Liver Resection and Transplantation in the Management of Hepatocellular Carcinoma: A Review

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Hepatocellular carcinoma (HCC) accounts for more than 80% of all primary liver cancers and is one of the most common malignancies worldwide. Most patients with HCC also suffer from concomitant cirrhosis, which is the major clinical risk factor for hepatic cancer and results from alcoholism, infection with the hepatitis B or hepatitis C virus, and other causes. HCC is often diagnosed at an advanced stage, when established treatment options provide limited benefit. Effective treatment for HCC includes liver resection and liver transplantation. Under most clinical circumstances, those options provide a high rate of complete response and are thought to improve survival. Partial hepatectomy is the therapy of choice in patients with HCC and a noncirrhotic liver. Usually, liver transplantation is not indicated for such patients, although in individual cases, transplantation may be considered. For most cirrhotic patients who fulfill the Milan criteria, liver transplantation is the ultimate treatment option. Liver transplantation restores liver function and ensures the removal of all hepatic foci of tumor as well as tissue with a high oncogenic potential for early tumor recurrence. Because of the present lack of available organs, living-donor liver transplantation (LDLT) is an increasingly popular alternative. LDLT enables recipients to avoid a long pretransplantation waiting time and increases the number of livers available for transplantation. It is also the most effective approach to reducing the dropout rate. Strategies to reduce tumor growth in patients who are awaiting liver transplantation are important to ensure that those individuals continue to fulfill the Milan criteria for transplantation. For that purpose, using ablative techniques or chemoembolization to control local tumor growth is useful.

Key words: *Hepatocellular carcinoma, Liver resection, Liver transplantation*

Hepatocellular carcinoma is the most frequently occurring primary malignant liver tumor [1]. Types of HCC vary by geographic location from a relatively rare tumor, like those found in North America and Europe, to a very common and highly malignant tumor that is characteristically encountered in sub-Saharan Africa and southeast Asia. HCC, which accounts for 80% of all primary liver cancers, is the fifth most common cancer and the third leading cause of death from cancer worldwide [1, 2]. Most patients with HCC also suffer from coexisting cirrhosis, which is the major clinical risk factor for hepatic cancer and is caused primarily by infection with either hepatitis B virus (HBV) or hepatitis C virus (HCV) [3]. However, both cirrhosis from nonviral causes (such as alcoholism) and primary biliary cirrhosis are also associated with an elevated risk of HCC. Furthermore, concomitant risk factors such as HCV infection in addition to alcoholism, tobacco use, diabetes, or obesity increase the relative risk of HCC development, as numerous studies in humans and animal models have shown [4-10].

The incidence of HCC varies by geographic area worldwide. Research has shown that southeast Asia and sub-Saharan Africa have an incidence rate of HCC that ranges from 150 to 500 per 100,000 population, primarily because of the endemic nature of hepatitis B and C in those regions [11-13]. HCV accounts for almost 90% of all cases of HCC in Japan, and in China, hepatitis B infection is diagnosed in about 80% of patients with HCC [12-14]. In Europe and North America, however, despite a significantly lower incidence rate of 3 to 4 per

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100,000 population, a distinct increase in cases of HCC has been reported as a result of intravenous drug use, unsafe sexual practices, and other causes [15-17]. Because of a lack of effective HCV vaccination, underlying HCV infection is largely responsible for that increase. As a result of the interval between the onset of infection and the development of cirrhosis of the liver, the incidence of HCV-related HCC will continue to increase over the next several years [18]. In contrast to Asian populations, the percentage of Western patients with HCC but without underlying cirrhosis is considerable, and the development of HCC in cirrhotic individuals in the West is associated with a wider spectrum of underlying diseases. In the West, the percentage of virally engendered cirrhosis is lower than that in Asian regions, but alcohol-toxic or cryptogenic hepatic damage is observed more frequently in Western countries [14]. Thus, the etiologic pattern of HCC in Western regions of low risk for that disease differs appreciably from that in southeast Asia and sub-Saharan Africa.

The clinical course of HCC and the survival rates of patients depend on the stage of the disease at the time of diagnosis. However, the prognosis is generally dismal (the 5-year survival rate is less than 7%), particularly in populations at high risk for HCC [17, 19]. In sub-Saharan Africans and Chinese individuals, for example, the tumor usually exhibits a fulminant course, and the mean survival time ranges from 6 weeks to 6 months from the time of diagnosis [11, 20]. The resectability rate in this type of cancer is very low, and remission or prolongation of survival is rarely achieved with other nonsurgical treatment modalities. In European and North American patients, however, HCC often runs a mild course, although even those patients have a median survival of 1 to 8 months from the time of diagnosis [21]. Their tumors and those of Japanese patients are more likely to be amenable to surgery and more responsive to nonsurgical treatment [22-24].

Diagnosis

The detection of a focal hypervascular hepatic mass by means of noninvasive diagnostic tests (magnetic resonance imaging [MRI], computed tomography [CT]), a complete patient history, and an elevated level of serum markers enables an accurate diagnosis in most patients, especially those with coexisting cirrhosis. Alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin are the 2 most well-studied serum markers widely used in patient screening and diagnostic evaluations [25, 26]. According to 1 study, the major limitation of the noninvasive diagnosis of HCC is its high false-positive rate (up to 20% in patients with a tumor smaller than 3 cm and an AFP level of less than 100 ng/mL), which ultimately leads to unnecessary or inappropriate treatment [27]. However, no false-positive diagnoses were found in patients with a tumor smaller than 3 cm and an AFP level of more than 100 ng/mL or in those with a tumor larger than 3 cm, regardless of the AFP level. The variable radiographic appearance of HCC and its frequent coexistence with benign hepatic nodules such as macroregenerative and dysplastic nodules make the interpretation of imaging studies challenging. In addition, other mass-forming hepatic lesions (such as primary hepatic lymphoma) may be misdiagnosed as HCC [28, 29]. Nevertheless, with the advent of more accurate imaging techniques and the discovery of more sensitive tumor markers, the false-positive diagnosis rate may improve, thus restricting the use of biopsy to selected cases (eg, patients with a small nodule and a low AFP level). Although the histologic examination of a hepatic mass has long been considered the gold standard for the diagnosis of HCC, potential complications such as bleeding, tumor seeding, and false-negative diagnoses limit the indiscriminate use of the percutaneous biopsy of suspicious lesions for cytologic or histologic analysis [30]. Sampling errors and misclassifications have also raised significant concerns about the use of percutaneous biopsy in patients with suspected HCC.

Surgical treatment

Although surgery remains the only treatment for HCC in patients with or without cirrhosis, most individuals with HCC are ineligible for surgical intervention [31]. In eligible patients, the methods of surgical therapy are partial hepatectomy and liver transplantation, and the latter is the best available treatment for HCC in cirrhotic patients [3, 17, 31]. In addition to resection and liver transplantation, percutaneous ablation is considered a treatment option that offers a high rate of complete response and thus a potential for cure [32]. In selected patients, a 5-year survival rate of 60% to 75% can be achieved after surgery [33, 34]. However, in those with advanced HCC, the consequent improvement in long-term survival is poor because of the high rate of recurrence or the development of intrahepatic metastases that disseminate via the portal vein or spread to other parts of the liver [35, 36]. Nevertheless, the management of HCC has undergone major changes over the last few decades. Earlier detection enabled by screening methods that use ultrasonographic evaluation and AFP analysis in

high-risk populations, more accurate patient assessment, advances in imaging, improved surgical techniques, and the availability of local treatment options have improved outcomes. Current information regarding the general treatment of HCC (with special emphasis on surgical treatment in patients with either a noncirrhotic or a cirrhotic liver) will be reviewed in this report.

HCC in patients with a noncirrhotic liver. Only 5% of the cases of HCC in Western countries (as opposed to 40% in Asia) develop in a noncirrhotic liver [37]. When HCC occurs in a noncirrhotic liver, solitary tumor nodes that are limited to 1 liver lobe and lack satellite foci are frequently present. Without predisposing cirrhosis, HCC is often not diagnosed until the tumor causes symptoms because of its size and the patient has begun to experience a sensation of upper abdominal pressure or pain. Sometimes HCC is an incidental finding revealed by ultrasonographic studies.

Liver resection. The treatment approach for patients with HCC and without cirrhosis should be based on factors such as extrahepatic tumor manifestation, tumor size, the number and distribution of nodules, the relationship of the tumor to local anatomic landmarks, and the functional reserve capacity of the remaining parenchyma. In such patients, curative resection should be considered whenever possible.

Pretreatment imaging studies such as high-resolution triple-phase CT and MRI, either with or without angiography, can be used to match patients and their most appropriate treatment. Positron emission tomography (PET) is also useful in the identification of extrahepatic metastases that considerably influence clinical decision-making. These types of studies aid in detecting intrahepatic and extrahepatic disease, vascular invasion, and underlying liver disease (especially cirrhosis). Knowledge about the relation of the tumor to regional anatomic structures such as large vessels is crucial because it provides valuable information about resectability. Furthermore, volumetric studies can be used to define the residual parenchyma exactly. If there is any suspicion of lymph node metastasis or peritoneal dissemination, diagnostic laparoscopy with intraoperative ultrasonography is useful, and if multiple metastases are confirmed, explorative laparotomy can be prevented as a result of upstaging [38].

The determination of hepatic reserve is also significant when resection is considered. The healthy liver has a great capability for regeneration and adjusts to the metabolic requirements of the host after liver resection due to hypertrophy of the residual liver. Therefore, even in patients with a large tumor, extensive resection is possible. In an otherwise healthy liver, up to 75% of the parenchyma can be resected.

Patients with a localized unilobar tumor in a noncirrhotic liver or Child class A cirrhosis with adequate remnant liver parenchyma may be considered for partial hepatectomy (lobectomy). Partial hepatectomy usually ensures a safety margin of at least 1 cm and is associated with an operative mortality rate of less than 5% [39, 40]. From an oncologic perspective, anatomic resection that may include satellite lesions is more effective than limited resection without a surrounding margin. Therefore, only the presence of small peripheral tumors without vascular invasion justifies a segment-orientated resection. For patients with inadequate or borderline remnant parenchyma, hypertrophy of the prospective liver remnant can be induced by preoperative portal vein embolization [41]. However, the use of portal vein embolization of the hepatic lobe that hosts the tumor to induce compensatory hypertrophy in the nonaffected liver before major resection is controversial. Uncontrolled tumor progression as a result of the proliferation of malignant cells stimulated by this method and the risk of variceal bleeding resulting from acute portal hypertension are some of the concerns [42]. In certain circumstances, an unfavorable location of the tumor and involvement of the confluence of the 3 hepatic veins and either the caval vein or the retrohepatic caval vein can render resection by conventional techniques impossible. In these rare cases, special techniques such as in situ or ante situm resection can be used [43].

The overall long-term results after resection are favorable. However, only 20% to 30% of patients with HCC are eligible for resection because of advanced or multifocal disease or inadequate functional hepatic reserve [44]. In patients with solitary lesions of less than 5 cm, no vascular invasion, and a negative surgical margin of at least 1 cm, the 5-year survival rate after resection has been reported to be greater than 70% [33]. In a series consisting of 68 patients with HCC in a noncirrhotic liver, an overall 5-year survival rate of 40% was achieved even when extensive resection had been performed. Thirty-three percent of those patients remained free of recurrence [45]. Similar results were observed in a large series in which patients with HCC in a noncirrhotic liver demonstrated a survival rate of 58% after 3 years and 42% after 5 years [46]. Another study revealed that the results of resection depended on the tumor stage: In patients with stage I or stage II

HCC, a 5-year survival rate of 63% was noted, and in those with stage III HCC, a survival rate of 51% was observed [47]. Despite earlier detection, safer surgical procedures, and more aggressive treatment of HCC, recurrence (as a result of multicentric carcinogenesis or intrahepatic metastases from the primary tumor) is likely. In selected patients, repeat resection provides good long-term benefits and is an option for those with solitary peripheral tumors that can be treated with segmental or atypical resection. In patients with adequate functional reserve capacity and no extrahepatic tumor growth, the 5-year survival rate after repeat resection has been reported to be as high as 86% [48].

Liver transplantation. When compared with liver resection, the results of liver transplantation in patients with HCC and without cirrhosis are less favorable. Previous studies have shown that patients who underwent liver transplantation for HCC fared no better than those who underwent resection, unless coexisting cirrhosis was present [49]. The reported 3- and 5-year survival rates were 30% and 26%, respectively, in noncirrhotic patients who underwent transplantation for HCC and 45% and 38%, respectively, in patients with HCC and cirrhosis [47]. The lack of sufficient liver donation is an additional major limitation to the use of liver transplantation. Therefore, transplantation is not indicated for patients with HCC in a noncirrhotic liver. However, subsets of patients, such as those with tumor recurrence after prior extensive resection or inadequate hepatic reserve, may benefit from liver transplantation. In such cases, the duration of disease-free survival and the age of the patient should be considered [50].

HCC in patients with cirrhosis. For HCC in patients with cirrhosis, choosing the most appropriate treatment option is difficult because HCC is a tumor of multicentric origin. In most of those patients, who often present in poor physical condition, preexisting liver damage has preceded the development of the tumor [1, 51]. Portal hypertension and (in particular) the reduced functional capacity of the cirrhotic liver significantly increase the perioperative risk. In addition, cirrhosis is usually a precancerous stage that is associated with the risk of multifocal tumor development, which considerably increases the risk of recurrence. These facts influence 2 significant decisions regarding surgery: patient selection and the choice of the surgical therapeutic method. When compared with resection, transplantation has the advantage of eliminating HCC as well as precancerous tissue.

Liver resection. When indications for resection are considered, long-term survival provided by other therapeutic options and the maintenance of adequate liver function should be kept in mind [52]. The resection margin of HCC in cirrhotic patients does not represent a significant predictive factor for recurrence, unless residual tumor directly invades the raw surface of the liver [53]. In most HCC patients, tumor recurrence results from disseminated tumor, and in the remaining patients, recurrence is caused by metachronous tumors that arise in the oncogenic cirrhotic liver, as is typical in the cirrhosis that develops after hepatitis C infection [52]. Because it is difficult to prevent recurrence by resection with an adequate safety margin, resection (preferably segmentectomy or subsegmentectomy rather than wedge resection) should be as limited as possible [54]. Because of the threat of insufficient liver function coupled with a greater risk of mortality, the decision to perform major resection should be considered with caution.

The reduced functional reserve capacity in patients with cirrhosis of the liver limits the choice of surgical therapy. Various tests have been developed to quantify liver function. The hepatic reserve can be estimated by means of the traditional Child Turcotte Pugh (CTP) classification. In general, Child class A or Child class B patients may tolerate a resection of up to 50% and 25% of liver parenchyma, respectively [55]. However, evaluating hepatic reserve by means of the CTP classification may lead to an inconsistent predictive value, because as Child class A patients may already have significant functional impairment and may demonstrate an increase in the bilirubin level as well as portal hypertension and fluid retention [56]. These features indicate advanced liver disease and preclude resection. Limited discriminatory ability, subjective interpretation of parameters, and variability in the measurement of laboratory parameters are further limitations of CPT. Therefore, in Europe and North America, the selection of optimal candidates for liver resection is usually based on the degree of portal hypertension and an elevated bilirubin level. A bilirubin concentration that is within normal limits and a hepatic vein pressure gradient of less than 10 mm Hg (measured by hepatic vein catheterization) are the best predictors of excellent outcome after resection and are associated with almost no risk of postoperative liver failure [57]. A platelet count below 100,000/mm^3 and splenomegaly are good indicators of portal hyper-

tension [37]. The hepatic reserve can also be assessed by monitoring the clearance of indocyanine green (ICG) [58], a compound that is cleared rapidly by liver cells and is excreted in unconjugated bile. In that evaluation, the decision of whether surgery is feasible is based on the degree of retention of the dye. In a healthy liver, the amount of ICG remaining in the blood circulation of the patient 15 minutes after its injection is less than 10% [59, 60]. If that level is greater than 40%, postoperative liver failure is likely, even with minimal resection. Apart from the factors mentioned above, the patient's nutritional state and the presence of concomitant diseases such as diabetes mellitus or coronary heart disease are also important and may influence outcome after resection.

Refined selection criteria and technical advances, including a broader knowledge of segmental anatomy, vascular occlusion techniques, and the use of intraoperative ultrasonography, have facilitated resection and improved outcome. Operative mortality rates have decreased to less than 5% [46]. A considerable decrease in intraoperative blood loss has been achieved by means of numerous technical improvements such as the use of ultrasonographic dissectors and bipolar and argon beamer coagulation. In individual cases, hilar occlusion (the Pringle maneuver) has become either unnecessary or the occlusion time can be shortened, both of which result in reduced ischemia-reperfusion damage. Despite a decrease in the operative mortality rate and improved results after resection, overall survival after the resection of HCC has changed little. Five-year survival rates exceeding 40% have been reported [61, 62], but at present, the interval of disease-free survival is shorter. The most significant predictive factors for early recurrence are the size and number of tumors, the presence of satellite nodules, the histologic grade, the severity of cirrhosis, and the serum AFP level [63]. Tumor size and the number of nodules are important factors that predict vascular invasion. According to 1 multicenter study, vascular invasion that predicted early recurrence and poor prognosis was present in 55% of the patients with tumors ranging in size from 5.1 to 6.5 cm and in 31% of patients with tumors 5 cm or smaller [62]. Tumor size is also a significant predictor of advanced tumor grade. According to the results of 1 study, a tumor size larger than 5 cm was an indicator of high histologic grade in more than 40% of patients with HCC [64].

Liver transplantation. Despite the difficulty of exposing patients to the risks and consequences of transplantation-associated immune suppression, liver transplantation is the ultimate treatment option in patients with HCC who fulfill the selection criteria. Transplantation restores liver function and ensures the removal of all hepatic foci of tumor as well as tissue with a high oncogenic potential for early tumor recurrence. Study results have generally shown a significantly higher probability for survival in patients with incidentally discovered tumors, no vascular invasion, a negative nodal status, a tumor size of less than 5 cm, and a tumor of lower histologic grade [47, 64-68]. Ringe and colleagues [47] demonstrated a 5-year survival rate of 26% after resection and a 69% survival rate after transplantation in cirrhotic patients with HCC. The decisive prognostic factor for patients with HCC is vascular invasion, which no system of medical imaging can accurately demonstrate at this time [69]. Therefore, the preoperative prognosis is still based on the number and size of tumor nodes demonstrated, because vascular invasion correlates with tumor size and number [64].

Because of the present lack of organs available, an accurate estimation of the patient's prognosis is important, and not every patient with HCC and cirrhosis can be treated with liver transplantation. Thus the need to obtain the optimal benefit from the limited number of organs available has prompted adherence to strict selection criteria, so that only those patients with early HCC and the highest likelihood of survival after transplantation are listed to undergo that procedure. Excellent results can be achieved in patients with solitary tumors of less than 5 cm and in those who have up to 3 tumor nodules, each of which is smaller than 3 cm. Adherence to these criteria (the Milan criteria) for transplantation has resulted in a 5-year survival rate exceeding 70%, a rate similar to that in patients who undergo liver transplantation for a nonmalignant disease [70]. In another study, excellent results were achieved in patients with solitary lesions of a maximum diameter of 6.5 cm, patients with a maximum of 3 lesions (the largest of which was no larger than 4.5 cm), and those in whom all tumor nodes together measured no more than 8 cm in diameter. The 1-year and 5-year survival rates of these patients were as high as 90% and 72%, respectively [71].

The selection criteria for liver transplantation to treat HCC can be expanded. However, the present shortage of liver grafts and the lack of data that define the new limits for liver transplantation in patients with HCC render the attempt to expand the listing criteria a very controversial issue. As a result of expanded listing criteria, the inclusion of patients

with more advanced cancer may result in a higher dropout rate that leads in turn to poor survival rates in an intent-to-treat analysis [72, 73]. Therefore, the ultimate therapeutic choice should always result from the analysis of each individual case and should be based on the experience and judgment of the transplantation team and not just on the statistical results derived from the literature. In our view, the routine expansion of the listing criteria beyond the standard Milan criteria is not recommended.

Methods of neoadjuvant therapy (primarily ablation by percutaneous ethanol injection [PEI] or radiofrequency and transarterial chemoembolization) may be used to provide tumor control in patients on a waiting list for liver transplantation. However, the efficacy of those methods cannot be conclusively evaluated, and when percutaneous methods are used, the risk of puncture-related seeding must be considered, even though the problem of seeding is usually restricted to poorly differentiated or peripheral tumors [74].

The wait for a donor organ to become available still presents the greatest challenge. Patients can reach a prognostically unfavorable stage because of tumor progression with subsequent deterioration of their clinical profile while waiting and may no longer fulfil the criteria for liver transplantation [71]. As a result, these patients must be removed from the waiting list. With a median waiting period of 62 days for transplantation, the 5-year survival rate in 1 study was 84% in patients with small solitary tumors. A median waiting period of 162 days significantly worsened the 5-year survival rate to less than 60% [75]. About 50% of HCC patients who were initially candidates for liver transplantation will become ineligible for transplantation if the median waiting period exceeds 1 year [72, 76]. In view of these problems, living-donor liver transplantation (LDLT) is increasingly discussed as an alternative. This option enables patients to avoid the long waiting time before transplantation. LDLT would also increase the number of available livers and is the most effective approach to reducing the dropout rate. The following arguments support the concept of living donation in patients with HCC and cirrhosis:

- Better clinical condition of the patient at the time of transplantation, because LDLT is a scheduled procedure, unlike cadaveric transplantation, which requires urgent surgery.
- Better graft function, because each graft is obtained from a healthy person without underlying major medical or surgical conditions, especially hepatic abnormalities.
- Optimal organ harvest, conservation, and reduced cold ischemia time (and as a result fewer complications and less graft dysfunction).
- A significantly reduced waiting time, a reduced risk of tumor progression, and potentially better long-term survival.

Whether LDLT is indicated in patients with HCC that exceeds the Milan criteria remains controversial [77, 78]. A recent survey of transplant surgeons from North America, Europe, and Asia revealed that 41% of the respondents favored LDLT for use in patients with HCC that exceeds the Milan criteria [79]. Patients who no longer fulfil the criteria because of tumor size or the number of tumor nodes may still retain the option of LDLT. Because a potential 5-year survival rate of around 50% in patients whose liver transplantation is justified by extended criteria has been described [72], transplantation would offer a better chance of survival than would all other therapeutic options. The practice of downstaging with the use of chemoembolization, ethanol injection, or radiofrequency ablation and then performing transplantation in patients with extensive HCC has provided gratifying results in some centers [80-82]. In 1 center-based experience, the 1-year recurrence-free survival rate in patients so treated, which was as high as 100%, confirms the benefits of that practice [82]. However, evidence-based universal guidelines for this important issue have not been established. Primary graft failure and the risk to the donor present ethical concerns that cannot be disregarded. Donor deaths and other complications, such as insufficiency of the donor's remaining liver (which required subsequent transplantation), have been reported [83]. The complication rate for liver transplantation in North America and Europe ranges between 9.2% and 40% for the donor, and the mortality risk in donors is still 0.3% to 0.61% [84, 85]. By contrast, data in Japan showed a complication rate of 12% with no perioperative deaths in living liver donors [86]. Meticulous surgical techniques and perioperative management, lean body mass in individual Japanese donors, and genetic factors were given as possible explanations for the zero transplant-related mortality rate in Japan. In general, however, morbidity after living liver donation strongly correlates with the expertise of the staff of the transplant center. Therefore, a combination of surgical expertise and thorough, individualized medical and psychologic evaluations is vital to ensure the lowest morbidity rate and best outcome, not only in the recipient, but also in the donor.

Nonsurgical treatment options

HCC in compromised patients

Percutaneous ablation. For patients who are not candidates for liver resection or transplantation because of poor hepatic reserve or comorbid conditions, percutaneous ablation offers the best treatment option. However, to our knowledge, there are no randomized controlled clinical trials that have compared the results of this treatment option with those of surgical therapy for HCC, and none of the ablation techniques has been shown to offer a definitive survival advantage. The principle of ablation is based on the destruction of tumor cells by the application of chemical substances, such as ethanol, or by using radiofrequency or laser to modify the temperature in the tumor via the delivery of heat. Of all those techniques, PEI has been the most investigated [87]. In individuals who do not fit the optimal surgical profile, PEI is as effective as surgery and is associated with a 5-year survival rate as high as 72% if the accurate selection of patients is performed [22, 87, 88]. The low rate of procedure-related complications and the low cost of PEI are additional advantages. The main drawback of this technique is the need for repeated injections in separate sessions and the inability to achieve complete necrosis in larger tumors.

In that regard, radiofrequency ablation (RFA) has been shown to be more effective in achieving complete necrosis in tumors larger than 2 cm and to require fewer treatment sessions [23]. RFA involves the delivery of energy created by radiofrequency waves to tumors to induce thermal damage and coagulative necrosis. Study results have shown that RFA is superior to PEI in terms of causing complete tumor necrosis (90% vs 80%) and in the number of required treatments (1.2 vs 4.8) [89]. However, RFA causes more complications such as pleural effusion, bleeding, and tumor seeding than does PEI [74, 89]. In addition, the effectiveness of RFA decreases as the tumor size exceeds 3 cm.

Chemoembolization. This approach can be used before liver resection to improve resectability, as a bridge to liver transplantation while awaiting organ availability, or as a palliative treatment, and it may offer patients with preserved liver function and no evidence of ascites a survival advantage [24]. Chemoembolization is based on the principle of arterial obstruction (obstruction of the hepatic artery during angiography via the use of agents such as an absorbable gelatin sponge, alcohol, etc, to induce ischemic tumor necrosis). This technique is effective because the growth of HCC depends primarily on the hepatic artery blood supply, but the healthy hepatic parenchyma has a dual blood supply (85% is supplied by the portal vein, and the remainder is supplied by the hepatic artery). The injection of a chemotherapeutic agent (usually cisplatin, doxorubicin hydrochloride [Adriamycin], or mitomycin C) before arterial obstruction (transcatheter arterial embolization) results in transarterial chemoembolization (TACE), a method by which regionally elevated levels of these agents in the liver can be achieved while concomitant systemic toxicity is avoided. When compared with controls, patients treated with TACE exhibited a decrease in tumor size of 16% to 61% and a 1-year survival advantage as high as 82% [32, 90-92]. Patients with portal vein thrombosis, decompensated cirrhosis, and end-stage cancer are poor candidates for TACE because of an increased risk of liver failure and death. In properly selected patients, however, this method has been found to be a safe and to offer a consistent improvement in survival.

Systemic treatment. A number of systemic chemotherapies have been evaluated in clinical trials. No single agent or combination of agents given systemically leads to reproducible response rates that show beneficial effect of systemic chemotherapy on survival rates [93]. Tamoxifen, octreotide, interferon, and interleukin-2 have not been shown to be effective in treating HCC in randomized controlled clinical trials [91, 94, 95]. However, there are a number of substances (gemcitabine, thymostimulin, alpha-I-thymosin, pravastatin, thalidomide, several antiangiogenic substances, cox-2 inhibitors) that should be the focus of active clinical research, and further clinical evaluation is necessary to discover effective adjuvant therapies that may reduce disease recurrence and improve survival.

Future strategies

In view of the limited therapeutic options for patients with advanced HCC, the development of new agents and strategies for this group of patients is of major relevance. A number of strategies have been proposed, including the transfection of tumor cells with gene-encoded viruses or synthetic vectors, the use of monoclonal antibodies as a method of cytoreduction, and immunotherapy based on the body's natural defence mechanisms; for example, the triggering of cytotoxic T-lymphocytes by antigen-stimulating cells that can destroy tumor cells effectively [96-98]. Moreover, a recent study has reported good effects of radiation therapy

in the treatment of unresectable HCC [99]. In the future, that method may provide local control of advanced HCC.

In conclusion, treatment options for patients with HCC must be selected on the basis of the patient's condition, the number and size of the hepatic tumors, the functional reserve capacity, and the available resources. For noncirrhotic patients with HCC who qualify for surgery, liver resection is the only treatment option. The surgical options for cirrhotic patients with HCC are liver resection and liver transplantation. Because of the threat of insufficient liver function coupled with a greater risk of mortality, resection should be limited to a very select group of patients. When the decision to resect is made, the possibility of a high rate of early recurrence from the multifocal growth of HCC in patients with cirrhosis, the development of synchronous occult secondary tumors in the liver, and the occurrence of metachronous tumors in patients with persistent cirrhosis must be considered. Primary liver transplantation should therefore remain the ideal choice of treatment for a cirrhotic patient with HCC, even when the tumor is resectable. Implementing strategies that reduce tumor growth in patients awaiting liver transplantation is important so that patients with HCC remain suitable to undergo transplantation. In an age in which donors are scarce and the waiting list continues to increase, LDLT has been shown to be a reliable method of providing a life-saving treatment. With an experienced surgical team and the appropriate selection of recipients and donors, the benefits of LDLT to the recipient outweigh the risks to the donor. Thus the possibility of LDLT, which will shorten the waiting period for liver transplantation, should be strongly considered.

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