction with jaundice and at times liver failure. Acalculous cholecystitis is another presentation. CMV antigenemia and PCR detection have made diagnosis rapid. Liver biopsy is important to establish the diagnosis of hepatitis. Pathologic examination shows inflammation and injury ranging from fatty changes to necrosis to fibrosis. Giant multinucleated cells and large nuclear inclusions can be encountered in hepatocytes and bile duct and epithelial cells.

Epstein-Barr Virus

Epstein-Barr virus (EBV) is a DNA virus and member of the Herpesviridae family. Infection persists for life because of the latency of the virus and it is usually transmitted by close personal or intimate contact via oral secretions. Some degree of liver involvement is encountered in almost all cases of EBV mononucleosis. It is usually mild with no major clinical manifestations and resolves spontaneously. The presence of jaundice may reflect either more severe hepatitis or an associated hemolytic anemia. Occasional cases of acute liver failure have been reported in both the immunocompetent and immunodeficient populations. Leukocytosis is usually present, with lymphocytosis and monocytosis. The monospot test is sensitive but not specific, but there is a reliable PCR test.

Herpes Simplex Virus

The prevalence of antibodies to herpes simplex virus (HSV)-1 is around 75% in most populations and around 20% have antibodies to HSV-2. Fulminant hepatitis is a rare complication of HSV infection; those at risk include neonates, the immunocompromised,

the malnourished, and pregnant adults. Fulminant hepatitis is usually associated with multiorgan failure and is associated with a high mortality. Clinical features include high fever, anorexia with nausea, abdominal pain, leucopenia, and coagulopathy. Liver biopsy is important in establishing the diagnosis. Microscopic examination shows diffuse eosinophilic intranuclear inclusion bodies, multinucleated cells, widespread necrosis, and inflammation. Cowdry A–type intranuclear inclusions are typical. Confirmation is by PCR.

Varicella Zoster Virus

Herpesvirus varicella (also called varicella zoster virus) is usually associated with mild hepatitis but occasionally causes acute liver failure. Up to one-fourth of children with varicella (chickenpox) show temporary mild biochemical liver abnormalities. Reye syndrome may be encountered during the convalescence period, especially in patients who receive aspirin. In such cases mortality can be as high as 30%. Fulminant fatal hepatic failure is uncommon, but generally affects immunocompromised patients. Confirmation of the diagnosis can be achieved by isolation of the virus from affected tissues.

SCREENING FOR HEPATOCELLULAR CARCINOMA

The incidence of HCC is variable across the world but is increasing in many countries.[11] In a few areas, like Japan and Singapore, it may even have decreased slightly.[12] Involvement of a multidisciplinary team in managing liver cancer is important because the disease most often arises in the setting of underlying liver disease and its management depends on assessing degree of liver decompensation, which is different from that of most other cancers.

Although there are now agreed-on guidelines, and screening has become widely accepted, there is only a single randomized controlled trial of surveillance versus no surveillance that has shown benefit of a strategy of 6-month surveillance with Ultrasound and alpha-fetoprotein.[13] In the cohort of patients that were followed as described, mortality was reduced by 37%. The goal of surveillance is to decrease mortality from the disease, or provide meaningful improvement in survival duration for those diagnosed. Surveillance can be recommended in HCC for certain high-risk groups, the goal being to detect early stage disease that has shown survival benefit with treatments like resection and especially transplant.

AASLD guidelines specify which groups are appropriate for screening based on increased risk: surveillance is deemed cost-effective if expected HCC risk exceeds 1.5%/y in patients with HCV infection and 0.2%/y in patients with hepatitis B. Some recent studies show that alpha-fetoprotein level alone lacks adequate sensitivity and specificity for effective surveillance, thus surveillance is based on US. The recommended screening interval is 6 months. Diagnosis is based on imaging characteristics and biopsy. Arterial uptake by a lesion with subsequent washout on dynamic imaging is the radiographically validated standard. Other studies have shown that screening with AFP alone is the most cost-effective, although most conclude that US and AFP are the most effective overall.[14]

Ultimately, surveillance is clearly beneficial and thus recommended for (**Box 3**): Asian hepatitis B carriers aged more than 40 years, any hepatitis B carrier with a family history of HCC, African or North American black people with hepatitis B, cirrhotic HBV carriers, hepatitis C cirrhotics, stage 4 patients with primary biliary cirrhosis, those with genetic hemochromatosis and cirrhosis, those with alpha1-antitrypsin deficiency and cirrhosis, and those patients with cirrhosis of any or unknown cause. For those

Box 3
Who should undergo HCC surveillance

- Asian hepatitis carriers more than 40 years of age
- HBV carriers with family history of HCC
- African/North American black people with HBV
- Cirrhotics
- Stage 4 primary biliary cirrhosis

Probable benefit from surveillance:

- HBV carriers less than 40 years of age
- Hepatitis C with stage 3 fibrosis
- Noncirrhotic nonalcoholic fatty liver disease

hepatitis B carriers younger than 40 years old, those with HCV and stage 3 fibrosis or less, and patients with noncirrhotic nonalcoholic fatty liver disease, the benefit of surveillance remains uncertain.

Current recommendations also vary with the size of a detected lesion or nodule: lesions less than 1 cm may be followed with ultrasonography examinations at 3-month intervals. If stable, this level of surveillance is all that is required. If growth in lesion size is appreciable, then computed tomography (CT) scan with contrast to further characterize the lesion is indicated. If a lesion is discovered that is greater than 1 cm, it is investigated with multiphase CT or contrast-enhanced magnetic resonance, and if lesions show the stereotypic pattern of arterial enhancement and venous washout, then the diagnosis of HCC is made. If imaging features are not diagnostic, biopsy may be considered, although sometimes small lesions (less than 2 cm) can be closely followed with attention to changes in their size or imaging characteristics.

WHEN TO OBTAIN A LIVER BIOPSY TO DIAGNOSE HEPATOCELLULAR CARCINOMA

Percutaneous liver biopsy for lesions suspicious for HCC is controversial and is in general not recommended, because the diagnosis can almost always be made confidently based on radiographic criteria: a new nodular-appearing cirrhotic liver that displays arterial enhancement and venous washout. In addition, concerns have been raised about the possibility of bleeding and spread of tumor along the needle track. The risk of these complications is estimated to be around 2% to 5%.[15–19] Other investigators have not observed an increased risk of tumor spread.[20–22] Cases should be considered individually and biopsy may prove useful in cases in which imaging is not diagnostic or even in cases of large liver tumors that would be considered for transplant if the tumor grade was well differentiated.[23] In addition, concerns over sampling bias still remain.[24]

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Hepatocellular Carcinoma

Current Management and Perspectives for the Future

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Objective: To review the literature on current management of hepatocellular carcinoma (HCC).

Background: Hepatocellular carcinoma represents one of the most common malignancies worldwide with a rising incidence in western countries. There have been substantial advances in the surgical and medical treatment of HCC within the past 2 decades.

Methods: A literature review was performed in the MEDLINE database to identify studies on the management of HCC. On the basis of the available evidence recommendations for practice were graded using the Oxford Centre for Evidence-based Medicine classification.

Results: Advances in surgical technique and perioperative care have established surgical resection and orthotopic liver transplantation (OLT) as primary curative therapy for HCC in noncirrhotic and cirrhotic patients, respectively. Primary resection and salvage OLT may be indicated in cirrhotics with preserved liver function. Selection criteria for OLT remain debated, as slight expansion of the Milan criteria may not worsen prognosis but is limited by organ shortage and prolonged waiting time with less favorable outcome on intention-to-treat analyses. Strategies of neoadjuvant treatment before OLT require evaluation within prospective trials. Transarterial chemoembolization is the primary therapy in patients with inoperable HCC and compensated liver function. Although systemic chemotherapy is not effective in patients with advanced HCC, there is recent evidence that these patients benefit from new molecular targeted therapies. If these agents are also effective in the neoadjuvant and adjuvant setting is currently being investigated. Furthermore, selective intra-arterial radiation therapy represents a promising new approach for treatment of unresectable HCC.

Conclusions: Recent developments in the surgical and medical therapy have significantly improved outcome of patients with operable and advanced HCC. A multidisciplinary approach seems essential to further improve patients' prognosis.

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Hepatocellular carcinoma (HCC) represents the sixth most common malignancy and the third most common cause of cancer-related death worldwide.[1] In the United States and Europe where chronic hepatitis C virus (HCV) infection represents the main risk factor[2] the incidence of HCC has been rising and is expected to further increase in the next 2 to 3 decades.[3] In Asia and Africa chronic hepatitis B virus (HBV) infection is the leading risk factor and might be further enhanced by exposure to Aflatoxin B_1. The majority of HCC patients (95% in the western, 60% in Asian countries) will develop the disease on the ground of preexisting liver cirrhosis. Presence of cirrhosis markedly increases the risk for HCC development. The annual HCC incidence for cirrhotic patients with HBV and HCV infection accounts for 2% to 6.6% and 3% to 5%, respectively.[2,4] Advances in diagnostic tools, surveillance programs, and survival of patients with cirrhosis are likely to further increase the incidence of HCC and the proportion of patients diagnosed at a potentially curative stage of disease. There has been major progress in the understanding of the disease and therapeutic options in the past 2 decades, which substantially altered the clinical management of patients with HCC. In this article, we present current evidence on the management of HCC patients and provide an outlook of further improvements that might be expected in the future. Recommendations were made using the classification by the Oxford Centre for Evidence-based Medicine (Grade of recommendation A–D).[5]

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STAGING OF HCC

Therapy for HCC patients should be based on the patient's prognosis, which in turn is complex to assess, as it depends on the tumor stage, the underlying liver function and the patient's physical condition. Several staging systems have so far been suggested without an overall consensus for any of these (Table 1).[6–9] Although The American Joint Committee on Cancer/Union internationale contre le cancer Tumor-Node-Metastasis staging system (AJCC/UICC TNM) adequately stratifies patients into prognostic groups,[10] it is only applicable to patients undergoing resection or orthotopic liver transplantation (OLT) and does not consider the underlying liver function. In 2009, the seventh edition of the TNM classification of malignant tumors was published.[11] Changes to the previous classification include a subdivision of T3 in T3a and T3b. Furthermore, the UICC stage IV is subdivided in stage IVA (positive regional lymph nodes) and stage IVB (distant metastases). However, the revised TNM classification requires validation. The Okuda and the Cancer of the Liver Italien Program (CLIP) classifications were introduced as clinical staging systems considering tumor features and hepatic function. The Okuda system was developed based on a retrospective analysis of 850 HCC patients[7] and has been found to be rather inaccurate for prognostic stratification of patients, in particular for patients at an early stage of disease.[12] The CLIP scoring system considers several factors related to tumor biology (ie, tumor morphology, AFP level, and portal vein thrombosis). Although it has been validated in a prospective manner,[13] the CLIP scoring system might be inadequate to identify patients at early stages of disease and it is probably rather helpful to identify patients with a poor prognosis. The Japan Integrated Staging score combines the Child-Turcotte-Pugh (CTP) class with the modified TNM stage according to the Liver Cancer Study Group of Japan (LCSGJ) and was developed to overcome this problem.[14] In a multicenter validation including more than 4500 patients the predictive value of the Japan Integrated Staging score was proven to be superior to the CLIP scoring system.[15] The Barcelona Clinic Liver Cancer (BCLC) staging system which was suggested in 1999 as a modification of the Okuda system[6] has been repeatedly validated for prognosis of patients with HCC.[16,17] It involves tumor-related parameters (tumor size, number of nodules, vascular invasion), patients' clinical condition (WHO Performance Status) and liver function (CTP classification). This information forms the framework for categorizing the

TABLE 1. Common HCC Staging Systems

AJCC/UICC tumor-node-metastasis staging system for HCC (7th edition; 2009)

Primary tumor

T_1	Single tumor without vascular invasion
T_2	Single tumor with vascular invasion or multiple tumors none > 5 cm
T_3	T_{3a}: Multiple tumors any >5 cm
T_4	T_{3a}: Tumor of any size involving a major branch of the portal or hepatic vein
	Tumor(s) with direct invasion of adjacent organs, other than the gallbladder, or perforation of visceral peritoneum

Regional lymph nodes*

N0	No
N1	Yes

Distant metastases

M0	No
M1	Yes

Stage I	T_1	N_0	M_0
Stage II	T_2	N_0	M_0
Stage IIIA	T_{3a}	N_0	M_0
Stage IIIB	T_{3b}	N_0	M_0
Stage IIIC	T4	N_0	M_0
Stage IVA	Any T	N_1	M_0
Stage IVB	Any T	Any N	M_1

Okuda staging system for HCC

	0 points	1 point
Tumor size	< 50% of liver	> 50% of liver
Ascites	No	Yes
Albumin (g/dL)	>3	<3
Bilirubin (mg/dL)	<3	>3

Stage I: 0 points; Stage II: 1–2 points; Stage III: 3–4 points

Cancer of the Liver Italien Programme staging system of HCC

Points	Cirrhosis	Tumor morphology	Alpha feto protein [ng/dL]	Portal vein thrombosis
0	CTP class A	Single, < 50% of liver	< 400	No
1	CTP class B	Multiple, < 50% of liver	≥ 400	Yes
2	CTP class C	Massive or 50% of liver		

CLIP score (0–6): sum of points for four variables

Barcelona Clinic Liver Cancer staging sytem of HCC

	PS	Tumor stage	Liver function
Stage A1 (very early)	0	Single tumor	No portal hypertension, normal bilirubin level
Stage A2 (early)	0	Single tumor	
Stage A3	0	Single tumor	Portal hypertension, normal bilirubin level
Stage A4	0	≤ 3 tumors, each up to 3 cm	Portal hypertension, elevated bilirubin level
			CTP class A–B
Stage B (intermediate)	0	Large multinodular	CTP class A–B
Stage C (advanced)	1–2	Vascular invasion or extrahepatic spread	CTP class A–B
Stage D (terminal)	3–4	Any tumor stage	CTP class C

Japan Integrated Staging score

	Score			
Variable	0	1	2	3
CTP class	A	B	C	–
TNM stage by LCSGJ	I	II	III	IV

JIS score (0–5): sum of points for the 2 variables

*Regional lymph nodes include hepatic artery, portal vein, hilar, hepatoduodenal ligament, inferior phrenic, caval lymph nodes. A minimum of 3 tumor-free lymph nodes are required for pN0 diagnosis.

AJCC/UICC indicates American Joint Committee on Cancer/Union internationale contre le cancer Tumor-Node-Metastasis (TNM) staging system; CTP, Child-Turcotte-Pugh classification; PS, performance status (WHO); LCSGJ, Liver Cancer Study Group of Japan.

disease in a *very early*, *early*, *intermediate*, *advanced*, and *terminal* stage. The BCLC concept directly links the stage of disease to respective treatment strategies and was recently updated because of data on patients with advanced disease[18] (Fig. 1). The prognostic value of these staging systems has been evaluated in several studies with inconsistent results.[16,17,19] Further studies on independent patient sets considering the variable predictive value of staging systems depending on the applied therapy are required to determine the most accurate staging system. However, staging of HCC in scientific reports should already be standardized to enable crosscomparability of the results from different studies. A clinical classification system considering the stage of disease and the underlying liver function such as the BCLC staging system should be used for initial staging. The disease of patients who underwent surgery (ie, resection or OLT) should be categorized additionally using the AJCC/UICC TNM classification. [*Grade of recommendation C*]

CURATIVE TREATMENT

Surgical Resection

If applied in well-selected patients surgical resection is the primary treatment in patients with HCC. Within the last years perioperative mortality could be reduced to less than 5% depending on resection extent and hepatic reserve.[20] The improved outcome is primarily results from advances in surgical and radiologic techniques and perioperative care and more cautious patient selection.

Preoperative Assessment of Liver Function

Because of the potential need for major resections and frequently diseased background livers, posthepatectomy liver failure is a major concern of liver resection in HCC patients. The *Child-Turcotte-Pugh (CTP) score* is the most common measure to assess liver function before hepatic resection, though it was introduced as a predictor of operative risk for cirrhotic patients undergoing surgery for portal hypertension.[21] By staging patients' clinical (presence of ascites and encephalopathy) and laboratory abnormalities (serum albumin, bilirubin, prothrombin time) a score is estimated categorizing patients into 3 grades of liver dysfunction (*CTP class A, B, C*). Although it has been shown that *CTP class B* and *C* patients are poor candidates for liver resection,[22] this score has proven insufficient to stratify the operative risk of patients with compensated cirrhosis (*CTP class A*). In particular in Asian countries further liver function tests are employed preoperatively. Among the various methods available such as the *monoethylglycinexylidide (MEGX) test* and the *galactose elimination capacity (GEC),* the *indocyanine green (ICG) clearance rate* represents the most common one. After injection of 0.5 mg ICG/kg, retention of this organic dye is measured in the peripheral blood at definite time points (usually after 15 minutes; ICG-R15). Indocyanine green is taken up by the hepatocytes and excreted via the bile in an adenosine triphosphate (ATP) dependant manner. It is not metabolized and does not undergo enterohepatic recirculation. Thus, its clearance from systemic circulation is a measure of hepatic blood flow and function. Because of the weakness of the ICG clearance rate to reliably predict perioperative risk in patients with CTP class A cirrhosis, it did not gain general acceptance. However, several studies showed a prognostic relevance of ICG clearance for hepatic resection in cirrhotic patients.[23,24] Using the ICG-R15 in the absence of hyperbilirubinemia and ascites, Imamura et al[25] reported no perioperative mortality in their series of 1056 hepatectomies. In general, a safe major hepatic resection is expected in cirrhotic patients with an ICG-R15 up to 10% to 20%.

The liver remnant volume may vary, particularly in patients with diseased livers because of compensatory hypertrophy. In addition to assessment of hepatic function and liver volume to be resected, volumetric analysis of the future liver remnant (FLR) has been suggested. Advances in imaging techniques enable 3-D modeling of the liver with accurate liver-segmentation and visualization of the arterial and venous supply and biliary drainage (Fig. 2). Liver volumetry is mostly performed using computer-assisted models of contrast-enhanced spiral CT. Several studies have shown an association between the volume of the FLR and hepatic function and postoperative mortality in HCC patients.[26,27]

Recently, the *LiMAx test* together with CT volumetry was suggested to assess function of the FLR, preoperatively.[28] The LiMAx test requires intravenous administration of ^{13}C-methacetin, which is metabolized by the cytochrome P450 1A2 system of the hepatocytes to paracetamol and $^{13}CO_2$. The latter is measured by continuous real-time breath analysis to calculate the $^{13}CO_2/^{12}CO_2$ ratio as an indicator of hepatic function. Despite the promising results of combined volume/function analysis, this approach needs further evaluation and the CTP remains the primary index for preoperative surgical risk evaluation of patients considered for hepatic resection. [*Grade of recommendation B*]

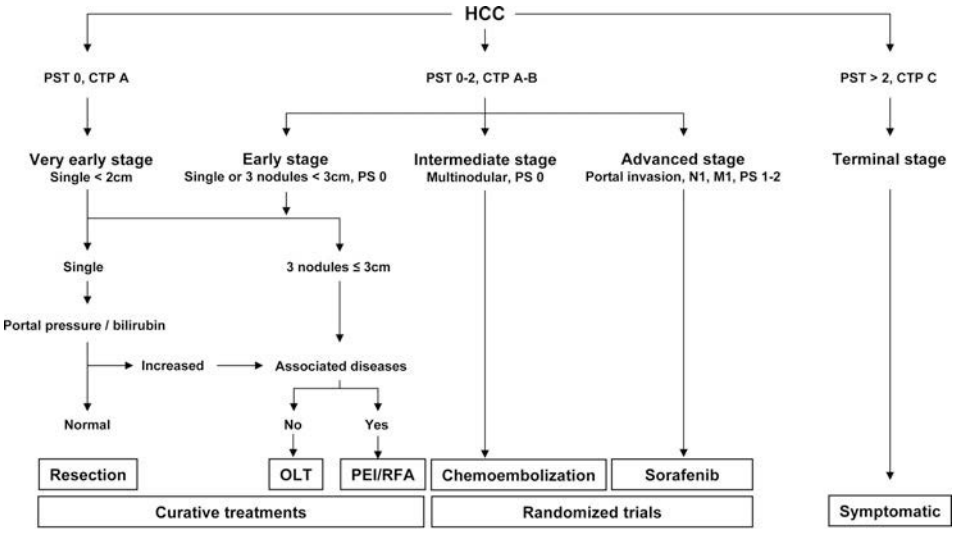

FIGURE 1. Barcelona Clinic Liver Cancer staging system and treatment algorithm.
CTP indicates Child-Turcotte-Pugh; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; PST, WHO performance status; RFA, radiofrequency ablation.

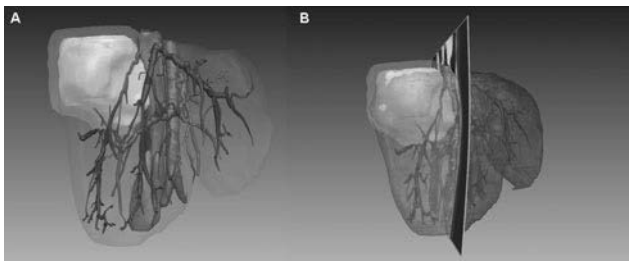

FIGURE 2. Planning of the surgical procedure by 3-dimensional reconstruction of CT scans.
A, Three-dimensional computation from a preoperative CT scan of a patient with HCC. Arteries red, portal vein purple, veins blue, gall bladder green, tumor, and safety margin yellow. B, Anterior 3-dimensional view of a virtually divided liver with calculation of resection and remnant liver volume.

Portal Vein Embolization

On the basis of the idea that an increase in the FLR will reduce the risk of posthepatectomy liver failure, the concept of portal vein embolization (PVE) has been introduced in 1986.[29] By occluding portal branches supplying the tumor-bearing liver segments, PVE causes atrophy of the ipsilateral liver with compensatory hypertrophy of the remaining liver (ie, the FLR). Although liver regeneration is impaired by fibrosis or cirrhosis, PVE may induce clinically sufficient hypertrophy even in these patients. In a nonrandomized trial of 55 patients (28 with HCC) Farges et al[30] demonstrated no positive effect of PVE on the postoperative course of patients with normal livers, whereas it reduced postoperative complications and duration of hospital stay in patients with chronic liver disease. The authors of a meta-analysis including 37 studies with 1088 patients (265 patients with HCC) concluded PVE to be a safe procedure, effective to induce hypertrophy of the liver remnant and to reduce the risk of poshepatectomy liver failure.[31] These data were confirmed in patients with HCC.[32] Portal vein embolization may also be used as dynamic liver function test. The lack of adequate hypertrophy after PVE indicates the inability of the liver to regenerate and should be considered as a contraindication to major liver resection.[30] Currently, PVE is recommended in cirrhotic patients, if a FLR less than 40% of the total liver volume is expected. At eastern institutions PVE has already been suggested for FLR of 40% to 60%, in case ICG-R15 values of 10% to 19% are obtained.[25] Besides these formal criteria potential comorbidities, such as hepatitis and diabetes should be considered when referring patients to liver resection. There are, however, no uniform guidelines incorporating these parameters. [*Grade of recommendation B*]

Technical Aspects of Surgical Resection for HCC

Various transection techniques have been developed to reduce blood loss and morbidity of hepatic resection. A meta-analysis of randomized controlled trials (RCT) revealed no advantage of these methods compared to the simple clamp-crushing technique.[33] The surgeon's experience together with the lesion's location should primarily determine the transection method. Further studies are needed to define the optimal transection technique in patients with liver disease. [*Grade of recommendation A*]

The curative resection margin in hepatectomy for HCC has not yet been defined. A narrow resection margin preserves tissue and alleviates the regenerative stimuli that might promote tumor growth, whereas it might fail to remove existing micrometastases. An RCT compared wide (2 cm) to narrow (1 cm) resection margins in HCC patients with a solitary tumor without macrovascular invasion and compensated cirrhosis CTP class A.[34] The authors reported decreased disease recurrence and improved survival for the wide margin group, which they attribute to strict selection criteria. Hence, HCC patients with a macroscopically solitary tumor without vascular invasion benefit from a margin of 2 cm, whereas those beyond these criteria are likely to already having distant micrometastases that cannot be cleared by a wider resection margin. [*Grade of recommendation B*]

Hepatocellular carcinoma has a strong tendency of vascular invasion. Tumor spread occurs primarily via the portal venous system, forming the pathological basis for intrahepatic metastases and early recurrence. Anatomical resections (segmentectomy or subsegmentectomy) include the associated portal branches and potentially remove satellite lesions and microscopically invaded vessels. Several reports favored anatomical resection regarding oncological outcome.[35–37] An analysis of 321 HCC patients with tumors less than 5 cm in diameter revealed a survival benefit of anatomic resection in noncirrhotic patients, whereas limited nonanatomic resection proved superior in cirrhotics.[38] Anatomical resection should thus be intended, if feasible and not contraindicated by the patient's liver function. In the remaining cases other therapies, that is, OLT and ablation, should be considered. [*Grade of recommendation B*]

The anterior approach technique has been introduced for (extended) right hepatectomy for large HCC.[39] The conventional approach requires complete mobilization of the right hepatic lobe for extrahepatic control of the right hepatic vein. In the anterior approach the parenchyma is transected starting from the anterior surface of the liver until the inferior vena cava is exposed and the right hepatic vein can be ligated.[39] Less manipulation of the liver is expected to reduce intraoperative blood loss, tumor cell dissemination and postoperative hepatic dysfunction.[40] In patients with a HCC at least 5 cm the advantage of the anterior approach with respect to perioperative complications and long-term outcome has been shown in a retrospective analysis and a prospective RCT.[41,42] [*Grade of recommendation B*]

The issue of vascular control during hepatectomy is of particular interest in surgery for HCC, as the underlying liver disease possibly increases the susceptibility of the liver to ischemia/reperfusion injury.[43] Intermittent portal triad clamping (ie, alternating periods of ischemia and reperfusion) and ischemic preconditioning (ie, a short period of ischemia and reperfusion followed by a prolonged period of ischemia) are methods to reduce ischemia/reperfusion injury. Transient clamping of the infrahepatic inferior vena cava offers a promising technique to reduce blood loss via the hepatic veins without the disadvantage of ischemia and is currently evaluated in an RCT.[44] A meta-analysis demonstrated hepatic resections to be safe without portal triad clamping, if modern guidelines of liver surgery are adhered to (eg, low central venous pressure).[45] However, if inflow occlusion is required, it should be carried out intermittently or after ischemic preconditioning. One should note that the available RCTs did not specifically evaluate patients with underlying liver disease. For lesions infiltrating the major hepatic veins or those adjacent to the cavohepatic junction combined inflow and outflow control (ie, hepatic vascular exclusion) may be applied with acceptable morbidity.[46] [*Grade of recommendation B*]

There is increasing data that laparoscopic surgery for HCC can be performed safely with lower perioperative morbidity and postoperative ascites, particularly in cirrhotics.[47–49] Furthermore, these studies consistently demonstrated no compromise in surgical margins and long-term outcome after laparoscopic resection of HCC. Recently, the position paper to an international consensus conference on laparoscopic hepatic resection was published.[50] Although the panel agreed that the laparoscopic approach is adequate in the hands of experienced surgeons, it is primarily indicated in patients with single lesions 5 cm or less in the peripheral segments of the liver. [*Grade of recommendation B*]

Selection of HCC Patients for Surgical Resection

In noncirrhotic HCC patients, surgical resection is the preferred curative treatment. These patients are likely to tolerate extended resections with acceptable morbidity. The noncirrhotic residual liver is less likely to develop de-novo HCC and might offer the option of reresection in case of disease recurrence. The 5-year survival after surgical resection of HCC in these patients may exceed 50%[35,51] (Table 2). The majority (>80%) of patient develops HCC in the context of cirrhosis. Cautious selection of cirrhotic candidates for surgical resection may enable moderate long-term outcome that has improved within the past 2 decades.[20,35,52,53] The BCLC staging system restricts hepatectomy to patients with a single HCC nodule less than 2 cm and well-preserved liver function (ie, CTP class A). Moreover, resection is recommended only for patients without clinical evidence of portal hypertension and normal bilirubin levels. In such patients resection is associated with almost no risk of posthepatectomy liver failure and excellent long-term survival.[54,55] However, Torzilli et al. reported acceptable outcomes for patients with BCLC stage B and C disease.[56] In general, tumor-related (ie, number, size and location of lesions, extrahepatic disease, involvement of major vasculature, required resection extent to achieve R0 situation) and patient-dependent factors (ie, physical condition, liver function, comorbidities) and the institution's experience should be considered before hepatectomy. Although extrahepatic disease and invasion of the portal vein trunk, inferior vena cava, and common hepatic artery are contraindications to surgical resection, lesion size, and number per se do not determine resectability. Excellent results were reported in patients who underwent resection for small and single HCC, respectively.[35,53,57] Despite the increased risk of recurrence due to the presence of vascular invasion and intrahepatic tumor cell dissemination in patients with large HCC and multiple lesions, available evidence still justifies hepatectomy in well-selected candidates[35,58,59] (Table 2). In particular, large but solitary HCC may be resected with good prognosis.[59] [*Grade of recommendation B*]

In western institutions, evidence of portal hypertension such as hepatic venous pressure gradient at least 10 mmHg, esophagogastric varices (grade 2 and 3), splenomegaly and thrombocytopenia (platelet count < 100.000/mm^3) are used to more precisely assess the perioperative risk.[54,60] Advances in hepatic surgery and perioperative management together with a more aggressive strategy of treating recurrent disease are likely to further extend indications for resection. Using a standardized protocol with preoperative treatment of varices and ascites, resection extent guided by ICG-R15 and aggressive treatment of recurrence, Ishizawa et al[61] reported a 5-year overall survival of 60% in 434 HCC patients with CTP class A, who had multiple tumors and/or portal hypertension. In a smaller study from Japan including 134 cirrhotic patients (CTP class A and B) esophageal varices were not associated with poor perioperative outcome and long-term survival on multivariate analysis.[62] One should note that in this study patients with esophageal varices represented a minority (n = 34) and underwent more limited resections. In an analysis of 241 cirrhotic HCC patients Cucchetti et al[63] reported similar perioperative outcome and survival of patients with and without portal hypertension, if patients had a similar preoperative liver function (assessed by the MELD score) and intraoperative course. Taking the results of these studies together portal hypertension *per se* is not a contraindication to resection in patients with HCC on cirrhosis. On the basis of thorough preoperative work-up surgical resection is generally indicated, if technically feasible and as long as the entire tumor burden can be removed with negative resection margins and sufficient postoperative hepatic function. [*Grade of recommendation B*]

Limitations and Benefits of Surgical Resection

Tumor recurrence is a persisting issue after surgical resection of HCC with and without cirrhosis.[58,64,65] Recurrent disease can result from intrahepatic dissemination of the primary tumor (true recurrence) or by de novo carcinogenesis. Microvascular invasion and satellite nodules are the main predictors of tumor recurrence[55,66,67] suggesting that the most cases are caused by intrahepatic dissemination. This distinction is important owing to the influence on prognosis and therapy. Late recurrence is more likely to result from new tumor development and curative resection, if feasible, might provide outcomes comparable to those of the index hepatectomy.[58,68] Tumor dissemination is more likely within the first 3 years after resection of the primary tumor[65] and mostly presents with multifocal and more aggressive tumors. In this scenario curative treatment is not recommended. Tumor recurrence, however, can to some extent be predicted based on the histological findings of the index hepatectomy specimens (ie, microvascular invasion and satellite lesions). The notion that high-risk patients benefit from being immediately listed for OLT needs to be backed by clinical data.[69]

The treatment strategy for recurrent disease is indeed controversial. Repeat hepatectomy may provide 5-year survival of up to 50%, but is usually associated with high incidence of rerecurrence.[70] Second and third hepatectomy for recurrent HCC may be equally safe and effective as the primary resection and may enable better results compared to the strategy of no repeat resection[71] Favorable long-term results have also been shown for local ablative treatment of HCC recurrence.[72,73] Liang et al[74] compared radiofrequency ablation (RFA) to repeat hepatectomy in patients who developed limited

TABLE 2. Long-Term Outcome of Patients with Hepatocellular Carcinoma Stratified for Prognostic Variables and Treatment Modality

Treatment	Prognostic Parameter	Variables	5-year OS [%]	5-year DFS %
Resection	Cirrhosis	HCC with cirrhosis	23–48	22–36
		HCC without cirrhosis	44–58	24–45
	Tumor size	HCC ≤ 3 cm	55–78	30–51
		HCC ≤ 5 cm	41–67	21–44
		HCC > 5 cm	29–56	22–23
	Number of nodules	Single	35–68	19–46
		Multiple	21–58	6–25
Transplantation	Milan criteria		59–83	62–92
	UCSF criteria		50–78	43–93

DFS indicates disease-free survival; OS, overall survival.

disease recurrence of up to 3 lesions with the largest up to 5 cm in diameter after hepatectomy for HCC. Both treatments yielded a comparable 5-year survival of 30.7% for hepatectomy and 39.9% for RFA. The Hong Kong group published their results for treating transplantable recurrent HCC after surgical resection with either salvage transplantation or nontransplant therapies such as second resection, RFA or transarterial chemoembolization (TACE). Although the direct comparison of both strategies did not show a significant difference in patients' long-term outcome, salvage transplantation provided better results in patients with stage II disease and early intrahepatic recurrence.[75] Secondary (salvage) transplantation might serve as a viable strategy for selected patients with recurrence restricted to the liver after previous resection. In patients with cirrhosis and compensated liver function resection before OLT might indeed be indicated from various perspectives:

Resection as primary therapy. Because of the organ shortage, hepatic resection might serve as primary therapy for HCC on cirrhosis with acceptable survival rates in selected patients (Table 2). The question whether to choose primary OLT or primary resection and salvage OLT for patients with small HCC on cirrhosis remains a matter of debate. Patients' outcome should be evaluated on an intention-to-treat (ITT) basis including patients with tumor progression while on the waiting list for primary OLT and those with recurrence after initial resection that exceeds transplant criteria. In their ITT analysis of 98 and 195 HCC patients who underwent primary resection and salvage OLT and primary OLT, Adam et al[76] demonstrated unfavorable 5-year overall (50% vs 61%; $P = 0.05$) and disease-free survival (18% vs 58%; $P < 0.0001$) for the group of patients who underwent initial resection. Remarkably, secondary OLT was associated with significantly higher operative mortality. Further studies, however, reported comparable overall survival of patients with early HCC treated with primary OLT or primary resection followed by salvage OLT in case of recurrence.[77–85] One should note that disease-free survival is reduced in patients undergoing primary resection (Table 3). Cherqui et al[86] reported their results on 67 patients with compensated cirrhosis and HCC meeting the Milan criteria who underwent primary resection. These authors showed excellent 5-year overall survival of 72% in the ITT population including 16 patients who underwent salvage OLT. In this study, a significant proportion of patients underwent laparoscopic liver resection (55%) and there was no mortality in patients who underwent salvage OLT. Despite the lack of controlled trials, the available evidence suggests the concept of primary resection and salvage OLT as an effective treatment in selected patients with early HCC on compensated cirrhosis. [*Grade of recommendation B*]

Liver resection as a bridge treatment to OLT. Although TACE is the most commonly applied treatment to prevent tumor progression in HCC patients listed for OLT, incomplete tumor necrosis may promote tumor progression.[87,88] Therefore, resection with complete tumor removal might be favorable in patients with small HCC on CTP class A cirrhosis. However, further investigation is needed due to the potential morbidity of resection. Furthermore, the outcome of patients undergoing OLT after resection of disease exceeding the Milan criteria needs to be evaluated.[89] [*Grade of recommendation D*]

Liver resection for patient selection. Liver resection with pathological analysis of the specimen allows clinicians to identify patients at high risk for recurrence (eg, microvascular invasion, satellite lesions). These patients may probably benefit from being listed for OLT immediately after resection, whereas patients with favorable tumor features might be followed-up and listed for salvage OLT in case of recurrence. This strategy may help to select patients with very unfavorable tumor features who are not eligible for OLT and those with disease beyond selection criteria with low-risk tumor biology who might still benefit from OLT. The promising preliminary results of this approach need validation in prospective studies using standardized treatment protocols.[69] [*Grade of recommendation C*]

Neoadjuvant and Adjuvant Therapy

Transarterial (chemo-)embolization is the most thoroughly investigated neoadjuvant treatment. The results of 3 RCTs do not support routine use of preoperative transarterial (chemo-) embolization before hepatic resection.[90–92] [*Grade of recommendation A*] However, sequential TACE and PVE might improve perioperative and long-term outcomes before major hepatic resection for HCC.[93]

There is currently no strong evidence supporting adjuvant therapy to reduce the risk of recurrence after curative therapy. Several trials including a small RCT of 60 patients that suggested a benefit of adjuvant capecitabine lack statistical power.[94] Further studies on adjuvant systemic chemotherapy, intra-arterial chemotherapy or the combination of both did not reveal a benefit on patients' long-term outcome.[95–98] Adoptive immunotherapy significantly improved recurrence-free survival in a trial of 150 patients. However, there was no significant difference in overall survival between both study groups.[99] In an RCT a significantly higher disease-free and overall survival at 3 years was reported for adjuvant intra-arterial treatment with ^{131}Iodine-labeled lipiodol.[100] Although this trial was prematurely closed after enrolment of 43 patients, the long-term results confirmed the survival advantage, though the effect became nonsignificant after a period of 8 years.[101] This result may reflect the effectiveness of the treatment against preexisting microscopic lesions, whereas it failed to prevent de novo carcinogenesis. However, as a false negative result (type II error) cannot be ruled out, these results together with the results from nonrandomized trials necessitate a well-designed confirmatory RCT before adjuvant therapy with intra-arterial ^{131}I-lipiodol can be recommended.

Although the earlier therapies address the issue of true recurrence from residual tumor cells, therapies also targeting the underlying liver disease have been employed to prevent recurrence originating from *de novo* tumors. An RCT of 89 patients revealed adjuvant administration of oral acyclic acid to significantly prevent true tumor recurrence.[102] In patients with HCC and viral hepatitis adjuvant interferon has been proposed because of its combined antitumor (antiproliferative and antiangiogneic) and antiviral actions. A meta-analysis revealed a significant benefit of adjuvant interferon regarding recurrence-free survival.[103] The results require cautious interpretation as the benefits of adjuvant interferon on late recurrence and survival remain unclear and the effectiveness of adjuvant interferon in HBV versus HCV-related HCC was not explored. Finally, the sample size of the individual studies and the pooled analysis was rather small. These data do not justify adjuvant interferon therapy as standard of care but warrant further investigation of interferon in a pegylated form and in combination with other agents such as ribavirin.[104] [*Grade of recommendation B*] Future trials on adjuvant therapy of HCC should evaluate individual therapies tailored to patients' risk profile (ie, high risk of true recurrence versus de novo tumor development; patients with HBC or HCV-related HCC) to identify subsets of patients that will most likely benefit from specific therapies.

Liver Transplantation

In the absence of metastases and macroscopic vascular invasion, OLT is the best available curative treatment of HCC on cirrhosis, as it removes the tumor burden and effectively treats the underlying liver disease, which limits patients' prognosis and serves for de novo carcinogenesis. In the early 1990s OLT was reserved for HCC patients with contraindications to resection due to insufficient hepatic reserve and/or tumor size and number. The 5-year survival of 15% to 40% was significantly worse than those of OLT for benign diseases and prompted the definition of stricter selection criteria.

TABLE 3. Recent Studies Comparing Long-Term Outcome of Patients with HCC Treated Primarily With Resection (and salvage transplantation) or Primary Liver Transplantation

First Author	Year	Primary Therapy	Sample Size	5-year OS Rate	5-year DFS Rate	Study Period	ITT Analysis
Lee[85]	2010	Transplantation	78	68%	75%*	1997–2007	Yes
		Resection	130	52%	50%		
Facciuto[84#]	2009	Transplantation	119	62%	—	1997–2007	Yes
		Resection	60	61%	—		
Del Gaudio[83]	2008	Transplantation	147	58%	54%	1996–2005	Yes
		Resection	80	66%	41%		
Shah[82]	2007	Transplantation	140	64%	78%*	1995–2005	Yes
		Resection	121	56%	60%		
Poon[81]	2007	Transplantation	85	44%	—	1995–2004	Yes
		Resection	228	60%	—		
Margarit[80]	2005	Transplantation	36	50%	64%*	1988–2002	Yes
		Resection	37	78%	39%		
Bigourdan[79]	2003	Transplantation	17	71%	80%*	1991–1999	Yes
		Resection	20	36%	40%*		
Adam[79]	2003	Transplantation	195	61%*	58%*	1984–2000	Yes
		Resection	98	50%	18%		
Belghiti[77]	2003	Transplantation	70	—	59%	1991–2001	No
		Resection	18	—	61%		
Figueras[78]	2000	Transplantation	85	60%	60%*	1990–1999	Yes
		Resection	35	51%	31%		

*Significant difference as reported in the original study; #4-year survival rates are reported for patient meeting the Milan criteria.
DFS indicates disease-free survival; ITT, Intention-to-treat analysis; OS, overall survival.

Selection Criteria of HCC Patients for Liver Transplantation

In a retrospective analysis of 48 patients Mazzaferro et al[105] reported an actuarial 4-year overall survival rate of 75% and a recurrence-free survival rate of 83%, if OLT was restricted to patients who had a single tumor of up to 5 cm or up to 3 tumors each 3 cm or less in diameter with no evidence of macrovascular invasion or extrahepatic disease. These results served as the basis for the so-called Milan criteria, which have been adopted by the United Network for Organ Sharing (UNOS) as selection criteria for HCC patients. Numerous subsequent reports confirmed these results and established OLT as therapy for HCC patients with cirrhosis[106–108] (Table 2). The excellent outcomes have in turn raised the question, whether selection criteria for HCC patients should be expanded. In their study Mazzaferro et al[105] could already show a 50% 4-year survival of patients whose disease extended their proposed criteria. Yao et al[107] from the University of California San Francisco (UCSF) provided further evidence that the Milan criteria can be expanded. Their study of 70 patients revealed no adverse impact on survival, if selection was broadened to a solitary tumor of up to 6.5 cm or 3 tumors or less with diameters of up to 4.5 cm, and a maximum total tumor size of 8 cm (5-year overall survival rate 75%). Although these data were obtained for tumor variables at explantation, prospective validation of the UCSF criteria based on preoperative imaging yielded similar results.[109] The largest analysis including 467 HCC patients revealed similar outcome of patients meeting the Milan and UCSF criteria both when assessing preoperative imaging and explant pathology, whereas a worse long-term survival was noticed for patients beyond the UCSF criteria.[110] The Milan and UCSF criteria can currently be recommended for selection of HCC patients for OLT. [*Grade of recommendation B*]

Optimal criteria for selection of HCC patients for OLT remain a matter of debate. Adherence to restrictive criteria is dictated by 3 major reasons: (1) lack of donor organs, (2) increased risk of recurrence, (3) increased rates of tumor progression, if patients with advanced disease will be listed. The limited number of available donors is the main restricting factor for OLT and contributes to prolonged waiting time. Prolonged waiting times are associated with increased drop out rates mainly due to tumor progression beyond current selection criteria. Expansion of selection criteria might increase the need for donor organs and by this is likely to further lengthen waiting periods, increase drop out rates and impair outcome on ITT analysis.

Expanded liver donor criteria (*rescue allocation*) address the lack of organs. A study on 45 cases of OLT with *rescue organs* that were rejected by other centers owing to medical and/or logistical reasons showed a 2-year recipient overall survival of 84.4%.[111] This study included 8 patients with HCC who all fulfilled the Milan criteria and were all alive at the end of the study period. A further retrospective study showed no significant difference in recurrence between recipients of standard and extended donor criteria allografts, despite more advanced disease in the latter group.[112] These results should prompt further prospective studies using extended donor criteria for patients with HCC.

At present, living donor liver transplantation (LDLT) and neoadjuvant therapy represent the 2 major strategies to address the lack of donor organs and prolonged waiting periods.

Living Donor Liver Transplantation

Initial results of Living donor liver transplantation (LDLT) for HCC have been promising with 3-year survival rates of 62% to 73%[113,114] (Table 2). The Hong Kong group reported a 5-year survival of 72% for recipients with HCC within the Milan criteria.[114] These authors observed higher recurrence rates after LDLT possibly due to proliferative stimuli of the regenerating liver graft. This finding is supported by Fisher et al[115] who reported higher recurrence rates at

3 years in the LDLT patients, whereas Soejima reported recurrence-free survival of 100% and 74% in patients within and beyond the Milan criteria, respectively.[116] LDLT may offer transplantation to patients beyond the Milan criteria. A study of 56 HCC patients treated with LDLT showed that 15 of the 20 patients who did not meet the Milan criteria had a median recurrence-free survival of 12 months. As those who developed disease recurrence survived for a median of 20 months the authors suggested to apply different selection criteria for LDLT.[117] A recent study of 25 HCC patients exceeding the UCSF criteria confirmed poor recurrence-free and moderate overall survival.[118] However, as a complex procedure it requires an experienced team and is still associated with donor morbidity of up to 40% and mortality of up to 0.5% raising ethical considerations.[119] Most studies reported on Asian populations, which are known to primarily develop HCC due to chronic HBV infection. Although recurrence of hepatitis C has been reported to be more severe in living donor than in cadaveric OLT, data on hepatitis C patients are scarce. Long-term data on overall and recurrence-free survival after LDLT are lacking for either type of underlying hepatitis. In selected cases surgical resection may improve outcome of isolated intrahepatic recurrence after LDLT.[120] Also the issue of primary graft nonfunction (PNF) after LDLT, in particular in patients beyond the Milan criteria is unsolved. Although in some cases LDLT might be justified in patients with advanced disease, selection of patients and management of those with severe complications require further discussion.

Treatment Before Liver Transplantation

Although TACE causes marked tumor necrosis with good local tumor control, its advantage as a bridging tool preventing drop outs of patients listed for OLT remains unclear, as available data are derived from case series and cohort studies and their results are rather inconsistent.[121–123] A positive response to TACE has been shown to be associated with a prolonged 5-year survival of 71% as compared to 49%, if no neoadjuvant TACE was performed and 29% in case of treatment failure with TACE.[121] A study of 96 HCC patients with a median of 5 TACE sessions before OLT confirmed a 5-year survival of 80% in 50 transplanted patients with 34 of them initially exceeding the Milan criteria. Progression-free TACE but not the Milan criteria was identified as predictor for disease recurrence suggesting treatment response as selection criterion for OLT.[124] These results are supported by studies applying a downstaging protocol for patients who initially presented with disease outside the Milan criteria.[125] Chapman et al[123] enrolled patients with a single HCC 8 cm or less or 2 HCCs 5 cm or less or up to 5 HCCs with a maximum diameter 4 cm or less and a total tumor diameter 12 cm or less were in a study using TACE, RFA, percutaneous ethanol injection (PEI) or hepatic resection for downstaging. The authors reported comparable survival of OLT in patients who initially met the Milan criteria and those who met the Milan criteria after successful downstaging. In a further study patients with stable, progressive, or untreatable disease were prioritized for OLT with comparable survival as patients who had a complete or partial response.[126] Multimodal therapy consisting of TACE before OLT and systemic chemotherapy during and after surgery might be of benefit in patients with large tumors.[127] Although some authors suggest Sorafenib as a bridging therapy due to its impact on disease progression,[128] further data from randomized trials are required to evaluate this indication.[129] However, as long as there are no controlled trials the potential benefits of bridging patients to OLT and OLT after successful downstaging remain controversial. [*Grade of recommendation C*]

Perspectives of Patient Selection for Transplantation

Liver allocation follows a scoring system (MELD, Model for End-Stage Liver Disease) originally developed by the United Network for Organ Sharing Priority (UNOS) to prioritize patients with the highest short-term mortality risk. As it solely consisted of biochemical variables (ie, bilirubin, creatinine, INR), the MELD score would fail to assess the risk of disease progression and drop-out in patients with malignant disease and compensated liver function. Hepatocellular carcinoma patients eligible for OLT therefore receive additional points according to their tumor size and number with 10% point increase for every 3 months on the list. It has remained controversial, whether pre-OLT staging should include further diagnostic criteria. The Milan and the UCSF criteria solely rely on radiological findings, that is, the number and size of detectable lesions. Unfortunately, inaccuracy of radiological imaging remains a problem, particularly in cirrhosis. A cohort study including 789 transplant patients revealed accuracy of radiological imaging to be as low as 44% with the actual pathologic stage being as frequently over- as underestimated.[130] Furthermore, imaging does not detect vascular invasion as the underlying pathological condition for metastatic spread and tumor recurrence. Although tumor size is a risk factor for recurrence, it is a surrogate parameter for vascular invasion and poor differentiation.[131] This might explain why up to 20% of patients who meet restricted selection criteria develop recurrent disease[108,132] and others develop a large tumor without vascular invasion. Moreover, the kind of microvascular invasion may be of clinical relevance. A recent study revealed invasion of a vessel with a muscular wall and invasion of a vessel that is more than 1 cm from the tumor as specific features of microvascular invasion that are associated with poor prognosis.[133] Liver biopsy to assess tumor biology as part of the pre-OLT work-up might reduce the proportion of patients with recurrence and help to identify those who benefit from OLT though they do not meet the selection criteria. Cillo et al[106] excluded patients with poorly differentiated tumors, which reduced post-OLT recurrence to fewer than 10%. One should note that the accuracy of preoperative core biopsy to assess tumor differentiation is controversial.[134,135] In a retrospective multicenter study, the outcome of 1556 patients who underwent OLT for HCC (1112 patients beyond Milan criteria) was analyzed.[136] Although 5-year overall survival was 73.3% and 53.6% for patients within and beyond the Milan criteria, a 5-year overall survival of 71.2% was achieved in patients without microvascular invasion who met the up to 7 criteria (7 as the sum of the size of the largest tumor [in cm] and the number of tumors). Patients with more than 3 lesions of limited diameter might still experience good survival after OLT.[137,138] In a study analyzing the Scientific Registry of Transplant Recipients (SRTR) database of 6478 patients who received a primary OLT for HCC the Milan criteria were found to be too restrictive.[139] The authors suggested a new selection score consisting of AFP level less than 400 ng/mL and total tumor volume (TTV) less than 115 cm^3 that accurately predicted outcome and should be validated in prospective studies.

Genotype analysis can potentially further improve prediction of tumor recurrence.[140,141] The fractional allelic loss rate (FAL) of a group of 9 microsatellite markers, which are located close to or within known tumor suppressor genes has been reported to have a higher predictive value of tumor recurrence than vascular invasion.[142] Fractional allelic loss rate is calculated by division of the number of mutated microsatellites by the total number of included microsatellite markers. Schwartz et al[143] showed that microsatellite analyses may help to predict recurrence, particularly in disease beyond the Milan criteria. Apparently, assessment of tumor biology requires liver biopsy, which bears a 0% to 3.4% risk of tumor-tract seeding.[106,144,145] In almost all cases tumor seeding can be cured by local excision with no impact on survival.[146] In addition, marking of the needle track during biopsy and subsequent excision at OLT can possibly prevent tumor seeding.[147] In any case, the risks and benefits of incorporating tumor biology into selection criteria of HCC patients for OLT need to be evaluated within further trials.

Immunosuppression After Liver Transplantation for HCC

Immunosuppression after OLT for HCC is a subject of raising interest. The calcineurin inhibitors (CNI) cyclosporin and tacrolimus currently form the main components of immunosuppression, though their use in HCC patients is under debate owing to their potentially tumor-promoting action.[148] Because of its antiproliferative effects the mTOR inhibitor Sirolimus has been suggested for immunosuppression of HCC patients. In addition to data demonstrating antitumor activity of Sirolimus,[149] favorable effects on oncological outcome of HCC patients with acceptable toxicity and rejection rates were reported.[150] Although these data have been confirmed recently,[151] effectiveness and safety of Sirolimus-based immunosuppression in HCC patients is currently investigated a in multicenter RCT.[152]

Percutaneous Local Ablation

Patients not eligible for resection or OLT due to their medical condition might be candidates for local ablative therapies, which are commonly performed percutaneously under ultrasound guidance. The effectiveness of local ablative therapies depends on the degree of cirrhosis and the number and size of lesions, which should thus guide patient selection. The most frequent local therapies are PEI and RFA. Percutaneous ethanol injection is tolerated well, inexpensive and causes complete necrosis rates of 90% to 100% for tumors 2 cm or less. The necrosis rate rapidly declines to 50% for tumors of 3 cm to 5 cm in diameter.[153,154] Destruction of tumor cells by RFA results from local hyperthermia (ie, coagulative necrosis) induced by a single or multiple electrodes. Radiofrequency ablation leads to more complete tumor necrosis with increasing tumor size and requires fewer sessions compared to PEI.[155–159] As the degree of necrosis depends on the achieved temperature, RFA is less effective for tumors adjacent to major vessels. Moreover, RFA may increase the risk for peritoneal seeding in subcapsular tumors. Five RCT have so far compared outcome of patients with early HCC after PEI versus RFA therapy[155–159] (Table 4). Three trials and a meta-analysis reported a benefit of RFA regarding overall survival.[156–158,160] Four RCTs favored RFA compared to PEI regarding recurrence-free survival suggesting better local tumor control.[155–157] In contrast to previous reports, the RCT do not confirm a relevant difference in complications and thus favor RFA for treatment of patients with HCC less than 4 cm not eligible for surgery. [*Grade of recommendation A*] Moreover, RFA can be repeated successfully in cirrhotic patients with intrahepatic recurrence.[161]

Percutaneous local ablation in patients eligible for resection remains controversial. A nationwide analysis of more than 17.000 HCC patients revealed a lower 2-year recurrence rate after hepatectomy compared to percutaneous ablation (with no difference in overall survival).[162] An analysis of 235 patients with HCC and CTP class A or B cirrhosis, demonstrated RFA to be safe and effective for up to 3 lesions at least 5 cm.[163] Tumor size was a predictor of local recurrence but did not affect survival because of treatment of recurrent tumors with additional RFA sessions. Overall survival of patients who underwent RFA for disease meeting BCLC criteria for operable tumors was similar to that of patients undergoing hepatic resection (3- and 5-year survival rates: 82% and 76%). A Markov model analysis recently suggested that RFA followed by resection in case of initial local failure enabled almost identical overall survival to primary resection in patients with compensated cirrhosis and very early HCC (<2 cm).[164] Although 3 RCT on early HCC showed similar oncological outcome after surgical resection and local ablation,[165–167] a recent RCT including 234 patients meeting the Milan criteria favored resection compared to RFA with respect to overall and recurrence-free survival.[168] However, methodological issues of these trials that were, moreover, performed exclusively in Asian populations do not allow final conclusions on the value of local ablation as first-line treatment of early HCC. Further trials considering the stage and etiology of disease and patients' liver function are warranted. [*Grade of recommendation B*] For multifocal HCC a combined treatment of resection and RFA was suggested in patients with preserved liver function. Choi et al[169] reported a 5-year overall survival rate of 55% in 53 patients with no procedure-related deaths. The combination of hepatectomy and RFA may be a viable option for patients who are not eligible for OLT. [*Grade of recommendation C*]

NONCURATIVE TREATMENT

Transarterial Embolization and Chemoembolization

Along with growing size HCC lesions increasingly derive their blood supply from the hepatic artery, which forms the rationale for selective catheterization and obstruction of the tumor's feeding arterial vessel (transarterial embolization, TAE). Before embolization chemotherapeutic agents (eg, doxorubicin, mitomycin, cisplatin) can be injected as a suspension with lipoidol to retain the injected agents in the tumor (transarterial chemoembolization, TACE). The results of an RCT challenge the need for embolization after transarterial

TABLE 4. Characterstics of Randomized Controlled Trials Comparing Radiofrequency Ablation to Percutaneous Ethanol Injection for the Treatment of Hepatocellular Carcinoma

		Sample Size			CTP Class A/B		Complete Necrosis Rate (%)		
First Author	Year	RFA	PEI	Tumors	RFA	PEI	RFA	PEI	3-year OS Rate
Lencioni[155]	2003	52	50	Milan criteria	45/7	35/15	91	82	RFA: 98% PEI: 88%
Lin[156]	2004	52	52	1–3 lesions ≤4 cm	41/11	39/12	96	88	RFA: 74% PEI: 48%
Lin[157]	2005	62	62	1–3 lesions ≤3 cm	46/16	47/15	96	88	RFA: 74% PEI: 51%
Shiina[158]	2005	118	114	Milan criteria	85/33	85/29	100	100	RFA: 81% PEI: 67%
Brunello[159]	2008	70	69	1–3 lesions ≤3 cm	56/44	56/44	95	65	RFA: 63% PEI: 59%

CTP indicates Child-Turcotte-Pugh; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation.

chemotherapy.[170] However, TACE represents an effective treatment option for well-selected patients with unresectable, *intermediate stage* HCC. Despite objective response rates of up to 60% only 2% of patients are expected to develop a complete response.[171] Transarterial chemoembolization may be effective in tumors more than 10 cm in diameter. Because of potential necrosis to peritumorous liver parenchyma, main portal vein thrombosis (PVT) is considered a contraindication for TACE. For the same reason treatment with TACE should not be chosen for patients with an increased risk of liver failure (eg, tumor load >30%) or decompensated liver function.[172] Further contraindications include infiltration of adjacent organs, severe contrast agent allergy and severe coagulopathy. Finally, patients with extrahepatic disease are unlikely to benefit from TACE. However, TACE may be safe and effective in patients with main PVT who have preserved liver function and sufficient collateral blood flow.[173] Side effects may result from the injected agents (that is nausea, vomiting, alopecia, bone marrow depression, renal failure) or obstruction of the hepatic artery (ie, postembolization syndrome with right upper quadrant pain, nausea, fever) and are usually self-limited. Serious complications requiring additional therapy occur in less than 10% of patients and include liver failure, cholecystitis, and hepatic abscess formation. In 2003, a seminal meta-analysis revealed a significant 2-year survival benefit for the TACE compared to conservative or suboptimal therapies without proven antitumoral activity.[174] These results are in line with a prospective cohort study on 8510 patients with unresectable HCC from Japan.[175] Transarterial chemoembolization remains the reference treatment option for patients with unresectable HCC to which new therapies should be compared. [*Grade of recommendation A*]

Selective Intra-Arterial Radiation Therapy

Selective intra-arterial radiotherapy (SIRT), also known as radioembolization, is a minimally invasive procedure using radioactive microspheres to deliver tumoricidal radiation doses internally. External beam therapy has the risk of radiation induced liver disease (RILD), which can result from exposure to 40 Gy.[176] Radiation induced liver disease is a syndrome of anicteric hepatomegaly, ascites, and increased liver enzymes weeks to months after therapy due to pathological sequelae of radiation injury to normal liver tissue.[177] Much higher doses can be delivered cumulatively through SIRT without clinical manifestation of RILD.

Contraindications and Complications

There are 2 absolute contraindications to SIRT: (1) a ^{99m}Tc scan that demonstrates more than 30 Gy would be delivered to the lungs with a single infusion or up to 50 Gy with multiple infusions due to hepatopulmonary shunting; (2) delivery of microspheres to the gastrointestinal tract as shown by the pretreatment hepatic angiogram that cannot be avoided with current catheter techniques. The most common complication of SIRT is a postembolic syndrome that manifests as fatigue, abdominal pain, and fever. Other complications include cholecystitis, gastric ulceration, gastroduodenitis, pancreatitis, pneumonitis, and RILD. Most toxicities can be avoided by proper planning, delivery, and dosimetry.

Outcomes With Radioembolization

The role of SIRT for palliative treatment of unresectable HCC is evolving. There have been no RCTs comparing the efficacy of SIRT to other established first line therapies for inoperable HCC (eg, TACE). Recently, an analysis of 291 HCC patients who were treated with SIRT at various stages of disease was published.[178] The authors reported response rates of 42% and 57% based on WHO and EASL criteria. Selective intra-arterial radiotherapy offered a survival benefit in CTP class A patients independently of PVT, whereas only CTP class B patients without PVT obtained a survival benefit. Although these results together with previous data[179] demonstrate SIRT to be safe in patients with PVT, survival benefits may be limited to patients with PVT who have preserved liver function. Further studies confirmed the effectiveness of SIRT in advanced HCC[180] and, moreover, reported no difference and an advantage of SIRT compared to TACE regarding time-to-progression and toxicity, respectively.[181,182]

Selective intra-arterial radiotherapy may be useful to downstage patients to undergo resection, ablation, or OLT. In an analysis comparing TACE to SIRT for downstaging of HCC, higher partial response rates (61% vs 37%; $P = 0.07$) and successful downstaging (58% vs. 31%; $P = 0.02$) was achieved in the SIRT group.[183] Further studies confirmed the ability of SIRT to reduce the size of targeted lesions.[184,185]

Although SIRT seems safe and effective in selected HCC patients, level I evidence is lacking favoring SIRT for palliative treatment of advanced HCC and treatment before OLT. Furthermore, benefits of SIRT in combination with other therapies such as systemic targeted agents and as (neo)adjuvant therapy after curative treatment require further evaluation. At present SIRT can be recommended as palliative therapy for advanced HCC, though treatment should preferably be delivered in the setting of clinical trials. [*Grade of recommendation B*]

External Beam Radiation Therapy

Because of the low tolerance of the liver to radiation therapy (RT), the role of external beam RT in the management of HCC has traditionally been limited. Whole liver RT of 28 Gy to 35 Gy over 3 weeks carries a 5% risk of RILD.[186] As new RT delivery technologies have evolved the role of external beam RT for advanced HCC needs to be redefined and treatment within clinical trials is recommended.

Conformal Radiation Therapy

Improved imaging techniques that better define the tumor such as tumor immobilization, organ tracking to control for breathing, 3-D planning techniques and increased knowledge of the liver's partial volume tolerance to radiation have allowed delivery of increased doses. Ben-Josef et al[187] treated 128 patients with irresectable hepatic malignancies (35 patients with HCC) using conformal hyperfractionated RT with simultaneous hepatic arterial infusion of fluorodeoxyuridine as radiosentisizer. Overall, 38 patients (30%) had grade 3 to 4 toxicity with 5 cases of RILD (4%). A survival benefit was shown for a dose of at least 75 Gy (23.9 months) versus at least 75 Gy (14.9 months) ($P < 0.01$). Other studies using conformal RT support this dose effect.[188,189] [*Grade of recommendation C*]

Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) has been developed to deliver highly conformal radiation in high-doses to target volumes. By employing immobilization and accurate localization, potent doses can be delivered with minimal exposure to surrounding normal tissues due to a very rapid drop-off of dose beyond the target volume.[190] These doses are typically delivered in fewer than 10 fractions. A prospective study, in which 6 fraction SBRT was given in escalating doses (24 Gy to 54 Gy) was conducted on 31 CTP class A patients with small and large HCC unable to receive standard therapies. Portal vein thrombosis was present in 53% of these patients. Although liver function declined in 5 patients, there was no case of RILD or dose-limiting toxicity.[191] The ability of SBRT to provide local control without serious toxic side effects has also been demonstrated in smaller studies.[192,193] [*Grade of recommendation C*]

Proton and Heavy Ion Radiotherapy

Proton and heavy ion RT have also been studied in HCC. These positively charged particles are heavier than electrons and have a unique dose distribution. The protons are delivered in rapidly increasing doses, which deposits them at the end of the range of the beam within the patient at a depth that is determined by the particular beam energy. These properties favor them for deep tumors with maximal sparing of the normal tissue. The proton dose is reported in GyE (Cobalt gray equivalents), which is translated into equivalent photon dose in Gy. Twenty-four CTP class A or B patients with HCC tumors ranging from 2.1 to 8.5 cm were prospectively studied using carbon ion RT (49.5 to 79.5 GyE in 15 fractions).[194] The treatment was tolerated well other than grade 3-skin toxicity, and 5-year survival was 25%. A phase II trial showed a 2-year survival of 55% in 34 patients with unresectable HCC who received proton therapy (63 GyE in 15 fractions). Remarkably, 6 patients underwent OLT 6 to 16 months later.[195] The outcomes with proton and heavy-ion RT for HCC are among the best after RT. Unfortunately access to this modality is limited. [*Grade of recommendation C*]

Because of new radiation techniques and fractionation schedules RT is used more safely and effectively in the palliative treatment of HCC. Patients with CTP class B, patients with large tumors and HBV carriers are at increased risk for toxicity. Excellent local control has been seen with small tumors fewer than 5 cm, if sufficient doses are delivered. Randomized controlled trials are needed to support these findings before any of the various modalities of external beam RT can be included in standard treatment algorithms of HCC. As the experience with heavy ion RT demonstrates that if high enough doses of RT can be delivered, HCC can potentially be controlled, further evaluation of this treatment as a component within potentially curative treatment regimens for HCC patients should be considered.

Systemic Therapies

The potential of systemic chemotherapy to prolong survival of patients with unresectable HCC has been evaluated for several protocols.[196–198] Although anthracyclines are considered the most effective agents and single-agent doxorubicin regimens have been widely used; response rates of chemotherapy are low (< 20%) with no survival advantage. For reasons of toxicity, particularly in patients with underlying liver disease, systemic chemotherapy is neither recommended as first-line therapy nor as control treatment within clinical trials. [*Grade of recommendation A*] Expression of sex hormone receptors on HCC cells suggested tumor growth to be in part dependent on hormone stimulation. The promising initial data with the antiestrogen tamoxifen were disproved by a meta-analysis of 7 RCT[174] and a subsequent RCT of 420 patients.[199] [*Grade of recommendation A*] The known antimitotic effect of somatostatin and the expression of its receptors in HCC formed the rationale to treat patients with somatostatin (analogues). Encouraging effects[200] were not reproduced in larger RCT.[201,202] A survival benefit of somatostatin in advanced HCC with overexpression of its receptors requires further evaluation.[203] A phase III study comparing the combination of tamoxifen and the somatostatin analog octreotid to tamoxifen alone did not favor combined therapy in advanced HCC.[204] [*Grade of recommendation B*] First studies on interferon in patients with inoperable HCC demonstrated prolonged survival compared to doxorubicin and no antitumor therapy, respectively.[205,206] A subsequent RCT could not reproduce these data.[207] The combined treatment with systemic chemotherapy interferon did not improve survival either.[208] [*Grade of recommendation B*]

The disappointing results of conventional systemic therapies together with the growing understanding of the tumor's biology prompted the development of further therapies against molecular targets. These agents are applied either alone or in combination with systemic chemotherapy. Bevacizumab (Avastin), a recombinant, humanized monoclonal antibody against VEGF has been tested within 2 phase II trials of patients with advanced HCC. Zhu et al[209] evaluated efficacy and safety of bevacizumab in combination with gemcitabine and oxaliplatin (GEMOX-B) and reported objective response rates of 20% and a median progression-free survival of 5.3 months. Siegel et al[210] examined bevacizumab as single agent in patients with advanced HCC. In this phase II trial 13% of patients had objective responses the median progression-free survival was 6.9 months. The monoconal antibody cetuximab (Erbitux) targets the epidermal growth factor receptor (EGFR). Although a phase II study of cetuximab as a single agent in the treatment of advanced HCC failed to show antitumoral activity,[211] a further phase II trial of cetuximab in combination with gemcitabine and oxaliplatin showed response rates of 20%.[212] Erlotinib, a small molecule with specific receptor tyrosine kinase inhibitory effects against EGFR has been tested as a single agent in phase II trials showing modest disease-control.[213,214] A recent phase II trial on 40 patients with advanced HCC showed that 62% of patients who received bevacizumab and erlotinib achieved a 16-week progression-free survival with limited toxicity.[215] A confirmatory phase III trial is required to assess a potential survival benefit by this combined treatment.

Sorafinib (Nexavar) is an oral multikinase inhibitor with activity against raf-kinase, VEGF receptor-2/3 (VEGFR-2/3) and platelet-derived growth factor receptor beta (PDGFR-β) tyrosine kinases, thereby blocking cell proliferation and neoangiogenesis.[216] A multicenter, phase III trial on sorafinib as a single agent in patients with advanced HCC was stopped prematurely. The analysis of 602 patients demonstrated longer median overall survival [10.7 months vs 7.9 months; hazard ratio 0.69; 95% confidence interval (CI), 0.55–0.87] and median time to progression (5.5 months vs 2.8 months; HR = 0.58; 95% CI, 0.45–0.74) for the treatment group.[217] This study for the first time showed a systemic therapy to provide a survival advantage in advanced HCC. A further phase III trial confirmed these results in patients from the Asia-Pacific region.[218] Sorafinib received FDA and EMEA approval for treatment of HCC and should be considered as control treatment within future trials. [*Grade of recommendation A*] In line with these data combined therapy with sorafinib and doxorubicin was shown to be superior compared to doxorubicin alone.[219] Subsequent trials should assess application of sorafinib in combination with other molecular therapies or systemic chemotherapeutic compounds for treatment of advanced HCC.[220] Moreover, one might hypothesize that this drug might also improve outcome within neoadjuvant or adjuvant protocols of patients undergoing potentially curative therapy. Three phase II trials assessed clinical activity of the multitargeted tyrosine kinase inhibitor sunitinib in patients with advanced HCC.[221–223] Although antitumor activity was comparable to that observed in phase II trials on sorafenib,[224] there is evidence of higher (dose-dependent) toxicity of sunitinib.[221] However, efficacy and safety of both agents is currently compared within an ongoing phase III trial.

Perspectives in the Management of Hepatocellular Carcinoma

Although surgical therapy forms the cornerstone of curative treatment of HCC, patients should be treated within a multidisciplinary setting. Figure 3 summarizes the treatment algorithm of HCC at the University of Heidelberg. Advances in surgical management have enabled surgery in patients with more advanced tumors and underlying liver disease. Posthepatectomy liver failure remains a major concern and may be prevented by cautious patient selection and PVE. Failure of the liver to respond to PVE can be considered as biologic marker of insufficient functional capacity and these patients

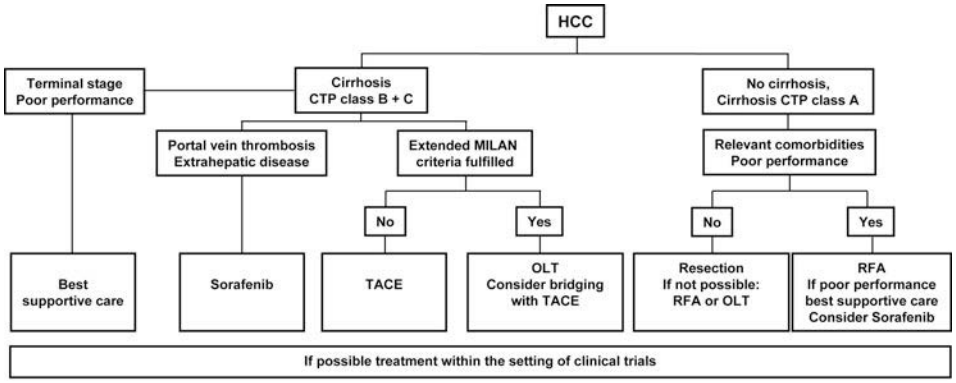

FIGURE 3. Treatment algorithm of HCC at the University of Heidelberg.
CTP indicates Child-Turcotte-Pugh classification; OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization. RFA is indicated for lesions with a maximum diameter of 3.5 cm (multifocal tumors) or 5 cm (single tumor) and a maximum number of 3 lesions per lobe. Extended Milan criteria: single lesion $\leq$ 6 cm or 2–3 lesions $<$ 3 cm.

are at increased risk of liver failure. The increasing experience with surgical therapy in HCC shows a survival benefit in selected patients with unfavorable tumor characteristics and has further established the indication for surgery. However, local ablative therapy might provide adequate treatment of early HCC. The selection of patients for curative treatment modalities remains controversial and requires further evaluation within prospective studies. Although introduction of well-defined selection criteria have improved long-term outcome of HCC patients undergoing OLT, the Milan criteria seem too restrictive. Besides careful expansion of the current radiological criteria, the strategy of involving histological and/or molecular markers, and response to neoadjuvant therapy are promising concepts to optimize patient selection. At present TACE and systemic sorafenib are accepted for treatment of intermediate and advanced HCC, respectively. Furthermore, innovative therapies such as SIRT may offer effective treatment in these patients. Molecular targeted therapy and in particular the promising initial experience with sorafenib opens a broad field of potential applications in HCC including adjuvant and neoadjuvant therapy. It is subject of current and future investigation to identify patients who benefit from molecular targeted therapy and invasive treatments. It should, however, be noted that despite increasing efforts to better understand and treat the disease, current recommendations for patients with HCC are based on a limited number of well-designed RCT, in particular in the field of surgical therapy. Randomized controlled trials should not only evaluate new surgical, interventional, and systemic therapies and their combinations within a multidisciplinary setting, but also assess the clinical value of biological markers to identify responders to specific therapies. Accomplishing these trials and achieving more individualized treatment remain major challenges to continue the progress that has already been made in the management of HCC.

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Salvage Versus Primary Liver Transplantation for Early Hepatocellular Carcinoma: Do Both Strategies Yield Similar Outcomes?

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Summary Background Data: In compensated cirrhotics with early hepatocellular carcinoma (HCC-cirr), upfront liver resection (LR) and salvage liver transplantation (SLT) in case of recurrence may have outcomes comparable to primary LT (PLT).

Objective: An intention-to-treat (ITT) analysis comparing PLT and SLT strategies.

Methods: Of 130 HCC-cirr patients who underwent upfront LR (group LR), 90 (69%) recurred, 31 could undergo SLT (group SLT). During the same period, 366 patients were listed for LT (group LLT); 26 dropped-out (7.1%), 340 finally underwent PLT (group PLT). We compared survival between groups LR and LLT, LR and PLT, and PLT and SLT.

Results: Feasibility of SLT strategy was 34% (31/90). In an ITT analysis, group LLT had better 5-yr/10-yr overall survival (OS) compared with group LR (68%/58% vs. 58%/35%; $P = 0.008$). Similarly, 5-yr/10-yr OS and disease-free survival (DFS) were better in group PLT versus group LR (OS 73%/63% vs. 58%/35%, $P = 0.0007$; DFS 69%/61% vs. 27%/21%, $P < 0.0001$). Upfront resection and microvascular tumor invasion were poor prognostic factors for both OS and DFS, presence of satellite tumor nodules additionally predicted worse DFS. Group SLT had similar postoperative and long-term outcomes compared with group PLT (starting from time of LT) (OS 54%/54% vs. 73%/63%, $P = 0.35$; DFS 48%/48% vs. 69%/61%, $P = 0.18$, respectively).

Conclusions: In initially transplantable HCC-cirr patients, ITT survival was better in group PLT compared with group LR. SLT was feasible in only a third of patients who recurred after LR. Post SLT, short and long-term outcomes were comparable with PLT. Better patient selection for the ''resection first'' approach and early detection of recurrence may improve outcomes of the SLT strategy.

Keywords: curative surgery, feasibility of salvage transplant, intention-to-treat analysis, recurrence, transplantable HCC

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The debate regarding the best initial curative surgical option (resection or liver transplantation) for early hepatocellular carcinoma (within Milan Criteria[1]) in a cirrhotic liver (HCC-cirr) continues. Although LT may be considered the optimal oncological option (the widest possible resection margins, and removal of the underlying cirrhotic liver that is at risk for the development of de novo HCC);[2] the shortage of organs has led many centers to adopt a strategy of resection first, and then LT in case of recurrence (salvage liver transplantation; SLT[3]) especially in Child-Pugh A (compensated) cirrhotics with solitary and peripherally located early HCC.

At our center also, we favor a policy of resection-first in early HCC-cirr patients. In our own previous study of 17 SLT patients, we found a higher operative mortality, increased risk of recurrence, and worse long-term survival compared to PLT.[4] Subsequently, several single center studies,[5–9] reviews, and meta-analysis[10–14] showed conflicting results. These reviews and meta-analysis are heterogeneous in terms of patient selection (selection criteria for resection and LT), endpoints used to assess outcomes (OS, disease-free survival, or time to recurrence), timing for these endpoints (1, 3 years, infrequently 5 or 10 years), and above all definition of SLT itself (LT for HCC recurrence in some, and for progression of liver disease in others). In addition, some studies have included both cirrhotic and non-cirrhotic patients with early HCC in the same analysis; this could indeed be a major confounding factor.

Probably only an intention-to-treat (ITT) analysis looking at long-term outcomes following resection-first or upfront PLT in initially transplantable cirrhotic patients (within conventional criteria) could prove or disprove the theory that the SLT strategy and PLT yield similar outcomes. In the present study, we compared outcomes following the SLT approach (resection-first with or without later LT for recurrence), versus primary LT on an intention-to-treat basis. For this ITT analysis, survival was calculated in the listed for LT group (group LLT) from the time of listing, so as to also include drop-outs, and starting from the time of resection in the resection-first group (group LR). In addition, we also compared outcomes between group LR and group PLT starting from the time of first surgical treatment (resection or PLT) so as to strengthen our ITT analysis results. Also, to analyze outcomes following SLT per se, we compared groups PLT and SLT with respect to perioperative and long-term outcomes starting from the time of LT in both groups.

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METHODS

From January 1990 to December 2012, 3842 liver resections and 2510 liver transplants were performed at Centre Hepatobiliaire, Hopital Paul Brousse, Villejuif, France.

We defined transplantable HCC-cirr patients as follows: (i) cirrhotic patients (≥ grade 4, Metavir) with HCC, (ii) patients ≤65 years of age, (iii) HCC within Milan criteria on preoperative imaging at the time of resection or PLT, and (iv) HCC proven on histopathology of the explanted/resected specimen.

SLT was defined as LT performed in cirrhotic patients with HCC recurrence after previous resection, ie, the true indication for listing the patient for LT was HCC recurrence.

We excluded the following patients from our study: (i) those in whom SLT was performed to treat liver function deterioration after resection (early or later period), (ii) those with incidental HCC on liver specimen, and (iii) patients initially thought to have HCC on imaging but no HCC (or having tumors other than HCC) on pathological examination of the explanted liver.

As shown in Figure 1, during the study period 342 HCC-cirr patients underwent primary resection, among these 138 patients were also initially transplantable. Of these, we excluded 8 patients, because they did not have HCC on the resected specimen (n = 4) or underwent SLT for deterioration of liver function (n = 4), respectively. Hence, 130 initially transplantable patients underwent a resection-first (with HCC proven on the resected specimen) with or without a subsequent SLT for recurrence (group LR).

On the other hand, 340 early HCC-cirr patients (with confirmed HCC on the explants) underwent primary LT (PLT) during the same period (group PLT).

To analyze the ITT survival, in the PLT arm, it was important to also include those patients who dropped-out on the waiting list after listing for LT. During the period of study, a total of 366 HCC-cirr patients were listed for PLT (group LLT), 26 of whom dropped-out in the waiting period (7.1%), and 340 had a PLT as mentioned above. So, we compared OS in group LLT (calculated starting from the time of listing for LT, thus also including drop-outs) versus group LR (where OS was calculated starting from the time of resection).

In addition, to compare group LR (n = 130) and group PLT (n = 340), starting from the time of first curative surgery (resection or LT, respectively); using our prospectively maintained database, we compared patient and tumor characteristics, postoperative results and long-term outcomes in these 2 groups. The OS and DFS in groups LR and PLT were calculated from the time of first surgery (resection in group LR, and transplantation in group PLT).

Among group LR patients, 99 patients had a liver resection alone, whereas 31 patients had a subsequent SLT for HCC recurrence (group SLT). To compare survival outcomes in groups PLT and SLT, the OS and DFS was calculated from the date of LT in a separate analysis.

At our center, the decision to resect or transplant a patient with early HCC-cirr is always taken in a multidisciplinary staff meeting attended by surgeons, hepatologists, pathologists, medical oncologists, and radiologists. The aim is to propose what the multidisciplinary team feels would be the best curative strategy for an individual patient based on current available evidence and results. Our general policy is to prioritize Child's A patients with peripheral lesions for resection rather than LT, and to offer LT to patients with deep-seated tumors and/or with decompensated Child Pugh B/C cirrhosis. Our follow-up protocol after resection or LT in HCC patients is: liver function tests and alpha-fetoprotein (AFP) levels every 4 months with alternate ultrasound Doppler examination and multi-detector CT scan of the chest and abdomen every 4 months during the first 2 years. After this, the same tests are repeated every 6 months.

In our study, we tried to specifically answer the following 4 questions, and did the relevant analysis for the same: (1) on an intention-to-treat basis, are the long-term survival outcomes similar with the resection-first and PLT upfront approach- ITT analysis from the time of listing for LT (thus also considering drop outs), and from the time of first surgery with curative intent (resection or PLT); (2) what are the factors that determine survival in early initially transplantable HCC-cirr patients—multivariate analysis to determine the factors affecting OS and DFS; (3) in early HCC-cirr patients, is the chance of getting transplanted the same after a primary resection (ie the feasibility of SLT approach) vis-à-vis a PLT (after also

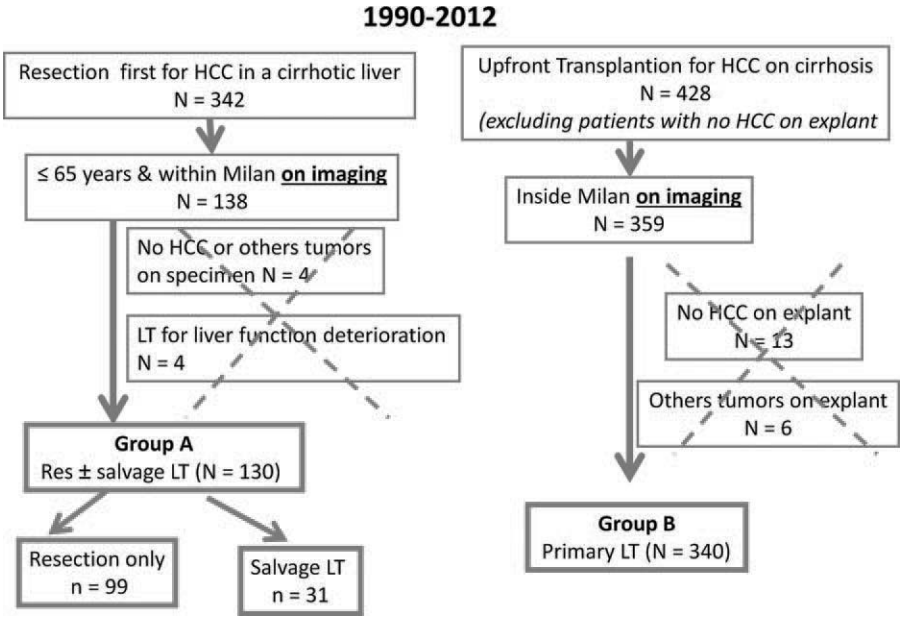


FIGURE 1. Patients undergoing primary resection or upfront liver transplantation for hepatocellular carcinoma. HCC, hepatocellular carcinoma;LT, liver transplantation;Res, resection.

considering drop-outs postlisting)—a systematic evaluation of the actual number and proportion of patients who finally underwent SLT when they recurred after a primary resection, and the reasons for fallout from the SLT strategy; and (4) are the perioperative and long-term outcomes following SLT and PLT similar—comparison of perioperative and long-term survival starting from the time of LT.

Statistical Analysis

Categorical and continuous study variables were compared between groups, using the χ^2 test and the independent-samples t test, respectively. Survival probabilities were estimated using the Kaplan-Meier method and were compared using log-rank tests. Multivariate analysis was performed using a Cox proportional hazards model to identify independent prognostic factors of survival in all patients. In multivariate analysis, factors with $P \leq 0.15$ in univariate analyses were tested, and at the end, $P \leq 0.05$ in the Cox model was considered statistically significant. All statistical analyses were performed using SAS, Version 9.1, software (SAS Institute Inc, Cary, NC).

To account for some differences in the baseline patient and tumor characteristics in groups LR and PLT that could have an impact on outcomes, we also performed the analysis using a propensity score to match population.[15] The propensity score was based on number of tumors, maximum tumor size, Child's class, AFP level at diagnosis, and etiology of liver disease (Hepatitis C). The 2 groups were paired on a 1:3 ratio, they were matched groups except for Child's class.

Again, it may be argued that there can be a bias in comparing the resection-first and PLT strategies with respect to Child's class in these 2 groups of patients. It is practically impossible to really compare these strategies Child's class to Child's class because it is a fact that centers all around the world (including ours) will offer resection-first to Child's A patients with early HCC-cirr, and PLT to Child's C patients. In order, to try and obviate this bias as well, we carried out the propensity score matched population analysis by further excluding Child's C patients from the PLT arm.

RESULTS

Patient Demographics and Tumor Characteristics

As mentioned before, of the 470 initially transplantable patients with confirmed HCC on the resected or explant specimen, 130 (28%) underwent primary resection with or without later SLT (group LR), whereas 340 (72%) patients underwent upfront PLT (group PLT).

As compared with group PLT patients, group LR patients were younger, were mostly Child Pugh A, and predominantly had solitary tumors on histopathology. There was no other difference between the 2 groups as regards gender, underlying etiology of chronic liver disease, alpha fetoprotein levels at diagnosis, preoperative ablative treatment, and maximum tumor size, microvascular tumor invasion or presence of satellite tumor nodules in the resected or explanted specimen (Table 1).

TABLE 1. Patient and Tumor Characteristics; Group LR Versus Group PLT

	GROUP LR Resection ± Salvage LT (n = 130)	GROUP PLT Primary LT (n = 340)	*P*
Age			
≤55 yr	95 (73)	214 (63)	**0.04**
>55 yr	35 (27)	126 (37)	
Sex			
Male	118 (91)	286 (84)	0.07
Female	12 (9)	54 (16)	
Child Pugh			
A	113 (87)	82 (24)	**<0.001**
B	9 (7)	162 (48)	
C	8 (6)	96 (28)	
Underlying disease			
Hepatitis C	50 (38)	154 (45)	0.64
Hepatitis B	22 (17)	58 (17)	
Alcohol	40 (31)	94 (28)	
Others	18 (14)	34 (10)	
Alpha fetoprotein at diagnosis			
≤100 ng/ml	113 (87)	304 (89)	0.45
>100 ng/ml	17 (13)	36 (11)	
Preoperative treatment (TACE/RFA)			
No	52 (40)	153 (45)	0.32
Yes	78 (60)	187 (55)	
Tumor maximum size (pathology)			
≤3 cm	86 (66)	245 (72)	0.23
>3 cm	44 (34)	95 (28)	
Number of tumors (pathology)			
1	88 (68%)	157 (46%)	**<0.001**
>1	42 (32%)	183 (54%)	
Microvascular invasion			
Present	45 (35%)	121 (36%)	0.84
Absent	85 (65%)	219 (64%)	
Satellite tumor nodules			
Present	34 (26%)	106 (32%)	0.29
Absent	96 (74%)	234 (69%)	

RFA = radiofrequency ablation, TACE = transarterial chemoembolization.
Bold values symbolise the differences between the groups PLT vs LR; that is those that are P value < 0.05.

On the other hand, when we compared histological tumor characteristics at the time of LT in SLT (n = 31) versus PLT (n = 340) patients; SLT patients had higher incidence of tumor nodules more than 3 (31% vs. 12%), maximum size of tumor >3 cm (29% vs. 26%), and MVI (48% vs. 34%) compared to PLT group; respectively. Hence, the recurrent tumor pathology was worse compared to that in PLT patients (data not shown).

Survival Outcomes

Intention-to-treat Analysis Including Drop-Outs After Listing in the LT Group: Group LLT Versus Group LR

We compared OS between group LLT and group LR. As mentioned before, the OS was calculated from the time of listing in the former group (thus including drop-outs also), and time of resection in the latter group. There were 26 drop-outs after listing for PLT (7.1% drop-out rate; 26/366) due to tumor progression (19 patients), appearance of a new tumor (1 patient), liver failure and death (2 patients), persistent alcohol intake (1 patient), or patient refusal after listing (3 patients). The 5- and 10-year OS were still better in the "listed for LT" LLT group compared with the "resection-first" LR group (68%/58% at 5 and 10 years vs. 58%/35%, $P = 0.008$; Fig. 2).

On multivariate analysis of factors predicting OS in the total cohort (n = 366 + 130), AFP level <100 ng/ml at the time of listing or resection, and getting listed for a LT were associated with better survival.

Group LR Versus Group PLT

Overall Survival

Intention-to-treat From the Time of First Curative Surgery. After a mean follow-up of 62 months (median follow-up 39 months) from the time of first curative surgical treatment (resection or LT), the overall survival (OS) in the 2 groups at 5 and 10 years were 58% and 35% in group LR versus 73% and 63% in group PLT, respectively ($P = 0.0007$; Fig. 3A).

PLT Versus Resection Only Versus Resection + SLT. When we looked individually at OS from the time of resection or LT after PLT versus resection only versus resection + SLT, there was no difference in the OS between the PLT and SLT group (5 and 10 year OS 73%/63% vs. 87%/62% for PLT and SLT, respectively; $P = 0.2$), but the OS was significantly worse with resection alone (5- and 10-year OS 44%/22%, $P < 0.001$; Fig. 3B).

Prognostic Factors for OS. We performed a univariate and multivariate analysis in the whole population (n = 470) to find out predictors of OS. Resection with our without subsequent SLT ($P = 0.002$) and presence of microvascular tumor invasion [MVI] ($P = 0.0003$) emerged as poor prognostic factors for OS (Table 2). Hence, in initially transplantable HCC-cirr patients (within Milan criteria, ≤65 years of age) the approach of resection-first with SLT, if possible in case of recurrence is associated with poor outcomes compared to primary LT, independent of other well known pathological factors like MVI. Though maximum tumor size more than 3 cm and AFP level >200 ng/ml were significant on univariate analysis they did not emerge as prognostic factors for OS on multivariate analysis.

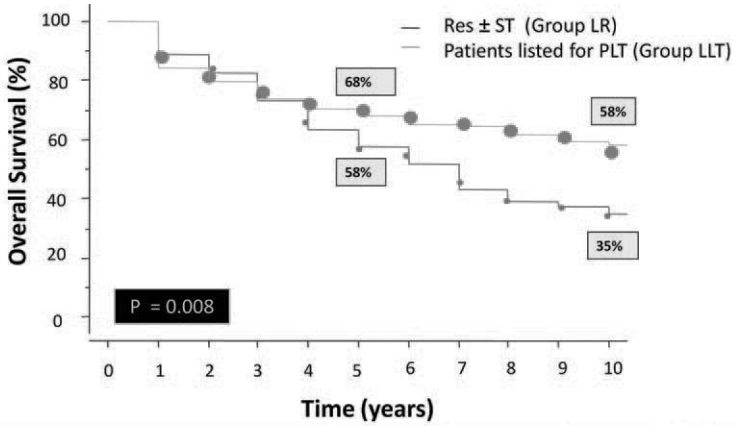
Disease-free Survival

Disease-free survival (DFS) was also calculated from the time of first surgical treatment (ie resection for group LR, and LT for group PLT). The median time to relapse after resection (in 61 patients) and PLT (in 29 patients) was 21 months (1.75 years) versus 14 months (1.2 years), respectively (P = ns).

The DFS in group LR at 5 and 10 years was 27% and 21%, whereas in group PLT it was 69% and 61%, respectively ($P < 0.0001$; Fig. 3C).

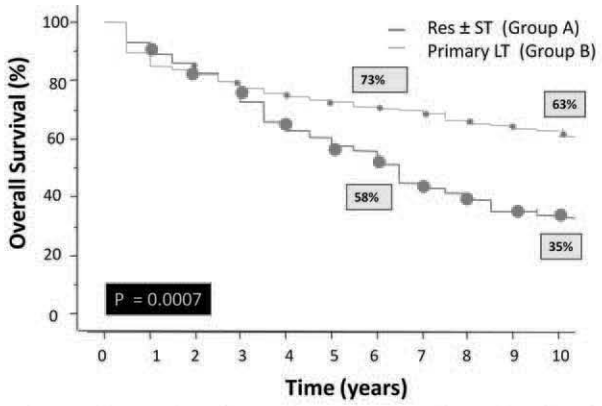
Prognostic Factors for DFS

Strategy of resection-first with or without subsequent SLT ($P < 0.0001$), presence of satellite tumor nodules ($P = 0.04$), and MVI ($P = 0.001$), were poor prognostic factors for DFS on multivariate analysis (Table 2).



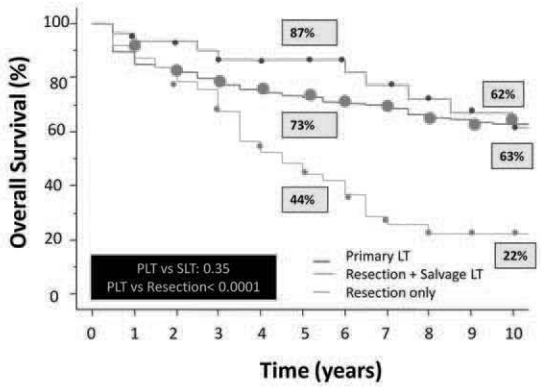
No. of pts at risk at different time points	GROUP	0 years	1	2	3	4	5	6	7	8	9	10
	LR	130	107	85	68	48	40	32	22	20	18	16
	LLT	366	302	253	200	177	146	126	117	98	87	76

FIGURE 2. Overall survival resection ± salvage LT [group LR] (n = 130) versus patients listed for PLT (including drop-outs) [group LLT] (n = 366). Res, resection.



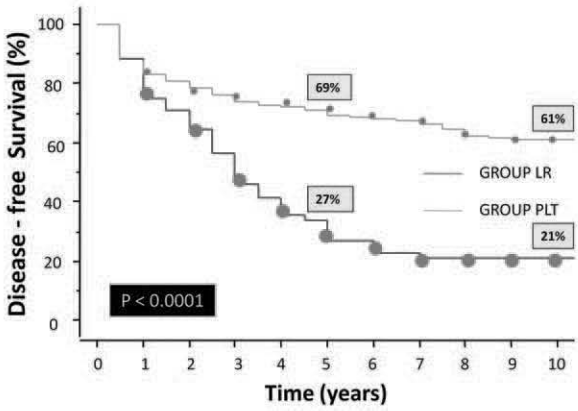
(A)

No. of pts at risk at different time points	GROUP	0 years	1	2	3	4	5	6	7	8	9	10
	LR	130	107	85	68	48	40	32	22	20	18	16
	PLT	340	279	212	182	159	135	119	106	91	80	67



(B)

No. of pts at risk at different time points	GROUP	0 years	1	2	3	4	5	6	7	8	9	10
	PLT	340	279	212	182	159	135	119	106	91	80	67
	SLT	31	29	28	24	22	21	18	15	14	13	12
	Resection	99	78	57	38	26	19	14	7	6	5	4



(C)

No. of pts at risk at different time points	GROUP	0 years	1	2	3	4	5	6	7	8	9	10
	LR	130	91	66	42	28	18	15	13	13	13	11
	PLT	340	274	205	176	154	129	115	104	90	79	67

FIGURE 3. A, Overall survival in group LR [resection ± salvage LT] (n = 130) versus group PLT [primary LT] (n = 340) patients. Res, resection. B, Overall survival in patients undergoing primary liver transplantation [PLT] (n = 340) versus salvage liver transplantation [SLT] (n = 31) versus resection only (n = 99). C, Disease-free survival in group LR [resection ± salvage LT] (n = 130) versus group PLT [Primary LT] (n = 340) patients.

TABLE 2. Multivariate Analysis for Overall and Disease-free Survival (n = 470)

	HR	95% Confidence Interval		P
		Lower	Upper	
Overall survival				
Resection ± SLT strategy	1.882	1.175	3.015	0.002
Microvascular tumor invasion	1.682	1.218	2.324	0.0003
Disease-free survival				
Resection ± SLT strategy	37.95	6.51	16.68	<0.0001
Microvascular tumor invasion	7.02	3.74	8.63	0.001
Satellite tumor nodules	9.34	3.48	7.94	0.04

Feasibility of the SLT Strategy in Early HCC-cirr Patients

Of the 130 initially transplantable patients who underwent primary resection, 10 patients (8%) died during follow-up (3 postoperative deaths, 4 patients had liver failure, and 3 due to other causes). Of the remaining 120 patients, 30 patients were alive without recurrence at last follow-up (23%), and 90 patients (69%) were alive with HCC recurrence.

Of the 90 patients who recurred after resection (35 recurred during the first year vs. 55 after the first year), SLT was possible in only 31 patients (34%). The reasons for nonfeasibility of SLT in 59 recurred patients were as follows; recurrence beyond Milan criteria in 37 (63%), age >65 years in 7 patients (12%), tumor progression on the waiting list in 5 (8%), loss to follow-up 4 (7%), recidivism to alcohol in 3 patients (5%), and refusal by 1 patient (2%). In total, 2 patients were on the waiting list for an organ at the time of data analysis (3%).

Hence, the feasibility of SLT among the recurred patients was 34% (31/90).

Comparative Perioperative and Long-term Outcomes of Patients Who Underwent Salvage LT Versus PLT

Perioperative Course

The perioperative mortality (death within the 90 days of LT or during the same admission) was not statistically different in the 2 groups; 4/31(13%) in SLT group versus 24/340 (7.1%) in the PLT group ($P = 0.27$). In the SLT group, 2 patients each died from cardiac arrhythmia and sepsis with multiorgan failure. All these deaths occurred in the period before the year 2000. The 1-year mortality was also was not significantly different between the 2 groups (13% in SLT versus 19% in PLT; $P = 0.52$).

Though it was not the immediate aim of our study, when we looked at the number of transfusions, operative time, postoperative complications, and rate of reoperation and retransplantation, there was no significant difference in between the PLT and SLT groups (data not shown).

OS and DFS From the Time of LT

The OS calculated from the time of LT in 371 patients who underwent LT either primarily (n = 340) or as a salvage procedure postresection (n = 31) was 73%/63% and 54%/54%, and in the PLT and SLT groups at 5 and 10 years, respectively ($P = 0.35$; Fig. 4A).

The DFS at 5 and 10 years after LT was 69% and 61% in the PLT group versus 48% and 48% in the SLT group, respectively ($P = 0.18$). Thus, though the DFS was slightly inferior post SLT compared with PLT, this difference did not reach statistical significance (Fig. 4B).

Of the 340 patients who had a primary LT, 29 had a recurrence (8.5%), 21 of these died (16 from widespread tumor recurrence). Among patients who underwent SLT (n = 31), 8 recurred (26%) and 7 died due to widespread tumor recurrence.

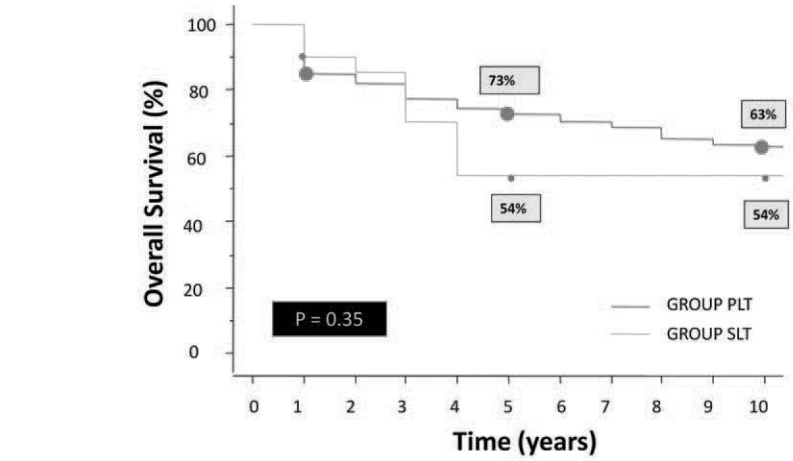
Survival Analysis Using Propensity Score to Match Populations

Using the propensity score method, the OS at 5 and 10 years was still better in the patients listed for LT (group LLT) versus those who had a primary resection (group LR); 5- and 10-year OS of 66% and 56% for group LLT versus 48% and 32% for group LR, respectively; $P = 0.004$. Since Child's C patients are rarely resected, the same analysis was performed after exclusion of Child's C patients (254 patients in group LLT vs. 122 patients in the group LR). After matching in a ratio of 1:3 (244 patients vs. 82 patients), the OS in group LLT was still better than group LR (64% and 55% OS at 5 and 10 years vs. 46% and 22%, respectively; $P = 0.004$).

DISCUSSION

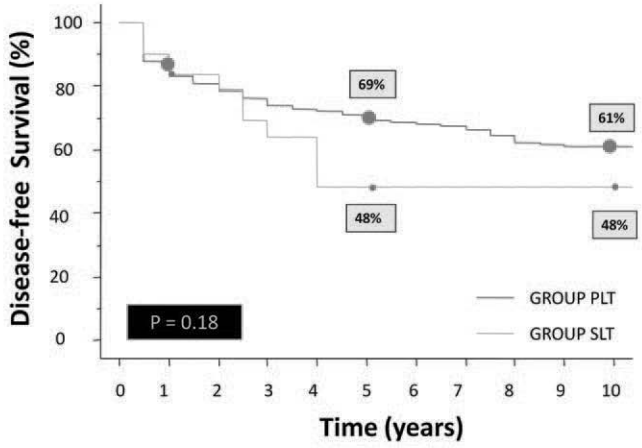
In our study, we found that in initially transplantable HCC-cirr patients, the intention-to-treat OS and DFS (from the time of listing for LT including drop-outs, from the time of first curative surgical procedure, and also using the propensity score method to match groups) were significantly worse in the resection-first with or without later SLT group (group LR) compared with the PLT group (group PLT). Though 31 is a small number, ours is probably the largest single center study of patients undergoing SLT (n = 31) for HCC recurrence alone after resection in cirrhotic patients. In those who did have the SLT (''success'' with resection-first and SLT for recurrence strategy), the perioperative and long-term outcomes from the time of LT were similar to the PLT group (OS and DFS were slightly worse in the SLT group, the difference was however not statistically significant). The low feasibility (34%) seemed to be the major deterrent to the wider use of the SLT strategy.

The SLT approach which was proposed for early HCC patients to cope with the lengthening waiting lists and organ scarcity,[3] is probably justified provided the postoperative results, tumor recurrence rates, and long-term survival are satisfactory. Over time, limited resection in compensated cirrhotics has become a next to ''zero mortality'' and minimal morbidity surgery. However, tumor recurrence still complicates 70% of cases at 5 years after resection, combining true recurrence (which usually arises within the first 2 years after resection), and de novo tumors[16,17] and is indeed the primary cause of patient death. These values are similar to results in our series. Of the 130 patients who had resection-first, 99 only had a resection (no SLT); 61 amongst them had a tumor recurrence, 35 of them died due to widespread recurrence of HCC. Of these 99 patients, 51 were alive at last follow-up. Of the 48 who were dead at last follow-up, 35 (73%) died of tumor recurrence, 13 (27%) died of other causes. In total, 2 of the largest series on resection for HCC, reporting a 10-year survival outcomes showed an OS of around 35% and DFS of 22% at 10 years after resection,[18,19] again results similar to our series. The challenge in achieving good outcomes with resection lies in selecting patients with lower chances of recurrence, and early detection of recurrences, which can be adequately managed with curative surgery (re-resection or salvage LT). There are no accurate, direct, or surrogate markers, to preoperatively prognosticate early HCC-cirr patients (by detecting MVI, satellite nodules, etc), the advent of molecular markers for diagnosis and prognostication may aid in this.[20] Secondly, even with state of the art imaging



(A)

No. of pts at risk at different time points	GROUP	0 years	1	2	3	4	5	6	7	8	9	10
	PLT	340	279	212	182	159	135	119	106	91	80	67
	SLT	31	25	18	13	10	10	10	9	8	5	5



(B)

No. of pts at risk at different time points	GROUP	0 years	1	2	3	4	5	6	7	8	9	10
	PLT	340	274	205	176	154	129	115	104	90	79	67
	SLT	31	24	17	12	9	9	9	8	8	5	5

FIGURE 4. A, Overall survival in patients undergoing primary liver transplantation [PLT] (n = 340) versus salvage liver transplantation [SLT] (n = 31). B, Disease-free survival in patients undergoing primary liver transplantation [group PLT] (n = 340) versus salvage liver transplantation [group SLT] (n = 31).

that is available today, the logistics of strict and stringent follow-up perhaps make early detection a truly uphill task in most centers around the world. Few centers have successfully detected recurrences early and performed SLT in up to 61% of patients with recurrence after resection,[8] but a majority of the studies have shown that only 22% to 28% of patients actually remain transplantable and can undergo SLT[6,7,21–24] after tumor recurrence (similar to our study in which the feasibility of SLT was 34% without significant difference related to the time within the study period).

To avoid drop-outs post initial resection in HCC-cirr patients, the proposed concept of pre-emptive transplant based on tumor characteristics in the resected specimen is interesting.[23] However, it would be more meaningful and practical if prognostication could be done in a less invasive manner in these cirrhotic patients (like with a core biopsy of the tumor), and resection could be avoided altogether. Further, proposing a pre-emptive LT in a patient with poor histological features may be questioned keeping in mind just and equitable organ allocation. In patients with recurrence, Fuks et al propose restricting SLT only to those who had favorable oncological factors on the resected specimen, which seems to be a valid selection criterion. Cherqui et al[8] found that the key to achieving good results with the resection-first strategy in patients with early HCC was selecting those patients with solitary tumor nodules requiring only a limited resection. However, the proportion of such patients (resection-first for a single nodule) was only 69% in our study. Very close follow-up postresection, and the utility of minimal access laparoscopic liver resection for peripherally located tumors thus obviating difficult surgery at the time of SLT were additional noteworthy findings in this study. Further, in addition to the 37 patients who could not be listed for SLT, when they recurred because they had tumors beyond Milan, 22 other patients also could not have a SLT. In total, 7 patients were more than 65 years of age, thus precluding their listing and 5 patients progressed on the waiting list and dropped out; these are practical issues faced with listing and maintaining HCC

patients on the DDLT list. A total of 8 other patients could not be transplanted for miscellaneous reasons as detailed before, these are some of the logistic issues faced, which are truly unavoidable, but a fact of daily practice in any transplant set-up.

If SLT is feasible after recurrence, the postoperative and long-term outcomes seem to be similar to PLT.[10–14] An additional advantage of the SLT strategy is that the good results with initial curative resection could help in avoiding immediate transplant and its attendant complications/immunosuppression, and could also extend the potential waiting time by theoretically solving the problem of tumor progression during the waiting period.[5,6,24–27]

A total of 4 meta-analysis and reviews[10,12–14] on the PLT versus SLT strategy have been published in the last 3 years. A randomized controlled trial (RCT) on this subject, would probably never be possible given the practical and logistic reasons for the same. The heterogeneity in patients and end point selection in various studies published on SLT, is evident from the fact that the studies included in the above 4 reviews, each performed just a year apart, are not the same. Further, while most centers have considered only patients with recurrences within Milan criteria for SLT, some centers have performed SLT even in patients who recurred with tumors beyond Milan (and even beyond UCSF).[26,28–31] As mentioned before, the definition of SLT in various studies is different; while most studies define SLT as transplant for patients who recur after resection, others also include patients who have had a transplant ''de principe'' (pre-emptive) after resection,[5,29] or for early or late deterioration of liver function after resection.[5–7,9,29,32,33] All these patients are included together in the meta-analysis,[10,13] which adds to the heterogeneity of data, and in addition a bias in the oncological outcomes especially in terms of long-term DFS, and indeed OS (which depends primarily on recurrence). Further, in most studies the results of SLT and PLT have been shown to be similar from the time of transplant.

Rather than determining the OS and DFS from the time of SLT and PLT, it would be more pertinent to note the outcomes of these patients on an ITT basis from the time of listing, and from the time of first curative surgical intervention (resection or transplantation), when the patients were transplantable. We found a better OS and DFS in groups LLT and PLT compared with group LR. The result of similar OS following PLT and SLT noted in various studies[10–14,34] also needs to be interpreted with a little caution. SLT group patients are ''a select group'' of recipients who have relatively preserved liver function, have a transplantable recurrence after resection (probably a favorable tumor biology), and are in a relatively better general condition. It is also pertinent to note that, though the meta-analysis concluded that outcomes were similar, the 5-year DFS was actually inferior in the SLT group in the meta-analysis, a finding similar to that in our study.

In the Western world, the ground reality is that there is a shortage of deceased donor organs, and it is not possible to primarily transplant all early HCC-cirr patients. It is also not our intention to propose this strategy. However, our results may be pertinent from at least 3 perspectives. Firstly, based on our results, we can give evidence-based information to our early HCC-cirr patients as regards the feasibility of SLT (maximum 50% based on experience of high volume centers) and long-term outcomes with the resection-first and later SLT versus PLT strategy. Secondly, although organ shortage impedes a ''generalized'' use of PLT for HCC in most countries, organ allocation is changing in every country for an ''optimal'' use of organs. Results of PLT in a patient with HCC should be weighed against the gain of life years in non-HCC patients, especially those with high MELD scores who are being increasingly transplanted nowadays with sometimes a questionable benefit. Cost effectiveness of the SLT versus PLT strategy also needs to be aptly considered. Landman et al[35] concluded in their study that under the Model for End-stage Liver Disease (MELD) system, in patients with HCC within the Milan Criteria, PLT increased survival and quality of life at decreased costs compared with resection or loco regional therapy followed by SLT. Finally, the need of the hour is to try and improve not only the selection of patients for the resection-first strategy (it is true that up to 20% of patients survive long-term with a resection alone and do not need a LT later), but also to initially predict recurrence and transplantability if recurrence does occur (to avoid the 50% drop-out from possible SLT) in initially transplantable HCC-cirr patients. Molecular biology and new pathological markers are no doubt the best candidates to try and accomplish this still unfulfilled objective. The prognostic markers found in our study namely microvascular tumor invasion, and presence of satellite tumor nodules may also aid in better prognostication.

Our study does have some limitations. It is a study based on a retrospective analysis of prospectively collected data over a long period of time during which the accuracy of imaging modalities, the ease of access to LT, the perioperative management etc may have changed to some extent. Also, the number of SLT patients is considerably less compared with those undergoing PLT or initial resection, although ours seems to be the largest single center series of SLT patients till date. Finally, we can never claim our conclusions to be as strong as those of a RCT or a study with a larger cohort of SLT patients and their outcomes.

In conclusion, the feasibility of SLT after initial resection in transplantable HCC-cirr patients in our study was 34%, which seems to be the Achilles heel of this strategy. PLT was associated with better OS and DFS on an ITT basis compared to initial resection with or without later salvage LT. However, the fact that patients who did ''succeed'' the resection first and later SLT strategy had good perioperative outcomes, and almost comparable OS and DFS as compared with PLT patients, suggests that a better selection of HCC-cirr patients for the ''resection first'' approach and close follow-up for recurrence may help in achieving better outcomes with the SLT strategy.

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Defining Long-term Outcomes With Living Donor Liver Transplantation in North America

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Objectives: To compare long-term survival of living donor liver transplant (LDLT) at experienced transplant centers with outcomes of deceased donor liver transplant and identify key variables impacting patient and graft survival.

Background: The Adult-to-Adult Living Donor Liver Transplantation Cohort Study is a prospective multicenter National Institutes of Health study comparing outcomes of LDLT and deceased donor liver transplant and associated risks.

Methods: Mortality and graft failure for 1427 liver recipients (963 LDLT) enrolled in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study who received transplant between January 1, 1998, and January 31, 2014, at 12 North American centers with median follow-up 6.7 years were analyzed using Kaplan-Meier and multivariable Cox models.

Results: Survival probability at 10 years was 70% for LDLT and 64% for deceased donor liver transplant. Unadjusted survival was higher with LDLT (hazard ratio = 0.76, $P = 0.02$) but attenuated after adjustment (hazard ratio = 0.98, $P = 0.90$) as LDLT recipients had lower mean model for end-stage liver disease (15.5 vs 20.4) and fewer received transplant from intensive care unit, were inpatient, on dialysis, were ventilated, or with ascites. Posttransplant intensive care unit days were less for LDLT recipients. For all recipients, female sex and primary sclerosing cholangitis were associated with improved survival, whereas dialysis and older recipient/donor age were associated with worse survival. Higher model for end-stage liver disease score was associated with increased graft failure. Era of transplantation and type of donated lobe did not impact survival in LDLT.

Conclusions: LDLT provides significant long-term transplant benefit, resulting in transplantation at a lower model for end-stage liver disease score, decreased death on waitlist, and excellent posttransplant outcomes. Recipient diagnosis, disease severity, renal failure, and ages of recipient and donor should be considered in decision making regarding timing of transplant and donor options.

Clinical Trials ID: NCT00096733.

Keywords: Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), deceased donor liver transplant, dialysis, graft survival, living donor liver transplant

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The first report of adult-to-adult living donor liver transplantation (LDLT) in the United States was in 1998,[1] followed by rapid expansion to numerous centers in the United States and Canada as a potential solution to the organ shortage and to decrease death on waitlist. However, although LDLT has grown exponentially in countries where deceased donor liver transplantation (DDLT) is limited or nonexistent,[2,3] it remains a very small percentage of total transplants in the United States.[4] Early reports demonstrating inferior outcomes in LDLT compared with DDLT,[5] and donor morbidity and mortality may have contributed to the limited growth in North America.[6,7] As experience increased, early posttransplant outcomes improved and single center reports demonstrated similar or even better outcomes of LDLT than those of DDLT,[8–11] and recent registry studies have demonstrated comparable outcomes between LDLT and DDLT across many indications.[12–14] Analyses from large unfunded registries, however, provide less detailed information than is possible from a federally supported multicenter observational cohort study.

The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) was established by the US National Institutes of Health in 2002 as the first multicenter study of donor and recipient LDLT outcomes. Recipient outcomes starting from the time a potential donor was evaluated, demonstrated the survival benefit of choosing LDLT as opposed to waiting for DDLT. Recipient survival with LDLT was superior to DDLT due mainly to decreased death on the waitlist.[15,16] An important early finding was the impact of the learning curve, with significant improvement in outcomes of LDLT

once a center gains experience.[17] A2ALL demonstrated similar early posttransplant outcomes between LDLT and DDLT overall and in subgroups of patients with hepatocellular carcinoma (HCC) or cirrhosis due to hepatitis C virus.[18–20]

The purpose of the current study was to compare outcomes after LDLT and DDLT in the A2ALL cohorts with follow-up to 10 years posttransplant and to identify factors associated with long-term patient and graft survival.

METHODS

Study Design

A2ALL is an observational cohort study designed to investigate outcomes in donors and recipients of adult-to-adult LDLT. A2ALL-1 enrolled potential liver recipients evaluated for living donation between January 1, 1998, and August 31, 2009. Starting in 2011, A2ALL-2 enrolled LDLT recipients who received transplant between September 1, 2009, and January 31, 2014, or previously enrolled in A2ALL-1. Subjects were enrolled pre- or posttransplant, but those enrolled posttransplant in A2ALL-2 had to be alive with their original graft at the time of enrollment. Patients were followed in A2ALL-1 through August 31, 2010, and in A2ALL-2 through May 31, 2014. Median follow-up time was 6.7 years (range: 0–15 years). Twelve North American centers (11 US, 1 Canadian) were involved, 9 in each phase, with 6 centers participating in both phases. Additional ascertainment of death and graft failure was available for patients who received transplant at US centers in the Scientific Registry of Transplant Recipients (SRTR) through September 30, 2014.

This study considers 1600 recipients who received transplants between January 1, 1998, and January 31, 2014. All recipients had a living donor evaluated for donation; some ultimately received a DDLT. LDLT recipients from the 9 centers in A2ALL-1 whose transplant was among the first 20 LDLTs at their center were excluded (n = 173) to minimize the learning-curve effect. All 3 centers that joined A2ALL-2 had performed more than 20 cases by their study entry on September 1, 2009. Clinical and laboratory data, patient and graft survival, and intraoperative information were collected. Missing center data were supplemented with data from the SRTR. The SRTR data include data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and have been described elsewhere.[21] The Health Resources and Services Administration, US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Each clinical center and the data-coordinating center had the study protocols and consent forms approved by the respective institutional review boards before enrolling patients.

Statistical Methods

Descriptive statistics (means, standard deviations, frequencies, and percentages) were calculated for demographic and clinical variables. Comparisons between LDLT and DDLT recipients were made using t tests for continuous variables and χ^2 or Fisher exact tests for categorical variables.

Subjects who enrolled in A2ALL-2 after transplant and were not previously enrolled in A2ALL-1 (n = 122) had their follow-up time left truncated at the time of enrollment to avoid giving credit for time at risk when any graft failure or death would not have been observed. Subjects who enrolled during A2ALL-1 and subsequently enrolled in A2ALL-2 had continuous follow-up available through SRTR. Unadjusted patient and graft survival curves were estimated using left-truncated Kaplan-Meier (implemented using software for Cox regression) and are shown graphically for LDLT and DDLT.

Multivariable Cox regression was used to test for differences in patient and graft survival between LDLT and DDLT (transplant type). Covariates tested included recipient age, sex, race, ethnicity, body mass index, diagnosis, medical severity at transplant (on ventilator or on dialysis), model for end-stage liver disease (MELD) score at the time of transplant, cold ischemia time, age of donor, and time on waitlist (US centers only). Calendar year of transplant and lobe donated were tested among LDLTs. The method of best subsets was used to guide model selection.[22] Potential interactions between transplant type and other covariates were explored after fitting separate models for LDLT and DDLT recipients by formally testing the interactions in models that included both transplant types. Forest plots were created to visually compare covariate effects between LDLT and DDLT. Adjusted survival curves for patient and graft survival by transplant type were also generated. The proportional hazards assumption was tested in all models.

Competing risks methods were used to compare causes of death and graft failure between LDLT and DDLT recipients. Cumulative incidence functions were plotted for each cause using the comprisk macro (mayoresearch.mayo.edu/mayo/research/biostat, modified to account for left truncation), and a generalized linear rank test was used to compare the cumulative incidence functions between LDLT and DDLT (compCIF macro, http://www.uhnres.utoronto.ca/labs/hill/datasets/Pintilie/SASmacros/compcif.txt, modified to account for left-truncation). All analyses were completed using SAS 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of LDLT and DDLT Recipients

After excluding 173 LDLTs that occurred during the first 20 cases at each of the 9 A2ALL-1 centers, 963 LDLTs and 464 DDLTs whose recipients had at least 1 living donor evaluated from January 1, 1998, to August 31, 2010 (9 centers), were enrolled in the A2ALL studies (Table 1). Of the 963 LDLT recipients, 834 received transplants at a US center, representing 86% of living donor transplants at these US A2ALL centers during the study enrollment periods, and 129 transplants were performed at a Canadian center. LDLT recipients enrolled in A2ALL did not differ by age ($P = 0.07$), sex ($P = 0.70$), or race/ethnicity ($P = 0.58$) from the 138 LDLT recipients who did not enroll, but a higher proportion of LDLT recipients who enrolled in A2ALL *versus* did not enroll were white (92% vs 88%, $P = 0.02$).

Compared with the DDLT recipients, LDLT recipients enrolled in A2ALL had a higher prevalence of white race (91% vs 84%, $P < 0.001$) and lower incidence of Hispanic ethnicity (13% vs 19%, $P = 0.005$) (Table 1). A smaller proportion of LDLT recipients had hepatitis C virus (35% vs 45%, $P < 0.001$) and HCC (16% vs 21%, $P = 0.02$) and a higher proportion had primary biliary cirrhosis (8% vs 3%, $P < 0.001$). There were no significant differences in age, sex, or body mass index between LDLT and DDLT recipients.

The DDLT recipients enrolled in A2ALL had more severe liver disease. MELD at evaluation and at transplant was significantly lower in the LDLT group ($P < 0.001$ for each); 16% had a MELD greater than 20 at the time of transplant compared with 43% of DDLT recipients (Table 1). More DDLT recipients received transplant from the intensive care unit (ICU) (11%) and 15% were hospitalized but not in the ICU at the time of transplant compared with 2% and 6% of LDLT recipients, respectively ($P < 0.001$). Significantly more DDLT than LDLT recipients were on a ventilator (6% vs 1%, $P < 0.001$), were on dialysis (5% vs 1%, $P < 0.001$), and had ascites (62% vs 46%, $P < 0.001$) at the time of transplant.

Among the 963 living donor recipients in A2ALL, there were 866 corresponding A2ALL donors who agreed to participate in the

TABLE 1. Recipient Characteristics at Transplant

	DDLT (n = 464)			LDLT (n = 963)*			
	N	Mean (SD) or Frequency	Range or %	N	Mean (SD) or Frequency	Range or %	*P*
Age	463	52.08 (10.49)	18–74	963	51.37 (11.48)	18–76	0.25
Female	464	182	39%	963	408	42%	0.26
Hispanic	463	87	19%	963	126	13%	0.005
Race	464			963			<0.001
White		390	84%		877	91%	
Black		33	7%		29	3%	
Asian		17	4%		31	3%	
Other		24	5%		26	3%	
Body mass index	412	26.78 (5.01)	13–50	919	26.54 (5.26)	15–55	0.42
Diagnosis (multiple diagnoses possible)	464			963			
Acute liver failure		19	4%		24	2%	0.10
Alcohol-related cirrhosis		86	19%		155	16%	0.25
Autoimmune hepatitis		20	4%		63	7%	0.09
Cryptogenic cirrhosis		53	11%		80	8%	0.06
HBV		12	3%		28	3%	0.73
HCC		98	21%		154	16%	0.02
HCV		210	45%		339	35%	<0.001
Hemochromatosis		3	1%		10	1%	0.47
Other metabolic liver disease		16	3%		21	2%	0.16
Malignancy other than HCC		7	2%		26	3%	0.16
PBC		12	3%		81	8%	<0.001
PSC		61	13%		162	17%	0.07
Other diagnosis		21	5%		90	9%	0.001
MELD at evaluation	452	16.77 (6.61)	6–40	538	14.55 (6.00)	6–40	<0.001
6–10		67	15%		130	24%	
11–10		267	59%		348	65%	
21–30		97	21%		44	8%	
31–40		21	5%		16	3%	
MELD at transplant	440	20.42 (8.92)	6–40	935	15.47 (5.90)	6–40	<0.001
6–10		52	12%		169	18%	
11–10		201	46%		614	66%	
21–30		118	27%		132	14%	
31–40		69	16%		20	2%	
Medical condition at transplant	462			567			<0.001
ICU		51	11%		9	2%	
Hospitalized not in ICU		70	15%		35	6%	
Not hospitalized		341	74%		523	92%	
Comorbidities							
Ventilator	461	28	6%	959	12	1%	<0.001
Ascites	455	284	62%	567	260	46%	<0.001
Dialysis	457	25	5%	957	7	1%	<0.001
Perioperative Characteristics	N	Median	IQR	N	Median	IQR	*P*
Duration of recipient surgery (hr)	421	5.78	5–7	533	7.57	7–9	<0.001
Total ischemia time (min)	442	486.50	364–600	847	98.00	71–140	<0.001
PRBCs†	439	6.00	3–11	557	4.00	2–8	<0.001
Recipient ICU LOS (d)	370	2.00	1–5	915	2.00	1–3	0.05
Recipient total LOS (d)	407	10.00	7–17	945	10.00	7–15	0.65

*Excludes LDLT cases ≤20.
†Collected in A2ALL-1 only.
HBV indicates hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LOS, length of stay; PBC, primary biliary cirrhosis; PRBC, packed red blood cells.

study. Mean donor age was 37 years (range: 18–63 years). Most were female (52%) and white (89%); 13% were Hispanic. The mean body mass index was 26 (range: 16–42). The majority were biologically related (65%).

Many perioperative characteristics were different between LDLT and DDLT. LDLT recipients had longer total operative time (median 7.6 hours vs 5.8 hours, $P < 0.001$) and shorter total ischemia time (median 98 minutes vs 487 minutes, $P < 0.001$) than DDLT recipients. Intraoperative blood transfusion requirements were lower in LDLT than in DDLT (median 4 vs 6 units, $P < 0.001$). Recipients of LDLT generally stayed in the ICU for a shorter period of time ($P = 0.05$) after the operation, but overall hospital length of stay did not differ significantly between the 2 groups ($P = 0.65$).

Posttransplant Mortality and Graft Failure

Unadjusted long-term mortality was significantly lower after LDLT than after DDLT [hazard ratio (HR) = 0.76, $P = 0.02$]; however, after adjustment for recipient sex, age, diagnosis, dialysis, MELD, and donor age, the mortality risk was similar (HR = 0.98, $P = 0.90$) (Figs. 1A, B). Unadjusted long-term graft failure risk was

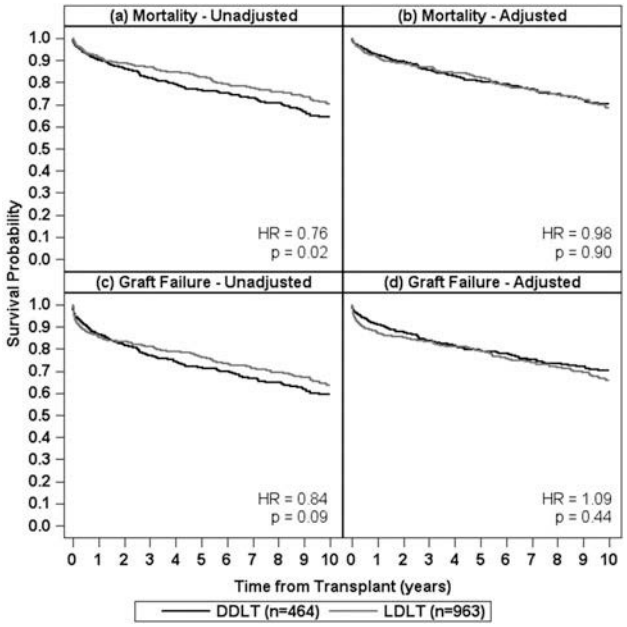

FIGURE 1. Survival plots of mortality and graft failure by transplant type. Panels A and B show unadjusted and adjusted probability of freedom from death. Panels C and D show unadjusted and adjusted probability of graft survival. Adjusted survival probabilities are presented for a 53-year-old male patient without non-HCC malignancy or PSC, not on dialysis at transplant, MELD of 16, and received a liver from a donor younger than 50 years. Adjusted graft survival probabilities are presented for a 53-year-old patient without autoimmune hepatitis, HCC, or PSC; a MELD of 16 at transplant; not on dialysis at transplant; and received a liver from a donor younger than 50 years.

marginally lower after LDLT than after DDLT, although it did not reach statistical significance, and similar when adjusted for recipient age, diagnosis, MELD, dialysis, and donor age (Figs. 1C, D).

Causes of death after LDLT and DDLT were similar (Fig. 2). In unadjusted competing risk analyses, DDLT recipients had a marginally higher cumulative incidence of death due to infection or sepsis ($P = 0.06$) and death due to graft failure ($P = 0.09$). The cumulative incidences of death due to other causes were not significantly different between LDLT and DDLT recipients.

The unadjusted cumulative incidence of retransplant was similar in both DDLT and LDLT ($P = 0.19$), but there was a higher cumulative incidence of death without retransplant among DDLT recipients ($P = 0.01$, Fig. 3). Among the specific causes of graft failure before retransplant, LDLT recipients had a higher cumulative

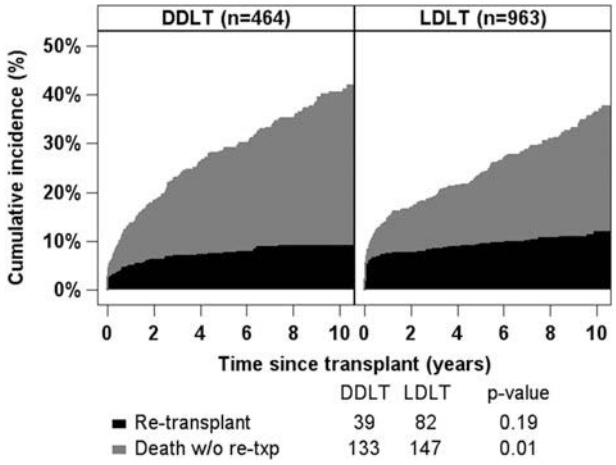

FIGURE 3. Unadjusted cumulative incidence for causes of graft failure (summarized as retransplant or death without retransplant) by transplant type.

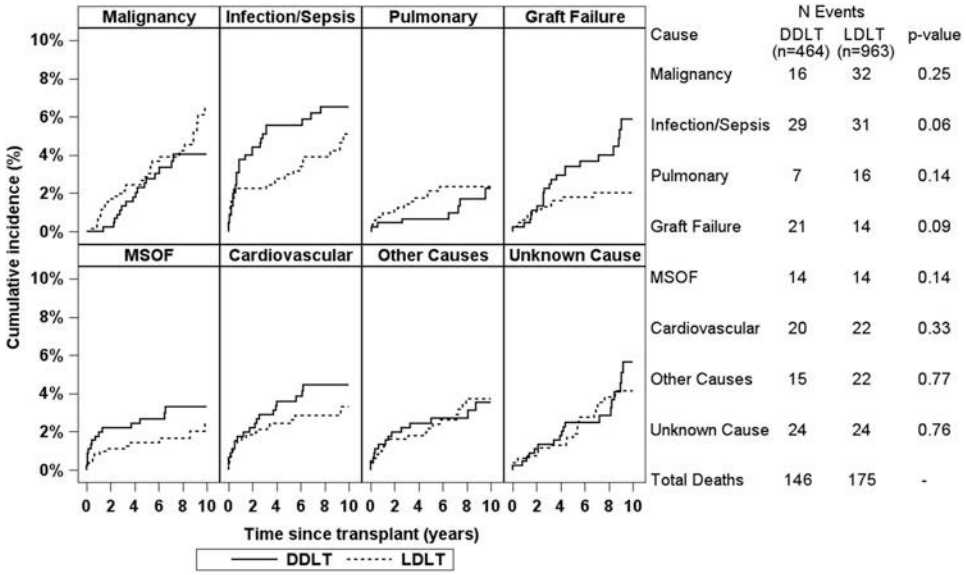

FIGURE 2. Unadjusted cumulative incidence for specific causes of death by transplant type. The number of deaths in each group due to each specific cause and *P* values from tests of differences between unadjusted cumulative incidence functions for LDLT versus DDLT are shown on the right. MSOF indicates multiple system organ failure.

incidence of graft failure due to vascular thrombosis than DDLT recipients ($P = 0.05$).

Predictors of Mortality and Graft Failure

Adjusted models of patients' death and graft failure for more than 10 years of follow-up showed no significant differences between recipients of an LDLT versus a DDLT. Female sex and diagnosis of primary sclerosing cholangitis (PSC) were associated with lower mortality risks (HR = 0.74, $P = 0.01$, and HR = 0.45, $P < 0.001$, respectively; Table 2). Dialysis at transplant was the strongest predictor of mortality (HR =3.59, $P < 0.0001$). Older recipient age and donor age more than 50 years also had a negative impact on recipient survival. Similar to the patients' survival model, PSC was also associated with a reduced risk of graft failure (HR = 0.66, $P = 0.02$), as was a diagnosis of autoimmune hepatitis (HR = 0.44, $P = 0.009$; Table 3). Dialysis at the time of transplant and older recipient and donor age were associated with increased risk of graft failure, similar to the patients' survival models. Unlike patients' survival, an increase in MELD score at the time of transplant was associated with a significant increase in the risk of graft failure in the combined model ($P = 0.04$).

Predictors of patients' death and graft failure in separate LDLT and DDLT models were largely overlapping, and no significant interactions between transplant type and other predictors were found for either patients' death or graft failure (Fig. 4). Within the LDLT group, variables that had significant adverse impact on the risk of patients' death included a diagnosis of HCC, dialysis at transplant, recipient age older than 55 years, and older donor age. Higher risk of graft failure risk was associated with HCC and older donor age, and female sex and diagnosis of PSC were associated with lower risk (see Supplemental Digital Content Tables 1A, B, available at http://links.lww.com/SLA/A825). Within the DDLT group, malignancy other than HCC (ie, cholangiocarcinoma), dialysis at transplant, and older recipient age resulted in decreased patients' survival, and dialysis and older recipient and donor age resulted in higher graft failure.

Additional variables were tested in the LDLT group alone (see Supplemental Digital Content Tables 2A and B, available at http://links.lww.com/SLA/A825) including era of transplant by A2ALL cohort, year of transplant, or right versus left lobe. None of these variables were found to be significant with regard to patient or graft survival. Time on waitlist was also analyzed for both DDLT and LDLT, and this did not influence adjusted survival in those patients receiving transplants.

DISCUSSION

LDLT has emerged as an important source of organs when there is a critical scarcity of deceased donor grafts. Although early outcomes with LDLT were thought to be inferior to DDLT, this comprehensive report from A2ALL demonstrates the durability and success of the LDLT procedure, with prolonged (5–12 years) follow-up of a well-characterized cohort in a carefully documented, multicenter study. We provide evidence that LDLT can have equal long-term outcomes to DDLT when risk-adjusted. Given the longer wait-times and higher MELD needed for DDLT, LDLT provides superior transplant outcomes over DDLT, as nearly all the risk adjustment variables reflect the greater severity of disease in DDLT that is prevented if the candidate chooses LDLT at an earlier stage.

The findings in this report represent a culmination of 16 years of LDLT research performed within the A2ALL consortium. A2ALL was the first multicenter study to investigate, in meticulous detail, the outcomes of both recipients and donors who consider and undergo living donor transplantation. One of the first important findings of A2ALL was the existence of a significant and steep learning

TABLE 2. Multivariable Cox Model: Mortality

Parameter	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	*P*
LDLT vs DDLT	0.98	0.77	1.27	0.90
Female vs male	0.74	0.58	0.94	0.01
Recipient diagnosis: malignancy other than HCC	2.16	1.13	4.11	0.02
Recipient diagnosis: PSC	0.45	0.30	0.69	<0.001
On dialysis at transplant	3.59	2.05	6.28	<0.001
Recipient age at transplant (per 10 yr), <55	1.20	1.00	1.44	0.05
Recipient age at transplant (per 10 yr), >55	1.65	1.27	2.15	<0.001
Donor age, yr >50 vs <50	1.49	1.14	1.94	0.003
MELD at transplant (per 5 points)	1.06	0.98	1.16	0.15

TABLE 3. Multivariable Cox Model: Graft Failure

Parameter	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	*P*
LDLT vs DDLT	1.09	0.87	1.37	0.44
Recipient diagnosis: autoimmune hepatitis	0.44	0.24	0.82	0.009
Recipient diagnosis: HCC	1.32	1.01	1.73	0.05
Recipient diagnosis: PSC	0.66	0.47	0.93	0.02
On dialysis at transplant	2.54	1.50	4.31	<0.001
Recipient age at transplant (per 10 yr), <55	1.03	0.89	1.19	0.71
Recipient age at transplant (per 10 yr), >55	1.39	1.08	1.78	0.009
Donor age, yr >50 vs <50	1.52	1.20	1.93	<0.001
MELD at transplant (per 5 points)	1.09	1.00	1.17	0.04

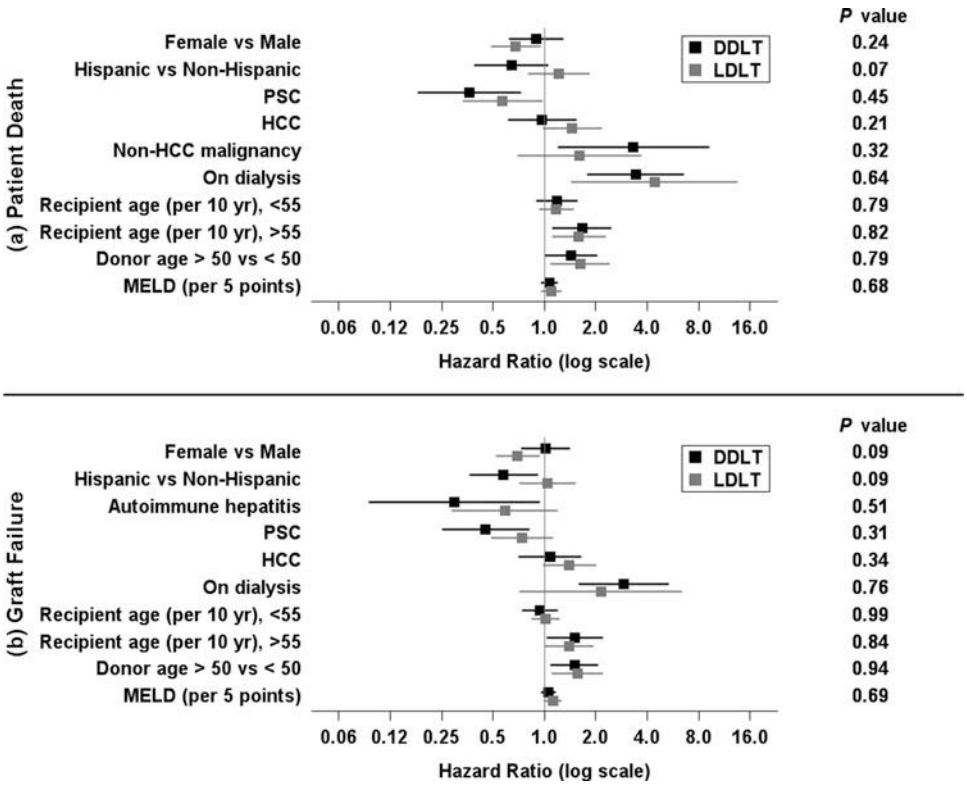

FIGURE 4. Forest plots showing estimated hazard ratios on the log scale for covariate effects associated with (A) patient mortality and (B) graft failure from separate Cox models for LDLT (gray boxes) and DDLT (black boxes) recipients; whiskers show 95% confidence intervals for true log hazard ratios. *P* values are from tests of interaction between each covariate and LDLT/DDLT in a combined model. Note that all *P* values greater than 0.05 imply no significant differences in log hazard ratios between LDLT and DDLT.

curve.[17] Because of the complexity of the operation, the initial LDLT recipients had more vascular and biliary complications than seen in DDLT recipients and more graft and patient loss.[17,20] Fortunately, the early graft failure and patients' mortality experienced by centers starting LDLT programs markedly improved after the first 15 to 20 procedures, true for both A2ALL and non-A2ALL centers.[23] Dysfunction of the segmental graft, or "small-for-size syndrome," remains a significant concern,[24] and the biliary reconstruction and postoperative complications continue to be the Achilles heel of LDLT,[25,26] but even these were less frequent after experience is gained.[20,27,28]

Because A2ALL followed potential recipients from the time a possible donor was identified, we were able to carefully assess waitlist mortality. Two landmark studies from A2ALL demonstrated that LDLT provides significant transplant benefit to candidates, even at low MELD scores, primarily because of less death on the waitlist.[15,16] In this report, the A2ALL consortium demonstrates that the posttransplant experience also adds to the benefit of LDLT. Risk-adjusted posttransplant patient and graft survival was not significantly different between DDLT and LDLT, confirming previous reports from the A2ALL retrospective cohort that have also shown similar posttransplant risk-adjusted survival overall and in specific patient cohorts such as those with HCC and hepatitis C virus.[18–20] Furthermore, the findings presented show a posttransplant benefit for LDLT when not adjusted for the "healthier" case mix of LDLT. This benefit can add to the substantial pretransplant benefit gained from earlier transplantation.

Several recent large registry reports have compared LDLT with DDLT with similar findings to those in this report. Hoehn *et al*[13] used a linkage between the University Health System Consortium and SRTR databases to compare 14,282 patients at 62 centers who underwent DDLT from 2007 to 2012 and 715 patients at 35 centers who underwent LDLT, performing a 1:1 propensity score-matching approach using age, MELD, and pretransplant status. They found no difference in length of stay, costs, patients' survival, or graft survival, but higher readmissions for LDLT.[13] More recently, Goldberg *et al* [12] analyzed graft and patients' survival using the national OPTN/United Network for Organ Sharing (OPTN/UNOS) data from 2002 to 2012 and found unadjusted graft survival to be significantly higher after LDLT (after the first 15 LDLTs), and equivalent to DDLT overall when adjusted for recipient characteristics. There was substantial improvement over time and superior outcomes of LDLT in autoimmune hepatitis and cholestatic liver disease at experienced centers.[12] Kashyap *et al*[14] performed a retrospective analysis of US national data for patients who received transplant between February 2002 and October 2006, and demonstrated higher unadjusted survival after LDLT than after DDLT; for patients with autoimmune hepatitis, PSC, and primary biliary cirrhosis, they found similar outcomes for the 2 graft types after adjusting for covariates.

When a deceased donor is not available, even status 1 and high MELD patients likely benefit from LDLT. However, because the allocation system in North America prioritizes the sickest patients, these candidates have a greater chance to receive a deceased donor offer. In this report, we did not find disease severity by MELD to be a

significant predictor of posttransplant patient survival for LDLT or DDLT. However, LDLT recipients received transplants within a lower range of MELD scores compared with those generally needed to access a deceased donor organ. A higher MELD was associated with reduced graft survival, but this was true for both LDLT and DDLT. Urrunaga et al[29] analyzed OPTN data for adults with acute liver failure who were listed for liver transplantation as status 1 or 1A and underwent LDLT (N = 21) or DDLT (N = 2316) between October 1987 and April 2011. They found no strong evidence that the unadjusted survival probabilities for adults with acute liver failure who underwent LDLT were inferior to those who underwent DDLT,[29] and recent reports from Japan and Korea demonstrate patients' survival exceeding 70% for acute liver failure.[30,31] Several reports from large centers have also shown acceptable outcomes in selected patients with higher MELD scores or renal insufficiency.[32–35]

These results strongly support the concept that after 15 to 20 cases, LDLT centers have reached a "steady state" following their initial learning curve and can confidently contend that posttransplant outcomes for LDLT are essentially equivalent to DDLT and better if pretransplant morbidity and mortality is considered. This is extremely important when one considers that some of the risk factors contributing to poor outcome, such as renal failure, can be avoided if LDLT can be performed in a more timely fashion than DDLT. Both improved pre- and posttransplant survival in experienced centers suggests that in a patient with a suitable living donor, LDLT should be considered the preferred procedure performed before the progressive deterioration of liver disease, similar to the benefits offered to patients with kidney disorder when transplantation is performed before the initiation of dialysis.[36,37] We also know that the MELD score, although an excellent tool to risk-stratify candidates on the waitlist, has its limitations, and many patients with lower MELD scores with decompensated cirrhosis have an elevated risk of death as well.[38–41] Waiting too long for a deceased donor offer at a higher MELD score often results in death on the waitlist and potentially a higher risk of graft failure and/or death after transplant. If LDLT is a viable option with an appropriate donor, patients with symptomatic or decompensated liver disease can receive transplant earlier, with lower MELD scores, less renal failure, and better nutritional status, resulting in less death on the waitlist and better postoperative outcomes.

Our findings regarding clinical variables impacting posttransplant outcome and other results reported in recent publications delineate which recipient and donor characteristics can result in optimal results. In addition, they provide important information and potential recommendations for recipients when discussing the LDLT option. An important finding is that donor's age has significant impact on both patient and graft survival in the LDLT group, and this may influence which donor is chosen if the recipient has multiple choices.

When discussing LDLT, the donor must always be taken into consideration. Although this report focuses on recipient outcomes, A2ALL has comprehensively reported on donor recovery and outcomes, providing information that can contribute to the increased safety of donation. In both the retrospective study and the prospective cohort, A2ALL has shown that approximately 40% of donors experience some sort of complication after donation.[42,43] Although most complications were minor (Clavien grades I and II) and 95% resolved within the first year, there were significant events and even donor deaths reported at A2ALL centers.[44] It is critical that we strive to decrease these risks if we are to increase the number of LDLT performed in North America. The A2ALL consortium has detailed data on liver regeneration and recovery in the donor and found variables associated with better outcomes and identified issues in the donor including liver function, laboratory tests, psychosocial concerns and quality of life that will require long-term follow-up and merit further study.[45–49] We should continue to be aware of potential long-term effects of donation, both physical and psychosocial. Having identified and characterized the most common reasons for donor morbidity, it is then possible to address the issues and decrease their incidence.

There are some limitations to this study. First, it includes both retrospective and prospectively collected data and was an observational study, not a randomized trial between LDLT and DDLT. It does, however, reflect the actual practice at experienced LDLT centers. In addition, the timing of placing a patient on the waitlist reflects actual center-specific practice patterns and was not by protocol.

CONCLUSIONS

The A2ALL multicenter prospective study in LDLT has demonstrated that there is a significant and sustained benefit to liver transplant candidates with LDLT compared with DDLT. This benefit occurs not only during the waitlist period but also by providing real benefit after transplantation by offering transplantation at a lower MELD, before disease progression associated with renal dysfunction and other life support requirements ensue. Our results provide evidence that when a deceased donor organ is not immediately available, as is usually the case, LDLT should be considered a primary liver transplant option early in the course of transplant evaluation.

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DISCUSSANTS

R.W. Busuttil (Los Angeles, CA):

Since the first adult living donor transplant performed by Dr. Masatochi Makuuchi from Japan in 1994 and the first adult right lobe living donor transplant performed by Professor C.M. Lo from Hong Kong in 1997, adult living donor transplantation has indeed experienced varied enthusiasm in the United States and other western countries due to a variety of recipient issues but most importantly due to concerns for donor safety.

This is in contrast to many Asian centers, in which there is little option for cadaveric donors, and thus living donor transplantation in adults is indeed the primary option. As an example, at the ASAN Medical Center in Seoul, Korea, more than 4000 living donor transplants have been done since 1992, with excellent results.

Despite the concerns mentioned, adult living donor transplantation is performed in a number of centers in the United States for a very highly selected and generally low-acuity patients.

Dr. Olthoff and her colleagues have presented an excellent analysis of the 10-year long-term outcome of 963 living donor transplants performed in 11 United States and 1 Canadian center, which were a part of A2ALL consortium.

In this study, they compared 963 living donor transplants with 464 deceased donor liver transplants that had at least 1 living donor evaluation. When comparing the 2 groups, recipients of living donor transplants were healthier, both at the time of evaluation and at the time of transplantation, with lower MELD scores and in less need of pretransplant ICU, dialysis, and ventilator support. Thus, it is not surprising that the blood requirement in postoperative ICU stay was shorter, although total length of stay was the same. Furthermore, when adjusted for disease severity, sex, age, and MELD score, the mortality risk was the same between living donors and deceased donors.

I have several questions for the authors.

1. You argue that living donor transplantation could decrease death on the waiting list compared with deceased donor transplantation. However, would you not expect this with a lower cumulative MELD score of 11 or less at the time of transplant in the living donor group.

In addition, Dr Merion and his colleagues reported in the American Journal of Transplantation in 2004 that performing transplant in patients with MELD scores of less than 15 results in more deaths than not performing a transplant at all, thus perhaps making liver transplantation futile in this subset of patients. In your study, greater than 60% of living donor patients had a MELD score of less than 15. Could you please comment?

Second, it seems that recipient cancer, whether HCC or malignancy other than HCC, has detrimental effects on recipient and graft survival. However, these are usually the patients who are poorly served by the MELD system. Can you comment on how these data should influence physicians and patients on whether to proceed with living donor transplantation?

Third, this report did not mention any of the complications typically associated with living donor transplantation, neither vascular nor biliary. What was the incidence of these complications, how do they compare with deceased donor transplantation, and how do these affect the recipient and graft survivals?

Although you briefly mentioned donor morbidity and mortality, could you please expand on the number of Clavien 3 and 4 complications and donor deaths that may have occurred in this A2ALL series? Furthermore, what impact did these deaths have on the specific centers and other programs?

Finally, with the increasing acuity that we are seeing in our recipient pool, as an example, at our center, the median MELD score is 35 or greater, living donor transplantation seems unfeasible in this group of patients. No more than 20 living donor transplants were done in recipients with MELDs greater than 30. What is your view based on your study in using living donor transplantation for this patient group?

Response From K.M. Olthoff:

You are right in that the MELD scores were relatively low within our group. Because A2ALL followed these potential recipients from the time of evaluation, we were able to carefully assess our waitlist mortality and found that there is waitlist mortality both at the low and high MELD scores.

The 2 landmark studies by Carl Berg that came from A2ALL showing the benefit of transplantation with living donor instead of waiting for deceased donor show that living donor transplantation is also very beneficial at low MELD scores, even lower than MELDs of 15, when we looked at the outcomes over the MELD era. This may differ from what was published earlier by Merion in that these LD

grafts are of high quality, and a lot of transplants are done in very low MELD scores with deceased donors using extremely marginal grafts.

We also know that the MELD score, while an excellent way to stratify candidates by risk on the waitlist for allocation, has its limitations. There are many patients with lower MELD scores with decompensated cirrhosis and an elevated risk of death. These patients might be just the very ones who benefit the most from living donor transplantation. A patient with a low MELD score can jump to a very high MELD score in a very short period of time and then become too sick for transplant or die on the waitlist.

As far as your second question with regard to HCC and other malignancies, we did find that malignancy other than HCC affected posttransplant survival. Most of these were likely cholangiocarcinomas. We already know in the transplant community that these patients have poor posttransplant outcomes and most of these were in the deceased donor cohort.

We also found that HCC had a negative effect on patient and graft survival in the living donor cohort. This was significant in the combined model for patient survival and almost significant in the separate model as well for patient survival. We know that currently, patients with HCC who are awaiting a deceased donor transplant have to wait for at least a year, if not longer, in many parts of the country. This may provide an unintended benefit in that it imposes a mandatory observation period for us to observe what the biological aggressiveness of the cancer might be.

Living donor transplantation eliminates this waiting time, which might decrease the drop-off from the waitlist from tumor progression, but it might also allow for transplantation of a more aggressive HCC that you don't identify if you have no time to observe and watch the progression of the tumor.

We have to be very, very careful about the patients with HCC on whom we perform transplant with living donor, so we try not to transplant very aggressive tumors to avoid early recurrence and thereby have futile transplants. Perhaps new progress in the molecular analysis of these tumors will help us determine which patients have the best posttransplant survival. In the meantime, I think a short period of observation is probably best before proceeding quickly with living donor transplantation in patients with HCC.

With regard to the question about complications, we had previously reported on the posttransplant complications from the retrospective data. The complications from the prospective data have been a subject of a previous presentation at the ASLD and a forthcoming publication. We found that there were similar incidence of posttransplant complications between the 2 groups. However, it was obvious that biliary leaks and strictures are higher in the living donor cohort, up to 24% for leaks and strictures, and only 10 to 14% in the deceased donor group. We also know that hepatic artery thrombosis is higher in the living donor group, about 6% versus 2%. This leads to a slightly higher risk of graft failure and retransplantation in the living group for vascular complications.

Preliminary analysis of this data also shows that if you have at least 1 biliary complication, it is associated with a higher risk of death or graft failure. This was true for both living donors and deceased donors. Interestingly, complications such as edema, cardiac issues, ascites, and bleeding are higher in the deceased donors, which probably goes along with the more severe disease of these patients at the time of transplantation.

We also looked at small-for-size syndrome in the living donor grafts. This will also be a forthcoming publication. I prefer to call it segmental graft dysfunction because it's not just about the size, but we've found that there was an incidence of small-for-size syndrome of about 16% in the living donor group. If a graft develops segmental graft dysfunction, there is about a 5 times greater risk of graft loss than in the other grafts.

As far as donor morbidity and mortality, I think that this is probably the most important question to ask. We cannot forget that if we want to increase living donor transplantation, we have to ask for more living donors. We have 2 reports that show that 35% to 40% of donors have some sort of complication that occurs in the postoperative period. Fortunately, less than 3% are Clavien grade 3 or 4. In the comprehensive report by Abecassis et al from A2ALL, we found that nearly all the complications occur within the first 30 days, nearly all are reversible, and most resolve within the first year.

With regard to mortality, there have been 6 donor deaths within the A2ALL group. Four were in A2ALL 1. Only 1 of those was a perioperative death. Three were well beyond a year. One was a suicide and 2 were accidents. There were 2 perioperative deaths at 2 of the most experienced A2ALL centers in A2ALL 2. They were well-publicized, and they were devastating both personally and publicly for these centers. Both these centers took a voluntary pause in their living donor program. They both brought in external consultants, reassessed their protocols and procedures, and both have successfully restarted their living donor programs. Donor morbidity and mortality is a very important thing to think about in living donation.

As far as the final question of transplantation and high MELD, when a deceased donor is not available, as in Asian countries, even status 1 and high-MELD patient likely benefit from living donor transplant. We know that this can be done successfully by reports from our colleagues in Asia, where deceased donor isn't an option, and from our colleagues in Toronto. But they have also shown that it's a very specific high-MELD patient who does well with LD. It is important to remember that the great majority of their living donors are also lower MELD patients, similar to the United States.

We are fortunate in the United States because of the abundance of deceased donors, and we don't have to perform transplant in patients with very high MELDs with living donors. Our allocation system prioritizes them so that patients with MELD scores over 25-30 will likely receive a deceased donor offer rather than having to rely on a living donor. We did not find disease severity in this study to be a significant predictor, but, as you said, our patients were within a very narrow group of MELD scores. As the MELD increases in this country, the benefit of transplanting at a lower MELD scores will gain even more importance because that is where you do have a living donor available, whereas a deceased donor is not available until MELD scores are very high.

G. Klintmalm (Dallas, TX):

Results today, I think, are very important for 1 major reason. In an intention-to-treat analysis, living donor liver transplant provides a superior 10-year survival. This is due to mortality of patients on the waitlist for cadaver donors. It's fundamentally important information to give to physicians and to the patient sitting down for the first time to discuss what are their treatment options when they finally face end-stage liver disease. The conclusion is that LDLT should be considered the primary option early in the course of liver failure.

My first question relates to the deteriorating outcome once serious, truly end-stage complications of liver failure develop in the recipient, renal failure, respiratory failure, ICU, and so forth. When do you say to the donor that the recipient's condition is too far advanced to expose the potential donor to a very major procedure with a 40% complication rate and sometimes prolonged recovery? At such a time, the recipient's MELD score should be high enough to compete for cadaver donor anyway.

My second question is with regard to the donor. It is not only that graft survival is negatively impacted by advanced donor age but also that recovery of the donor becomes more difficult. When do you say that the donor is too old to donate? And this age of social sensitivity, do the emotional ties between donor and recipient

influence what the donor age limit? When is the recipient too old to justify exposing the donor to the procedure?

Finally, in '67, Roy Calne named the biliary reconstruction the Achilles heel of liver transplantation. With the wealth of data of A2ALL, are there any recommendations you would make for the biliary reconstructions? Microscope for all reconstructions? Stenting for all? Choledochojejunostomy for all?

The A2ALL project has been an unmitigated success, not only for the participant but also for the patients and the entire liver transplant community all over the world.

Response From K.M. Olthoff:

As far as your first question on who is too sick, I think that is a question we still struggle to answer. The question of who is too sick is a question that we should ask for both living donor and deceased donor. I believe that the avoidance of progression of these patients to this stage is one of the primary goals of living donor transplantation. We know that all MELDs of 30-plus are not the same, and we have to be careful about which patients with high MELDs we choose to transplant, both with living donors and deceased donors. The very high MELDs, we might be willing to risk using a deceased donor on; but we may not wish to risk a living donor on someone with a very high MELD score.

As far as a donor who is too old, I think the older the donor, the higher the risk to both to donor and recipient. There's no specific age cutoff, and it's more of a biologic age and not necessarily a chronologic age. Our center uses 50, but we've used donors who are 55. Other centers use 55 or 60. Half a liver that's older than 50, older than 45, and simply just does not function, and a liver that's 25.

The biliary complications will always be there. We are still working and struggling on decreasing that. We published data on the biliary complications in the living donor. Each center has its different way of approaching it. At our center, we have maintained that the most important aspect to minimize biliary complications is maintaining good blood supply to the recipient bile duct, and minimal dissection around the donor bile duct, and we have avoided stenting. I think that summarizes our experience. I can't speak for all the A2ALL centers at this time.

C. Broelisch (Duesseldorf, Germany):

I have nothing to disclose.

You and your group should be congratulated for such seminal work over the last decade. Your report indeed is encouraging to embark on more widely use of the living donor transplants and is really in accordance with previous publications from your institution and from others in Europe and particularly from over in Asia.

The convincing argument for the decision-making progress is the argument for the MELD that provides a comparable scoring but many times does not reflect severity of disease. Despite reports, however, that MELD stage does not influence graft and patient survival, although we have heard a different opinion today, your data presented a significant increase in the risk of graft failure for the LDLT cohort when MELD increases beyond 20.

Where would you draw a line, or is it possible to draw a line, to reject a candidate for a living donor when a live donor could be available? Would it be a certain MELD score, recipient age, donor age, primary diagnosis, or the present clinical condition, or a combination of all of that?

My second question relates to the incidence of retransplantation. An LDLT recipient who received transplant at an earlier stage practically is bypassing the long waitlist but had to be reconsidered for retransplantation, giving him or her a better chance for a longer life. However, by aiming at equal chances for a graft even at a time of shortages, would you argue for a minimum MELD to justify an early live donor transplantation because ultimately we all depend on cadaveric organ donation.

Your report will focus on recipient outcome, which is the ultimate interest and motivation of the donor. The donor incidences thus far reported did not show any relation to the recipient outcome; they happened unexpectedly due to several medical or technical factors, which comprise the learning curve. With more than your 900 cases, is there a continuation of adverse effects, like severe morbidities or even mortalities, or is the learning curve still going on?

When we initiated living donor liver transplantation in 1989 in the United States at the University of Chicago, at that time to overcome the waitlist shortage for children, we estimated morbidity rates of less than 15% in analogy to reported complications after partial hepatectomy. The first 2 cases, however, taught us to preferentially use the small left lateral lobe for the pediatric recipient. However, it was disputed that we would never need living donor transplants, and the risk of the donor, since we just presented the options for a split procedure. Before we now embark, according to your recommendation, on a more adjusted and more appropriate use of the live donors, is there a need to revive the split sharing, or would the graft quality prevent such an endeavor?

Finally, after 20 years, we can state that no child anymore has to die on the waitlist because of combined use of living donors and split transplants. Personally, I believe that we have to strive for a similar situation for all adult patients.

Response From K.M. Olthoff:

Where to draw the line, that's really the question, isn't it? I don't think there's a specific MELD score; it's more a combination of factors that influence outcome. A younger donor graft of good volume may work relatively well in an older recipient, but in an older recipient with a higher MELD score, a smaller left lobe may not work. I think it's more a matter of incorporating all these different factors. In development is a living donor risk score in living donation, incorporating donor and recipient factors to help centers assess risk.

As far as retransplantation, a very small percentage of LD recipients require retransplantation. I don't think there's a minimum MELD score for transplantation. As I mentioned before, there are many patients with low MELDs who have very severe liver disease.

With regard to split liver transplantation, I think that in the living donor experience, it takes significant planning with regard to the vessel and the bile ducts and that sort of thing to do a right-left living donor split, much more so than a left lateral segment and right trisegment. I think, although it's been attempted and tried, deceased donor right-left split has not grown in the United States, and because it's a surgical procedure that's just not in a controlled environment without the preoperative planning, I really don't think that that's going to grow much in the United States. The complications may outweigh the supposed benefits, as much as we would like to, to minimize the need for living donors.

Olthoff KM, Smith AR, Abecassis M, Baker T, Emond JC, Berg CL, Beil CA, Burton JR, Jr., Fisher RA, Freise CE, Gillespie BW, Grant DR, Humar A, Kam I, Merion RM, Pomfret EA, Samstein B, Shaked A. Defining long-term outcomes with living donor liver transplantation in North America. *Ann Surg.* 2015;262(3):465-475; discussion 473-465.

Preoperative Cholangitis and Future Liver Remnant Volume Determine the Risk of Liver Failure in Patients Undergoing Resection for Hilar Cholangiocarcinoma

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BACKGROUND: The highest mortality rates after liver surgery are reported in patients who undergo resection for hilar cholangiocarcinoma (HCCA). In these patients, postoperative death usually follows the development of hepatic insufficiency. We sought to determine the factors associated with postoperative hepatic insufficiency and death due to liver failure in patients undergoing hepatectomy for HCCA.

STUDY DESIGN: This study included all consecutive patients who underwent hepatectomy with curative intent for HCCA at 2 centers, from 1996 through 2013. Preoperative clinical and operative data were analyzed to identify independent determinants of hepatic insufficiency and liver failure-related death.

RESULTS: The study included 133 patients with right or left major (n = 67) or extended (n = 66) hepatectomy. Preoperative biliary drainage was performed in 98 patients and was complicated by cholangitis in 40 cases. In all these patients, cholangitis was controlled before surgery. Major (Dindo III to IV) postoperative complications occurred in 73 patients (55%), with 29 suffering from hepatic insufficiency. Fifteen patients (11%) died within 90 days after surgery, 10 of them from liver failure. On multivariate analysis, predictors of postoperative hepatic insufficiency (all $p < 0.05$) were preoperative cholangitis (odds ratio [OR] 3.2), future liver remnant (FLR) volume < 30% (OR 3.5), preoperative total bilirubin level >3 mg/dL (OR 4), and albumin level < 3.5 mg/dL (OR 3.3). Only preoperative cholangitis (OR 7.5, $p = 0.016$) and FLR volume < 30% (OR 7.2, $p = 0.019$) predicted postoperative liver failure-related death.

CONCLUSIONS: Preoperative cholangitis and insufficient FLR volume are major determinants of hepatic insufficiency and postoperative liver failure-related death. Given the association between biliary drainage and cholangitis, the preoperative approach to patients with HCCA should be optimized to minimize the risk of cholangitis. (J Am Coll Surg 2016;223:87–97. © 2016 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Hilar cholangiocarcinoma (HCCA) is a relatively uncommon neoplasm originating from malignant transformation of the epithelium of the proximal bile duct. Although the tumor typically involves the biliary confluence, the tumor may extend proximally to second- and third-order biliary branches. Management of HCCA is

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Abbreviations and Acronyms
FLR = future liver remnant
HCCA = hilar cholangiocarcinoma
OR = odds ratio
PVE = portal vein embolization

difficult, mainly because the tumor location, close to the vascular hilar structures and liver parenchyma, makes complex hepatic resection with bile duct excision necessary for a chance for long-term survival.[1] Also, the lack of effective adjuvant treatment makes surgical resection the only potentially curative treatment for this tumor.[2]

In the majority of patients, the first symptom of HCCA is obstructive jaundice, which is associated with high postoperative morbidity and mortality rates, mainly because of infections and hepatic insufficiency.[3] Preoperative biliary drainage has become a routine procedure in the preoperative management of HCCA. The goal of this procedure is to prevent cholestasis-associated toxic effects[4] and to improve liver regeneration after both liver resection and portal vein embolization (PVE), when PVE is necessary.[5] Though several groups tried to demonstrate benefits of biliary drainage before liver resection for HCCA, no clear conclusion was reached. In contrast, preoperative biliary drainage has been reported to increase the incidence of postoperative cholangitis.[6]

A recent multicenter study of mortality after liver resection for HCCA, preceded or not by biliary drainage, revealed that preoperative biliary drainage may be beneficial for patients undergoing right hepatectomy but not left hepatectomy.[7] This divergent effect may be due to cholangitis after unnecessary biliary drainage before left hepatectomy, which is associated with a lower risk of hepatic insufficiency than right hepatectomy.[8]

The aim of this study was to determine the factors associated with postoperative hepatic insufficiency and liver failure-related death in patients undergoing major liver resection for HCCA, with a focus on the impact of preoperative biliary tract infections.

METHODS

All patients who had undergone hepatectomy for HCCA from 1996 through 2013 at 2 tertiary care institutions (Department of General Surgery and Surgical Oncology of Mauriziano Umberto I Hospital in Turin, Italy, and Department of Surgical Oncology of The University of Texas MD Anderson Cancer Center in Houston, TX) were retrospectively identified from institutional databases. Patients' full medical records, including hospital charts, surgical records, and pathology reports, were retrieved. Patients were included in further analyses only if surgery had consisted of a macroscopically curative major or extended hepatectomy with common bile duct resection and Roux-en-Y biliary-enteric anastomosis (hepatopancreatoduodenectomy were excluded); pathologic evaluation had confirmed HCCA; and details were available on serum bilirubin and albumin levels before and after surgery, preoperative cholangitis associated or not with preoperative biliary drainage, type of biliary drainage, preoperative liver volumetry, and postoperative complications. Data collection and analysis were performed according to institutional guidelines and conformed to the ethical standards of the Helsinki Declaration.

Definitions

Hilar cholangiocarcinoma extension was defined according to the Bismuth-Corlette classification.[9] It was considered unresectable if a patient had locally advanced disease extensively involving the main portal vein proximal to its bifurcation or the common hepatic artery; encasement of the right or left portal branch with contralateral arterial involvement; or involvement of lymph nodes beyond the regional ones.

Major hepatectomy was defined as resection of 3 or more Couinaud segments. Extended hepatectomy was defined as resection of 5 or more Couinaud segments. Types of hepatectomy were classified according to the Brisbane 2000 terminology.[10] A resection was considered macroscopically curative when the margin was clear of tumor on microscopic examination (R0) or on macroscopic examination (R1). Operative mortality was defined as death before discharge from the hospital or within 90 days after surgery. Morbidity included any deviation from the normal postoperative course, and major morbidities were defined as any grade III or higher complication according to the classification scheme proposed by Dindo and colleagues.[11]

Preoperative cholangitis was diagnosed when 2 or more of the following conditions existed: body temperature higher than 38.5°C, white blood cell count more than 12×10^9/L or less than 4×10^9/L, or upper right abdominal pain in the presence of a positive bile culture.[12]

Hepatic insufficiency was defined as a postoperative serum bilirubin level exceeding 7 mg/dL or, in patients with preoperative jaundice, as a higher serum bilirubin level than the preoperative level on postoperative day 5 or thereafter.[13,14] Death from liver failure was defined as postoperative death directly related to progressive hepatic insufficiency. Postoperative bile leak, hemorrhage, and sepsis were defined according to internationally accepted criteria.[15-17]

Preoperative management

Computed tomography, magnetic resonance imaging, and in some patients, cholangiography were used to assess longitudinal tumor extension along the bile duct; involvement of the portal vein and/or hepatic arteries; invasion of the liver parenchyma; and presence of hepatic or extrahepatic metastases. All patients included in the study underwent CT volumetry of the future liver remnant (FLR). When the estimated FLR was considered insufficient, preoperative PVE of the contralateral liver was performed.[18-20] Liver resection was scheduled at least 4 weeks after PVE if sufficient hypertrophy was achieved.

At MD Anderson Cancer Center, preoperative biliary drainage was performed in almost all patients presenting with jaundice. At Mauriziano Umberto I Hospital, indications for preoperative biliary drainage were cholangitis refractory to antibiotics, the need for PVE in a patient with serum bilirubin level higher than 10 mg/dL, hyperbilirubinemia-induced malnutrition, and anorexia causing a marginal performance status. Decompression of the biliary tree was achieved by percutaneous transhepatic biliary drainage of the FLR with internal-external drainage whenever possible, or by endoscopic retrograde biliary drainage. If the patient was referred to our centers with a malfunctioning biliary drainage catheter, this was replaced preoperatively with a new catheter placed by a percutaneous approach. In cases of post-biliary drainage infection, resection was planned after clinical resolution of cholangitis with adequate medical treatment.

Surgical procedures

Beginning in 1997, laparoscopic exploration to rule out peritoneal carcinomatosis was performed routinely at Mauriziano Umberto I Hospital and selectively at MD Anderson Cancer Center. A right subcostal incision extended to the left of the midline or an inverted "L" incision was performed.[21] A midline split was sometimes necessary. Intraoperative liver ultrasonography was performed to assess resectability. Then the common bile duct was divided above the pancreas, and intraoperative frozen section evaluation was performed. The parenchymal transection technique was chosen by the surgeon. At MD Anderson Cancer Center, the "2-surgeon technique," with both an ultrasonic dissector (used by the primary surgeon) and a saline-linked cautery (used by the second surgeon), was used in most cases.[22] At Mauriziano Umberto I Hospital, liver resections were performed using a similar technique with an ultrasonic dissector together with bipolar forceps, with continuous irrigation and absorbable suture clips to ligate smaller vessels or bile ducts or suture ligature to ligate larger vessels or bile ducts. Total hepatic inflow occlusion (Pringle maneuver) for periods of up to 15 minutes, alternating with 5 minutes of restored inflow, was used in the majority of cases at MD Anderson Cancer Center and in the early cases at Mauriziano Umberto I Hospital. In the later cases at Mauriziano Umberto I Hospital, pedicle clamping was performed only when persistent or major bleeding occurred during parenchymal transection.[23] During liver resection, extrahepatic vascular inflow and outflow were routinely controlled when possible, with ligation and section of appropriate portal vein and hepatic artery branches and hepatic veins.

Statistical analysis

Statistical analysis was performed with SPSS (version 20.0, SPSS Inc.). Categorical data were expressed as frequency (percentage) and compared by chi-square or Fisher's exact test as appropriate. Continuous data were expressed as median (range) and compared by the Mann-Whitney U test. Associations of perioperative variables with hepatic insufficiency and death from liver failure were first assessed at univariate analysis. Perioperative variables with a value of $p < 0.2$ at univariate analysis were entered into a multivariate logistic regression analysis in a backward stepwise manner. A value of $p < 0.05$ was considered statistically significant in all analyses.

RESULTS

Patient characteristics

A total of 133 patients met the inclusion criteria and represented the study population; the majority of them ($n = 98$, 74%) were treated after 2000. Patient characteristics are summarized in Table 1. Hilar cholangiocarcinoma was classified as type II in 19%, III in 71%, and IV in 10% of patients. Jaundice was the presenting symptom in 116 patients. Preoperative cholangitis before or after biliary drainage occurred in 42 patients. Preoperative biliary drainage was performed in 98 patients, and preoperative PVE was performed in 32 patients. Median (range) preoperative levels of albumin and total bilirubin were 3.6 mg/dL (2 to 4.9 mg/dL) and 1.9 mg/dL (0.2 to 32 mg/dL), respectively.

Resection consisted of excision of the entire extrahepatic bile duct combined with an en bloc major ($n = 67$) or extended ($n = 66$) hepatectomy, including in most patients (89.5%) a caudate lobectomy (caudate process, paracaval portion, and Spiegel lobe) ($n = 110$) or resection of Spiegel lobe only ($n = 9$). Portal vein resection and reconstruction were performed in 28 patients (21%). In 1 patient, the portal vein resection was combined with hepatic artery resection.

Table 1. Characteristics of the Whole Study Cohort and Comparison of Patients With and Without Preoperative Biliary Drainage

Characteristic	Whole study cohort (n = 133)	Preoperative biliary drainage (n = 98)	No preoperative biliary drainage (n = 35)	p Value
Median age, y (range)	66 (35–84)	65 (40–84)	67 (35–82)	0.262
Male sex, n (%)	84 (63)	62 (63)	22 (63)	0.996
Jaundice at diagnosis, n (%)	116 (87)	91 (93)	25 (71)	0.002
Cholangitis at diagnosis, n (%)	7 (5)	5 (5)	2 (6)	0.892
Any preoperative cholangitis, n (%)	42 (32)	40 (41)	2 (6)	<0.001
Preoperative PVE, n (%)	32 (24)	31 (32)	1 (3)	<0.001
Tumor type, n (%)*				0.544
II	25 (19)	17 (17)	8 (23)	
IIIa	55 (41)	43 (44)	12 (34)	
IIIb	40 (30)	27 (28)	13 (37)	
IV	13 (10)	11 (11)	2 (6)	
FLR volume ≥ 30%, n (%)	83 (62)	59 (60)	24 (69)	0.380
Median albumin level, mg/dL (range)	3.6 (2–4.9)	3.6 (2–44)	3.7 (2–4.9)	0.691
Median total bilirubin level, mg/dL (range)	1.9 (0.2–32)	1.7 (0.2–21)	5.5 (0.2–32)	0.040
Right hepatectomy, n (%)	24 (18)	18 (18)	6 (17)	0.871
Extended right hepatectomy, n (%)	56 (42)	48 (49)	8 (23)	0.007
Left hepatectomy, n (%)	43 (32)	26 (27)	17 (49)	0.017
Extended left hepatectomy, n (%)	10 (8)	6 (6)	4 (11)	0.307
Vascular resection, n (%)	28 (21)	21 (21)	7 (20)	0.859
Median operation time, min (range)	440 (190–1,300)	452 (190–1,300)	435 (135–590)	0.558
Median intraoperative blood loss, mL (range)	577 (50–3,500)	578 (70–3,500)	550 (150–1,500)	0.620
R0 resection, n (%)	114 (86)	82 (84)	32 (91)	0.260
Overall complications, n (%)	102 (77)	78 (80)	24 (69)	0.186
Major complications (Dindo III–V), n (%)	73 (55)	56 (57)	17 (49)	0.382
Hepatic insufficiency	29 (22)	23 (24)	6 (17)	0.437
Bile leak	24 (18)	18 (18)	6 (17)	0.872
Sepsis	17 (13)	13 (13)	4 (11)	1
Abdominal hemorrhage	9 (7)	7 (7)	2 (6)	1
Death, n (%)	15 (11)	12 (12)	3 (9)	0.758
Liver failure	10 (8)	8 (8)	2 (6)	0.989
Sepsis	2 (1.5)	1 (1)	1 (3)	0.459
Abdominal hemorrhage	3 (2)	2 (2)	1 (3)	1

*Type according to Bismuth-Corlette classification.
FLR, future liver remnant; PVE, portal vein embolization.

Overall, 102 patients (77%) suffered from postoperative complications and 73 (55%) from major complications. Among patients suffering from major complications, 29 had hepatic insufficiency, 24 had bile leak, 17 had sepsis, 9 had abdominal hemorrhage, and 31 had abdominal collections requiring drainage by an interventional radiologist. Postoperative death occurred in 15 patients and was due to liver failure in 10 patients. No significant changes in the mortality rate were observed over time, nor were differences found between centers. Vascular resection did not significantly increase the mortality rate (14.3% in patients undergoing vs 10.5% in those not undergoing vascular resection; p = 0.519).

Comparison of patients with and without preoperative biliary drainage

Of the 98 patients who underwent preoperative biliary drainage, 50 had percutaneous transhepatic and 48 had endoscopic retrograde biliary drainage. Patients who did and did not undergo preoperative biliary drainage are compared in Table 1. The 2 groups did not differ significantly in terms of age, sex, tumor type, FLR volume, operation time, intraoperative blood loss, and postoperative characteristics (all p > 0.050). Extended right hepatectomy was more often performed after preoperative biliary drainage, unlike left hepatectomy. Patients who underwent preoperative biliary drainage were

Table 2. Univariate and Multivariate Analysis of Factors Associated with Postoperative Hepatic Insufficiency

		Patients with hepatic insufficiency (n = 29)		Univariate analysis		Multivariate analysis*	
Factor	**n**	**n**	**%**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Age ≥ 65 y							
Yes	67	13	19	0.752 (0.329–1.720)	0.500		
No	66	16	24	–	–		
Male sex							
Yes	84	19	23	1.14 (0.480–2.701)	0.766		
No	49	10	20	–	–		
Jaundice at diagnosis							
Yes	116	25	22	0.893 (0.268–2.979)	0.854		
No	17	4	23	–	–		
Preoperative biliary drainage							
Yes	98	23	23	1.482 (0.548–4.011)	0.438		
No	35	6	17	–	–		
Preoperative cholangitis							
Yes	42	14	33	2.533 (1.086–5.912)	0.029	3.170 (1.090–9.221)	0.034
No	91	15	16	–	–	–	–
Preoperative PVE							
Yes	32	9	28	1.585 (0.636–3.948)	0.323		
No	101	20	20	–	–		
Tumor type†							
IV	13	5	38	2.202 (0.652–7.444)	0.204		
III	95	21	22	2.081 (.567–7.636)	0.269		
II	25	3	12	–	–		
FLR volume							
<30%	50	16	32	2.53 (1.09–5.847)	0.030	3.484 (1.25–9.708)	0.017
≥30%	83	13	16	–	–	–	–
Albumin level < 3.5 mg/dL							
Yes	49	18	37	2.965 (1.24–7.094)	0.015	3.26 (1.232–8.654)	0.017
No	67	11	16	–	–	–	–
Total bilirubin level > 3 mg/dL							
Yes	54	15	28	1.882 (0.771–4.59)	0.165	4.028 (1.291–12.565)	0.017
No	79	14	18	–	–	–	–
Vascular resection							
Yes	28	9	32	2.013 (0.794–5.106)	0.141	1.951 (0.651–5.842)	0.232
No	105	20	19	–	–	–	–

*All factors with a p value < 0.2 in the univariate analysis were entered in the multivariate analysis. Body mass index was not included in the analysis because of missing data for 33 patients.
†According to Bismuth-Corlette classification.
FLR, future liver remnant; OR, odds ratio; PVE, portal vein embolization.

more likely to have jaundice at diagnosis (93% vs 71%; $p < 0.001$) and to undergo preoperative PVE (32% vs 3%; $p < 0.001$).

Although patients who did and did not undergo preoperative biliary drainage had similar rates of cholangitis at presentation, the overall rate of preoperative cholangitis was significantly higher in patients who underwent preoperative biliary drainage (41% vs 6%; $p < 0.001$). Among the 35 patients who did not undergo preoperative biliary drainage, preoperative cholangitis occurred in only 2 patients and was controlled preoperatively with antibiotics. In contrast, among the 98 patients who did undergo preoperative biliary drainage, 5 had cholangitis at diagnosis and an additional 35 (36%) developed cholangitis after undergoing biliary drainage. As a result of biliary drainage, the preoperative median bilirubin level was

Table 3. Univariate and Multivariate Analysis of Factors Associated with Death from Postoperative Liver Failure

		Liver failure death (n = 10), n (%)		Univariate analysis		Multivariate analysis*	
Factor	**n**	**n**	**%**	**OR (95% CI)**	**p Value**	**OR (95% CI)**	**p Value**
Age ≥ 65 y							
Yes	67	5	7	0.984 (0.271–3.571)	0.98		
No	66	5	7	–	–		
Male sex							
Yes	84	8	9	2.474 (0.504–12.15)	0.265		
No	49	2	4	–	–		
Jaundice at diagnosis							
Yes	116	10	9	1.5×10^8 (0.00–∞)	0.998		
No	17	0	0	–	–		
Preoperative biliary drainage							
Yes	98	8	8	1.467 (0.296–7.26)	0.639		
No	35	2	6	–	–		
Preoperative cholangitis							
Yes	42	8	19	10.471 (2.12–51.81)	0.001	7.544 (1.46–38.99)	0.016
No	91	2	2	–	–	–	–
Preoperative PVE							
Yes	32	3	9	1.389 (0.337–5.72)	0.649		
No	101	7	7	–	–		
Tumor type†							
IV	13	1	8	0.955 (0.108–8.447)	0.967		
III	95	7	7	1.043 (0.086–12.71)	0.973		
II	25	2	8	–	–		
FLR volume							
<30%	50	8	16	7.69 (1.56–38.46)	0.012	7.19 (1.39–37.037)	0.019
≥30%	83	2	2	–	–	–	–
Albumin level < 3.5 mg/dL							
Yes	49	6	12	2.114 (0.563–0.793)	0.267		
No	67	4	6	–	–		
Total bilirubin level > 3 mg/dL							
Yes	54	3	6	0.617 (0.152–2.502)	0.499		
No	79	7	9	–	–		
Vascular resection							
Yes	28	2	7	0.933 (0.187–4.661)	0.932		
No	105	8	8	–	–		

*All factors with a p value < 0.2 in the univariate analysis were entered in the multivariate analysis. Body mass index was not included in the analysis because of lacking data for 33 patients.
†According to Bismuth-Corlette classification.
FLR, future liver remnant; OR, odds ratio; PVE, portal vein embolization.

lower in the preoperative biliary drainage group (1.7 mg/dL vs 5.5 mg/dL; p = 0.040).

Risk factors for hepatic insufficiency and death from liver failure

Predictors of hepatic insufficiency and death from liver failure are shown in Tables 2 and 3. In univariate analysis, risk factors for hepatic insufficiency were preoperative cholangitis, FLR volume < 30%, and preoperative albumin level < 3.5 mg/dL. In multivariate analyses, these 3 factors and bilirubin level > 3 mg/dL independently predicted hepatic insufficiency. Specifically, the risk of developing hepatic insufficiency was about 3.5-fold higher in patients with FLR volume < 30%, preoperative cholangitis, and albumin level < 3.5 mg/dL, and about 4-fold higher in patients with bilirubin level > 3 mg/dL.

Preoperative cholangitis and FLR volume < 30% were the only predictors of death from liver failure, both in

Table 4. Comparison of Patients Who Did and Did Not Develop Preoperative Cholangitis

Characteristic	Preoperative cholangitis (n = 42)	No preoperative cholangitis (n = 91)	p Value
Median age, y (range)	69 (46–84)	64 (35–82)	0.086
Male sex, n (%)	29 (69)	55 (60)	0.339
Jaundice at diagnosis, n (%)	37 (88)	79 (87)	0.837
Preoperative biliary drainage, n (%)	40 (95)	58 (64)	<0.001
Endoscopic retrograde biliary drainage	27 (64)	21 (36)	0.002
Percutaneous transhepatic biliary drainage	13 (33)	37 (64)	
Preoperative PVE, n (%)	14 (33)	18 (20)	0.089
Tumor type, n (%)*			
II	11 (26)	14 (15)	0.299
III	28 (67)	67 (74)	
IV	3 (7)	10 (11)	
FLR volume < 30%	21 (50)	29 (32)	0.045
Median albumin level, mg/dL (range)	3.7 (2.0–4.4)	3.55 (2.0–4.9)	0.308
Median total bilirubin level, mg/dL (range)	1 (0.3–20.9)	3 (0.1–30.2)	0.001
Overall complications, n (%)	40 (95)	62 (68)	<0.001
Major complications, n (%)	31 (74)	42 (46)	0.003
Hepatic insufficiency	14 (33)	15 (16)	0.029
Bile leak	13 (31)	20 (22)	0.265
Sepsis	5 (12)	12 (13)	0.837
Abdominal hemorrhage	–	–	–
Death, n (%)	10 (24)	5 (5)	0.002
Liver failure	8 (19)	2 (2)	0.001
Sepsis	1 (2)	1 (1)	0.572
Abdominal hemorrhage	2 (5)	1 (1)	0.186

*Type according to Bismuth-Corlette classification.
FLR, future liver remnant; PVE, portal vein embolization.

univariate and in multivariate analysis, and independently predicted a risk of death from liver failure about 7.5-fold higher, compared with the risk in patients who did not have preoperative cholangitis or who had an FLR volume ≥ 30%.

Comparison of patients with and without preoperative cholangitis

Patients who developed and did not develop preoperative cholangitis are compared in Table 4. There was a trend toward higher median age and higher rate of preoperative PVE in patients with cholangitis, but these differences were not significant. An FLR volume < 30% was significantly more common among patients with preoperative cholangitis. Among the 98 patients who underwent preoperative biliary drainage, cholangitis was more common with endoscopic retrograde biliary drainage than with percutaneous transhepatic biliary drainage (p = 0.002).

Compared with patients without preoperative cholangitis, patients with preoperative cholangitis had a higher risk of overall (95% vs 65%; p < 0.001) and major complications (74% vs 46%; p = 0.003), mainly due to a higher risk of hepatic insufficiency (33% vs 16%; p = 0.029), and a higher risk of death (24% vs 5%; p = 0.002), mainly due to a higher rate of death from liver failure (19% vs 2%; p = 0.001).

The effect of cholangitis on early outcomes differed according to the FLR volume. When the FLR volume was < 30%, rates of hepatic insufficiency and death from liver failure were significantly higher among patients with preoperative cholangitis than among patients without (p = 0.040 and p = 0.004, respectively) (Fig. 1). Conversely, when the FLR volume was ≥ 30%, cholangitis did not affect rates of hepatic insufficiency or death from liver failure (p = 0.621 and p = 0.416, respectively) (Fig. 2).

DISCUSSION

Consistent with previous reports,[3,24-26] results from our study confirmed high rates of major complications and death after liver resection for HCCA, with hepatic insufficiency emerging as the most common major complication and liver failure emerging as the most common cause of death. By investigating predictors of hepatic insufficiency and death from liver failure, we confirmed

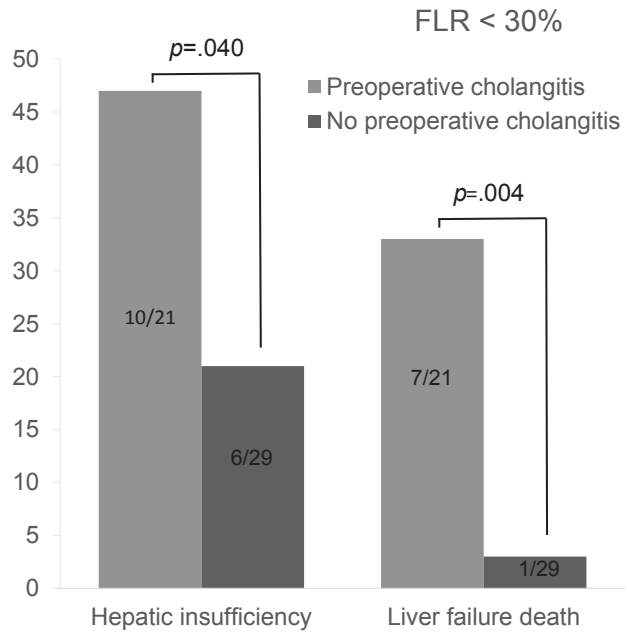

Figure 1. Effect of cholangitis on early postoperative outcomes in patients with future liver remnant (FLR) volume < 30%.

the importance of an adequate FLR volume in improving short-term results of surgery, and we showed for the first time an independent and strong association of preoperative cholangitis with an increased risk of both hepatic insufficiency and death from liver failure.

The association between an insufficient FLR volume and higher risks of hepatic insufficiency and death from liver

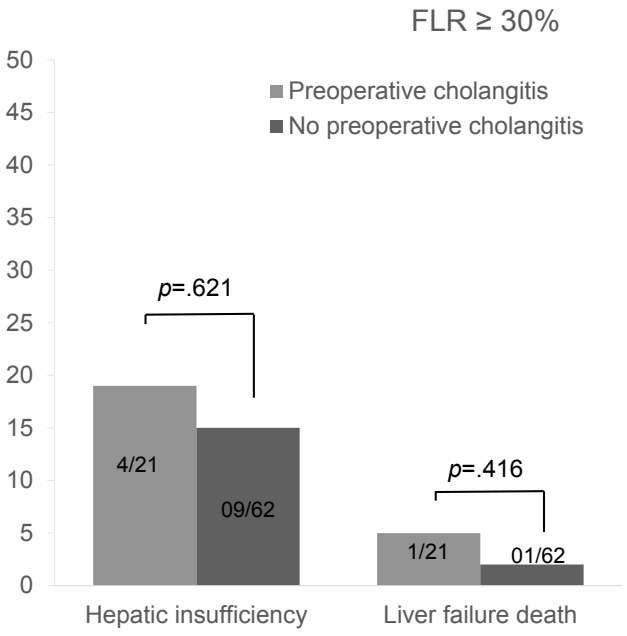

Figure 2. Effect of cholangitis on early postoperative outcomes in patients with future liver remnant (FLR) volume ≥ 30%.

failure after major hepatectomy was an expected result and is consistent with results from previous studies.[27-29] In this context, preoperative PVE to increase the FLR volume and thereby improve results of surgery was important; among 32 patients whose FLR was initially considered insufficient and who consequently underwent PVE before operation, 15 (47%) achieved an FLR volume higher than 30%, and none of these patients developed postoperative hepatic insufficiency or died of liver failure.

We also found an independent association between preoperative serum bilirubin level higher than 3 mg/dL and a higher risk of hepatic insufficiency. High preoperative serum bilirubin level was previously reported as an independent predictor of death after liver resection for HCCA.[7] Several studies have shown that hepatic resection in jaundiced patients can be associated with higher mortality and morbidity rates due to hemorrhages, subphrenic abscesses from biliary fistulas, sepsis, and liver failure.[7,30-33] Experimental studies shed light on the mechanisms underlying these associations, showing that cholestasis makes the liver parenchyma more susceptible to ischemia/reperfusion damage and inflammation, likely because of a reduction of antioxidant activity and an increase in the inflammatory response.[34,35] In our study, of 98 patients who underwent preoperative biliary drainage, 65 (66%) had their jaundice relieved preoperatively and had a serum bilirubin level lower than 3 mg/dL at the time of surgery. The median interval between preoperative biliary drainage and surgery was significantly longer among patients whose jaundice was relieved (56 days) than among patients operated on with persistent jaundice (33 days; $p < 0.001$), suggesting that among patients undergoing preoperative biliary drainage, delay of the operation to obtain complete relief of jaundice may be beneficial.

Serum albumin is a marker of the synthetic capacity of the liver and has traditionally been used to assess liver function in the context of the Child-Pugh classification. Consistent with previous reports, we found that low preoperative albumin level was associated with an increased risk of hepatic insufficiency. Although hypoalbuminemia in patients with sepsis may be simply a result of the infection, low albumin levels in other patients might identify patients with impaired nutritional status according to the Nutritional Risk Index, which can be used to identify patients who require a preoperative nutritional intervention to reduce the risks of surgery.[36] We speculate that in such patients, optimizing the nutritional status, especially with immunonutrition, might reduce the incidence of complications. While we await the results of the NCT02041871 trial (registered at clinicaltrials.gov) evaluating the interest of preoperative immunonutrition in unselected patients undergoing liver resection for cancer,

we believe that malnourished patients should receive oral nutritional support.

The most interesting finding of this study was the strong association between preoperative cholangitis and poor outcomes after liver resection. Several authors[6,27,37,38] have reported that biliary drainage before liver resection for HCCA is associated with higher rates of postoperative infectious complications, suggesting a correlation between biliary contamination due to the biliary drainage procedure and development of infections after liver resection. However, none of these previous studies found a direct association between preoperative biliary drainage and an increased risk of major complications or death, suggesting that while preoperative biliary drainage contributes to adverse short-term outcomes in some patients, others may benefit from this procedure. In this context, our study is important because it is the first western study to show an association between preoperative cholangitis and postoperative hepatic insufficiency and death from liver failure. Our findings are consistent with those of a previous study[39] that showed that the incidence of hepatic insufficiency after major hepatectomy was 71% in patients without and 88% in patients with preoperative cholangitis. However, the rates of hepatic insufficiency in this previous study were extremely high as a consequence of the criteria adopted to define this complication. Therefore, based on this previous evidence, the exact impact of cholangitis on post-resection outcomes was poorly defined and difficult to substantiate in discussions with patients about surgical risk.

The data from this study, in which we used an internationally recognized and validated definition of hepatic insufficiency and the modern practice of reporting of mortality through 90 days, offer a clear and novel insight into the problem of preoperative biliary drainage-related cholangitis. Even when controlled preoperatively with antibiotics, cholangitis may be associated with persistent subclinical biliary tract infection, which predisposes to the development of postoperative infections and impairs the regenerative capacity of the liver. In fact, experimental data obtained in a rat model indicate that segmental cholangitis significantly reduces the liver regeneration rate after partial hepatectomy.[40] Consistent with those experimental findings, in patients with preoperative biliary drainage-related cholangitis, the increase in the FLR volume per day after PVE is lower than that in patients without cholangitis.[39]

We also found that among the 98 patients who underwent preoperative biliary drainage, preoperative cholangitis was significantly more common after endoscopic retrograde biliary drainage (67.5%) than after percutaneous transhepatic biliary drainage (32.5%; $p = 0.002$). This is similar to the findings of previous studies reporting higher rates of cholangitis and lower rates of technical and therapeutic success after endoscopic retrograde than after percutaneous transhepatic biliary drainage.[41,42] Interestingly, a subgroup analysis also showed that the detrimental effect of preoperative cholangitis on surgical outcomes might be attenuated by large FLR volumes. Therefore, in patients experiencing preoperative biliary drainage-related cholangitis, surgery should not be performed, even if cholangitis has been controlled, until the FLR has reached a safe volume of 30%.

This study has some limitations. First, the retrospective nature of the study introduces selection biases. Second, given the long study period, there may have been heterogeneity in the preoperative use of both preoperative biliary drainage and PVE. However, the study reflects the use of PVE and preoperative biliary drainage over time, which was based on the clinical evaluation of individual patients. In this context, we offer the following recommendations: First, in jaundiced patients with insufficient FLR volume, preoperative biliary drainage should be performed before PVE to induce FLR volume increase. Second, only the FLR should be drained, if possible; bilateral preoperative biliary drainage should be limited to patients with segmental cholangitis or with uncertain longitudinal tumor extension.

CONCLUSIONS

In conclusion, preoperative biliary drainage remains an important strategy to allow FLR volume to increase in patients needing PVE, to treat jaundice-induced liver or renal failure, and to correct severe undernourishment or hypoalbuminemia. However, preoperative biliary drainage is frequently complicated by cholangitis, which is associated with an increased risk of hepatic insufficiency and death from liver failure after liver resection. Strategies to reduce the risk of preoperative biliary drainage-induced cholangitis, such as the pre-emptive prolonged use of antibiotics before and after the procedure, frequent checks and changes of the catheter, and use of external drains whenever possible, should be further investigated in order to optimize the outcomes of patients with HCCA.

Author Contributions

Study conception and design: Ribero, Zimmitti, Aloia, Ferrero, Vauthey

Acquisition of data: Ribero, Zimmitti, Shindoh, Forchino, Amisano, Passot, Vauthey

Analysis and interpretation of data: Ribero, Zimmitti, Shindoh, Forchino, Amisano, Passot, Vauthey

Drafting of manuscript: Ribero, Zimmitti, Passot, Vauthey
Critical revision: Aloia, Shindoh, Ferrero

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Discussion

DR DAVID M NAGORNEY (Rochester, MN): Clearly, these data confirm the significant rate of complications and mortality associated with resection of these tumors. Hepatic insufficiency was cited here as the most common major complication, and liver failure was the most common cause of death. Cholangitis was associated with preoperative drainage. Preoperative cholangitis and functional liver volume both strongly correlated with hepatic insufficiency and liver failure.

These data clearly show that preoperative management has consequences. The inter-relationship of cholangitis, hyperbilirubinemia, and liver function remnant are critical to perioperative outcome. Unfortunately, the management of infection, hyperbilirubinemia, and inadequate function of liver remnant volume requires intervention. It is the inter-relationship of these issues that continue to confound our management of these patients. But Dr Vauthey has provided some good insights.

First, regarding cholangitis, this is the first study from the West that confirms that cholangitis is associated with hepatic insufficiency and that cholangitis is related to biliary drainage. I think those of us who manage hilar cholangiocarcinoma have always been concerned about cholangitis. We simply did not know how to rate it until now. Regardless, drainage is here to stay. Drainage can be selective, you can do 1 duct, or you can do diffuse drainage or multiple ducts. Selective drainage, I think, has the greatest risk of cholangitis because undrained hepatic segments can lead to either subclinical or clinical cholangitis. So what do we do? Excluding those patients who have grossly atrophic liver, should the functional liver remnant be selectively or diffusely drained? In the absence of atrophy, should the nonremnant liver be drained or not? If so, how should we drain that liver? Finally, did you assess whether the type of drainage, that is, selective or nonselective, affected outcome?

Secondly, you stated that hepatic insufficiency was the major postoperative complication. No doubt liver failure is a major complication, but not necessarily hepatic insufficiency. The definition of hepatic insufficiency is clearly the key. If you look at the international study group classification, only B and C classification hepatic insufficiency require treatment. Although one-third of the patients had liver failure, was there a grade distribution of hepatic insufficiency in the remaining patients? Indeed, what percent of those patients required specific treatment? Would elimination of minor hepatic insufficiency have affected your conclusions that hepatic insufficiency is a major complication?

Finally, should you upsize the recommendation further than 30%, because there are a number of patients on whom you will operate and you will need to perform a bigger liver resection than you actually planned? The message here, I think, is important. I will be interested to see how surgeons and gastroenterologists incorporate this information into future practice.

DR JEAN-NICOLAS VAUTHEY (Houston, TX): I think you are pointing to very relevant issues here. The first issue is that we are really prisoners of our referrals as surgeons. It is a big problem. These patients are not referred to tertiary referral centers, and the number of procedures and the lack of an effective approach upfront contribute to worse outcomes. In this study, if you compare percutaneous to endoscopic drainage, the rate of cholangitis was more than twice as high in patients undergoing endoscopic drainage. Proximal bile duct strictures require specific endoscopic skills and are very different from distal bile duct strictures. This needs to be taken into account when you manage these patients. To answer your question, the drainage should be targeted to the future liver remnant, ie the right or the left hepatic ducts. If jaundice improves and there is no cholangitis, you should avoid multiple drainage procedures and it is not necessary to drain all dilated ducts.

Regarding the question of hepatic insufficiency, we have used the peak bilirubin to define hepatic insufficiency for all our studies. It is different from the international definition, which includes the bilirubin and the international normalized ratio (INR) at day 5. Hepatic insufficiency based on peak bilirubin is a single, easy to

Ribero D, Zimmitti G, Aloia TA, Shindoh J, Forchino F, Amisano M, Passot G, Ferrero A, Vauthey JN. Preoperative Cholangitis and Future Liver Remnant Volume Determine the Risk of Liver Failure in Patients Undergoing Resection for Hilar Cholangiocarcinoma. *J Am Coll Surg.* 2016;223(1):87-97.