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Recent advances in the surgical treatment of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. The treatment of HCC is complex and complicated by the severity of associated chronic liver disease, the stage of HCC, and the clinical condition of the patient. Liver resection (LR) is one of the most efficient treatments for patients with HCC, with an expected 5-year survival of 38%-61% depending on the stage of the disease. Improved liver function assessment, increased understanding of segmental liver anatomy from advanced imaging studies, and surgical technical progress are important factors that have led to reduced mortality in patients with HCC. The indication for LR may be expanded due to emerging evidences from laparoscopic hepatectomies and combined treatments with newly developed chemotherapies. Liver transplantation (LT) is considered as an ideal treatment for removal of existing tumors and the injured/pre-neoplastic underlying liver tissue with impaired liver function and the risk of multicentric carcinogenesis

that results from chronically injured liver. However, LT is restricted to patients with minimal risk of tumor recurrence under immunosuppression. The expansion of criteria for LT in HCC patients is still under trial and discussion. Limited availability of grafts, as well as the risk and the cost of transplantation have led to considerable interest in expansion of the donor pool, living donor-related transplantation, and combined treatment involving LR and LT. This highlight presents evidence concerning recent studies evaluating LR and LT in HCC patients. In addition, alternative therapies for the treatment of early stage tumors and the management of patients on transplant waiting lists are discussed.

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Key words: Hepatocellular carcinoma; Surgical treatment; Hepatectomy; Liver transplantation; Laparoscopic hepatectomy; Tumor thrombi; Chemotherapy

Core tip: Liver resection (LR) is one of the most efficient treatments for patients with hepatocellular carcinoma (HCC). Advances in assessment and treatment, including emerging evidence from laparoscopic hepatectomies and combined treatments with newly developed chemotherapies, may lead to expanded indications for LR. Liver transplantation (LT) is an ideal treatment for chronically injured liver tissue with impaired liver function and risk of multicentric carcinogenesis. The expansion of criteria for LT in HCC patients and combined treatment involving LR and LT are under trial and discussion. This highlight presents and discusses recent studies concerning LR and LT in HCC patients.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the most common primary liver malignancy^[1]. The treatment of HCC is complex and challenging due to its well-known association with chronic liver disease (CLD), which can be caused by viral infection, alcohol consumption, metabolic syndrome, *etc.* The parenchyma underlying chronically injured liver tissue can display various histologic changes, including steatosis, inflammation, fibrosis, and/or cirrhosis. Combined with the risk of multicentric carcinogenesis, these histologic changes limit the possibility of curative treatments, which include liver resection (LR), liver transplantation (LT), and the local ablation of small tumors^[2].

LR is one of the most efficient treatments for HCC^[3,4]. Considerable progress over the past ten years in screening, early radiologic diagnosis, treatment of the underlying liver disease, and surgical techniques has resulted in revision of the indications for LR^[2]. Furthermore, improved liver function assessment, understanding of segmental liver anatomy using more accurate imaging studies, and surgical technical progress are the most important factors that have led to reduced mortality, with an expected 5-year survival of 38%-61%, depending on the stage of the disease^[5]. Despite these advances, less than 30% of HCC patients are eligible for LR^[3,4]. However, emerging evidence from laparoscopic hepatectomies^[6] and the use of combined treatments with newly developed chemotherapies^[7] may lead to expansion of the indication for LR (Table 1).

Impairment of liver function and the risk of multicentric carcinogenesis from chronically injured liver tissue lead to consideration of LT as the ideal treatment for removal of existing tumors and injured/preneoplastic underlying liver. However, LT is restricted to patients with minimal risk of tumor recurrence under immunosuppression^[8]. Expansion of criteria for LT in HCC patients is still under trial and discussion^[9,10]. The limited availability of donor grafts for LT, as well as the risk and cost of the procedure, has led to considerable interest for expansion of the donor pool and living donor-related transplantation^[11], and combined treatments involving LR and LT^[8,12].

This review presents and discusses recent advances in the surgical treatment of HCC (Table 2). Advances in the assessment of liver function are also described, along with discussion of patient management and combinatorial treatment options. In addition, a brief discussion is presented concerning nonsurgical methods that play an important role in HCC treatment, either alone or combined with surgical approaches. These methods include local ablation therapies, such as percutaneous or laparoscopic radiofrequency ablation (RFA)^[13], as well

Table 1 Treatment options for hepatocellular carcinoma within injured liver

Local ablation therapy	Only for small tumors (in size and number)
Liver resection	Most available and efficient treatment Applicable to < 30% of all HCC patients 5-yr survival of 38%-61% depending on the tumor stage 80% of patients recur within five years after resection
Liver transplantation	Ideal treatment for removal of existing tumor and underlying injured/preneoplastic tissue Tumor progression while on waiting list Patients with advanced/extensive HCC have very poor outcomes

HCC: Hepatocellular carcinoma.

Table 2 Summary of recent advances in liver resection for hepatocellular carcinoma

Established	<ul style="list-style-type: none"> Screening and early detection for high-risk patients (<i>i.e.</i>, with HCV or HBV infection, alcoholic, metabolic chronic liver disease, <i>etc.</i>) Diagnosis with contrast-enhanced imaging for the detection of early lesions Assessment of liver function (Child-Pugh classification, indocyanine green retention test, MELD score) Modulation of residual liver function with preoperative portal vein embolization Anatomic resection removing undetectable disseminated tumor foci in the same portal territory
Under discussion	<ul style="list-style-type: none"> Three dimensional-CT-assisted preoperative surgical planning facilitates: <ul style="list-style-type: none"> Unconventional types of liver resection Laparoscopic liver resection could be beneficial: <ul style="list-style-type: none"> For patients with severe liver dysfunction with lower morbidity For repeat resection As a bridging therapy for liver transplantation
Under trial or proposal	<ul style="list-style-type: none"> Adjuvant and/or combined therapy for advanced tumor Sorafenib Intraarterial 5-FU plus IFN therapy for hepatocellular carcinoma with VTT

CT: Computed tomography; HBV: Hepatitis B virus; HCV: Hepatitis C virus; IFN: Interferon; MELD: Model for end-stage liver disease; VTT: Venous tumor thrombosis; 5-FU: 5-Fluorouracil.

as a newly developed and promising approach involving transarterial radioembolization with radioactive substances such as ¹³¹I-iodine-labeled Lipiodol^[14] or microspheres containing yttrium-90^[15].

LIVER RESECTION

The largest study concerning LR for the treatment of HCC is from the Liver Cancer Study Group in Japan, which involved 27062 resected HCC patients treated between 1992 and 2003^[16]. This study reported 1-, 3-, 5-, and 10-year survival rates of 87.8%, 69.2%, 53.4%, and 27.7%, respectively, which are comparable to rates reported by other groups worldwide, without differences between Western and Eastern countries. Survival rates

as high as 60% at five years could have been achieved in Child-Pugh A patients with well-encapsulated tumors of ≤ 2 cm in diameter. Results from patients with good liver function and anatomic LR according to the architecture of the portal vein (although less than 10% of all patients) were comparable with those from patients with LT.

There are reports describing that significantly better overall and disease-free survival rates are achieved with anatomic LR for small solitary HCC compared to limited resection, without increasing the postoperative risk^[17,18]. Intrahepatic metastasis of HCC along the portal vein and the presence of satellite nodules within 2 cm of the main nodule is the basis for anatomic LR^[19], which involves the complete removal of tumor-bearing portal territory. Anatomic LR has the potential to remove undetected cancerous foci (portal vein metastases and satellite nodules) disseminated from the main tumor, and thus is recommended when possible in many reports.

The indication for and extent of LR in patients with HCC is influenced both by tumor extension and the severity of liver dysfunction. For the treatment of HCC patients with CLD, the degree of invasive surgical stress, especially to the impaired liver, should be considered in addition to the oncologic therapeutic effects. Patients with severe CLD can present with various signs (overt and preliminary), such as (1) deterioration of protein synthesis and metabolism; (2) gastrointestinal tract congestion, ascites, pancytopenia due to portal hypertension and hypersplenism; and (3) susceptibility to infectious diseases and hepatopulmonary syndrome (hypoxemia) due to increased shunt vessels^[20]. Cirrhotic patients have high morbidity and mortality following anesthesia and surgery^[21] and the risk from abdominal operations increases according to the preoperative Child-Pugh classification^[22] of the patients^[23].

Major histologic changes that are observed in patients with HCC can range from mild fibrosis (F1) to cirrhosis (F4). Patients with cirrhosis have a lower rate of regeneration after LR, more frequent association with portal hypertension, and a higher risk of tumor multiplicity/recurrence^[12,24]. Even in the absence of extensive fibrosis, steatosis and inflammation can also have a significant influence on the course after LR. The diseased liver parenchyma presents an operative risk due to the altered texture of the liver parenchyma, impaired liver regeneration, and deteriorated liver function, which lead to coagulation defects, increased risk of infection, *etc.*^[25]. Moreover, there is a close relationship between the volume of resected liver and postoperative morbidity/mortality of LR in patients with CLD. Therefore, there is limited indication for LR in cases of large tumors or small but centrally located tumors^[26]. LR in patients with HCC and CLD is complicated by the fact that it should be curative with the resection of the tumor vascular territories yet also preserve as much liver volume as possible to prevent postoperative liver failure.

Assessment and modulation of remnant liver function

A small remnant liver volume is associated with poor

postoperative liver function and a high mortality/morbidity after LR^[27]. Although the safety limit for the remnant liver volume in patients with normal liver is approximately 30% of the total liver volume (TLV), it is generally thought that a remnant liver volume of 40%-50% should be preserved in patients with CLD^[28]. The liver is characterized by its capacity to ensure normal function with a reduced functional volume and the ability to regenerate. However, the extent of fibrosis in the remnant liver, portal flow, and other factors can affect the ability of the liver to regenerate. Thus, the volume of future liver remnant (FLR) that is adequate will vary from patient to patient. Although the aim of preoperative assessment of liver function is to prevent postoperative liver failure, determining the postoperative functionality of a reduced-volume FLR and its capacity to regenerate is difficult. As there are no reliable stress tests to assess potential liver function, preoperative assessment in patients with CLD involves a combined interpretation of several biologic, morphologic, histologic, and hemodynamic factors.

One widely used method of biologic assessment is the Child-Pugh classification, which provides scores from grade A to C and was originally designed for predicting the prognosis of patients with portal hypertension undergoing shunting operations^[19]. Resection is contraindicated in grade C cirrhotic patients and restricted to very limited resection in grade B cirrhotic patients^[29]. However, the risk from liver surgery is increased even in grade A cirrhotic patients with apparently normal liver function, which necessitated the development of more sophisticated, quantitative liver function tests. Among the various methods available, the indocyanine green (ICG) clearance rate represents the most common test for predicting mortality after hepatectomy^[30,31]. A normal ICG rate in healthy patients is approximately 10%, and cutoff values predictive of safe major hepatectomies range from 14% to 17%^[32,33]. Minor resections can be performed for ICG clearance rates of up to 22%^[34], limited hepatectomies (without sacrifice of non-tumorous liver) for values up to 40%^[26], and limited wedge laparoscopic resections can possibly be tolerated for even higher values^[35,36]. The model for end-stage liver disease (MELD) score, which has been validated as an accurate predictor of survival among different populations of patients with advanced liver disease^[37,38], has only been retrospectively studied in two series of cirrhotic patients who had undergone LR for HCC^[37,38]. These studies indicated that a MELD score > 8 was associated with a higher risk of mortality, morbidity, and impaired long-term survival in these patients.

Preoperative portal vein embolization (PVE), first introduced by Makuuchi *et al.*^[39], has been widely recognized as an effective method for the preoperative volume modulation of small FLR. However, the degree of hypertrophy of the FLR after PVE is variable in patients with CLD^[27,40]. The absence of early hypertrophy in non-embolized liver following PVE is considered to be an indicator of low regenerative capacity that would contraindicate LR. Thus, the response to PVE represents a

valid dynamic stress test before major LR^[41]. It has been shown that sequential selective transarterial chemoembolization (TACE) before PVE can increase the rate of hypertrophy^[41,42], which may be effective for treatment of HCC in the event of inadequate FLR hypertrophy. As an additional means of anticipating postoperative liver failure, there are several reports using volumetric data from computed tomography (CT) to evaluate FLR volume proportional to body weight, body surface area, and TLV^[43,44], and to determine the hypertrophy rate from the FLR/TLV ratio^[45].

Anatomic resection and imaging

The anatomic territory of HCC, determined by the tumor size and location, can range from a subsegment to an entire lobe of the liver. Although anatomic resections are effective for treating small solitary HCCs, the benefit of segmental resection may only become apparent in tumors between 2 and 5 cm. Tumors < 2 cm in size, considered to have negligible risk for dissemination, can be treated by local ablative therapy with equal efficacy. For the tumors > 5 cm, the majority of patients will already have macroscopic vascular invasion or satellite nodules, leading to a high incidence of recurrence^[46]. In the case of central tumors with undefined vascular territory, recurrence rates and greater survival have been reported with 2 cm surgical margins compared to 1 cm margins^[47], though other studies report no difference between margins smaller or larger than 1 cm^[48,49]. However, an adequate margin of LR also depends on the tumor type (with/without capsules, with/without invasion outside the capsule, *etc.*), and is still under discussion.

Three-dimensional CT-assisted preoperative surgical planning allows for determination of resectability and changes to the operative strategy (resection modifications/extensions, intrahepatic vascular reconstructions, study of portal distribution and hepatic vein anatomy for adequate venous drainage, and study of biliary distribution for avoiding biliary fistula)^[50]. Preoperative surgical planning that incorporates imaging is particularly helpful for procedures requiring unconventional resection planes and/or involving central tumors. Furthermore, it allows for the adaptation of complicated anatomic LR to a greater number of patients, such as the adaptation of sub-subsegment anatomic LR for small tumors in highly injured liver and anatomic LR of combined territories for deep centrally-located tumors.

Laparoscopic LR

First successfully reported in 1992^[51], laparoscopic LR is a less invasive procedure than conventional open LR for the treatment of hepatic lesions^[52]. A comprehensive meta-analysis of 26 studies involving 1678 patients found that although laparoscopic LR procedures were associated with longer operating times, the oncologic outcomes were not different from open LR^[53]. However, there were advantages associated with laparoscopic LR, such as reduced blood loss, decreased portal clamp time, decreases

in overall and liver-specific complications, and shorter post-operative hospital stays. The recent technologic development of devices and accumulation of experience have led to an expansion of the indication for laparoscopic LR^[6,54].

Laparoscopic hepatectomy has the benefit of earlier intake, recovery and discharge, and reduced postoperative pain^[55]. The safety and feasibility of the laparoscopic approach and its short-term benefits for HCC patients with CLD have been demonstrated by many studies^[36]. Tranchart *et al*^[56] also reported better postoperative outcomes, without long- or short-term oncologic consequences, following laparoscopic LR of HCC for select patients. Laparoscopic LR may be particularly advantageous for patients with severe CLD, who often develop refractory ascites with open LR, which leads to fatal complications^[57,58]. Laparoscopic LR has the advantage of minimal ascites^[59], due to preservation of venous and lymphatic collateral circulation, which leads to lower risk of disturbance in water and/or electrolyte balance and hypoproteinemia that could trigger fatal liver failure. This feature could be the most remarkable specific advantage for laparoscopic LR. On the other hand, there are also disadvantages of laparoscopic hepatectomy, such as the motion restriction of the forceps on manipulation, the lack of sensation and 3-dimensional view, difficulty on handling large volume mass, the lack of good overview of operative field. Several strategies, such as uses of magnified view and multiple conversions of positioning during surgery for the use of gravity on the dissection (which is more easily used in laparoscopic than open operation), preoperative simulation with 3D-CT imagings, are applied to overcome these disadvantages. Therefore, there is a learning curve for laparoscopic hepatectomy, which surgeons should be experienced. Viganò *et al*^[59] demonstrated a learning curve effect by outcomes improvement in operative time, conversion rate, blood loss, need of pedicle clamping and its duration, postoperative morbidity, and hospital stay and reported that the shape of the learning curve is similar to left-sided colonic surgery, changing its direction after the 60th consecutive case. They also mentioned the results suggest that Laparoscopic hepatectomy is reproducible in centers regularly performing liver surgery, but requires specific training to advanced laparoscopy.

Patients who undergo LR are exposed to three different types of stresses: (1) general, whole-body surgical stress; (2) reduced liver function due to resected liver volume; and (3) surgery-induced injury of liver parenchyma and surrounding area, caused by destruction of the collateral blood/lymphatic flow by laparotomy and mobilization of the liver, and parenchymal injury by compression of the liver. Reduction of surgery-induced injury with laparoscopic LR should lower the risk for HCC patients with severe CLD. Laparoscopic LR also results in improved vision and manipulation in a small operative field under the proper conditions, including repeat hepatectomy with adhesions^[60]. These characteristics indicate

that laparoscopic LR may be superior to open LR under certain conditions. The laparoscopic procedure could also be an optional bridging therapy to LT for certain HCC patients with severe CLD.

Adjuvant and/or combined therapy for LR

Recurrence occurs in up to 80% of patients five years after LR^[61]. Two-thirds of these are early recurrences, occurring within two years, which is considered as dissemination from the original tumor^[62]. The factors related to this recurrence are tumor size, microvascular invasion, satellite nodules, α -fetoprotein levels, and nonanatomic resection. A large portion of delayed recurrences (after two years) may correspond to “*de novo*” tumors in the oncogenic chronically injured liver^[63]. Delayed recurrences are associated with the presence of cirrhosis (F4), hepatitis activity, and multi modularity, in addition to vascular invasion, and moderately or poorly differentiated HCC^[62].

Several strategies have been tested to prevent recurrence, such as preoperative chemoembolization^[64], chemotherapy, internal radiation^[65], adoptive immunotherapy^[66], and treatment with retinoids^[67]. Treatment with interferon is favored based on results of two meta-analyses^[68,69], though few good-quality studies are available. The efficacy of interferon and whether the effect is on early recurrence as an anti-cancerous agent or on delayed recurrence through the control of CLD activity, are still under discussion. The efficacy of sorafenib in advanced stages^[70] has encouraged evaluation of its use in earlier phases of the disease, with trials ongoing. However, there is no proven neoadjuvant therapy that can decrease or delay the incidence of intrahepatic recurrence after LR^[71]. Despite the fact that TACE can downstage HCC, prospective trials have failed to show any significant benefit of this treatment before LR^[72,73]. Although recurrence following LR is associated with a poor outcome in most cases, there is growing evidence that some patients with only intrahepatic recurrence will benefit from more aggressive approaches^[74,75]. Multimodality therapy of recurrence, including TACE, percutaneous ablative therapy, and re-resection could result in prolonged survival for recurrent patients, with an overall 5-year survival rate of 20%^[74].

Vascular invasion of HCC, particularly portal and hepatic venous tumor thrombus (VTT), is one of the indicators of patient prognosis, and the development of tumor thrombi in a major branch of the veins is a frequent terminal feature of HCC. The prognosis of such patients is extremely poor, and survival is limited to a few months after diagnosis^[76-78]. For these advanced HCCs, conventional therapies like TACE and percutaneous ablative therapy are not indicated due to lack of efficacy and associated complications^[78,79]. LT is also a contra-indication for such cases^[80]. Although several reports suggest LR is feasible for patients with VTT, the outcome is unsatisfactory, with a median survival of 6-12 mo^[76,77,81,82], except for the cases with VTT located in the segmental or sectoral branches^[83]. Several approaches, including combined

radiotherapy and TACE, have been attempted to improve the outcome with unsatisfactory results^[84-87]. There are recent reports showing that combination therapy with interferon- α and trans-arterial 5-fluorouracil is a promising candidate for treatment of advanced HCC with VTT and intrahepatic metastasis^[88-90], and as a postoperative adjuvant^[91] and a multimodal treatment^[7] for resectable HCC. Several clinical trials are currently underway to further evaluate this combination therapy.

LIVER TRANSPLANTATION

LT is the ideal treatment for the removal of existing tumors and replacement of chronically injured and pre-neoplastic liver. Furthermore, it also prevents the development of postoperative complications associated with portal hypertension and liver failure. LT is not limited by liver function, and in select patients with limited tumors, survival is similar to LT for other indications^[92,93]. However, patients with extensive HCC have very poor outcomes, whereas most patients with small tumor loads can be cured. Due to the shortage of available organs, there are discussions concerning the selection of patients with HCC for LT, and the control of tumors in patients on the waiting list^[94]. Furthermore, an international consensus conference (involving 300 experts from five continents) was recently held in order to develop internationally accepted standards and guidelines^[95].

Criteria for listing candidates

A meta-analysis conducted by Germani *et al*^[96] found that the diameter of the largest nodule or total diameter of nodules was the best predictor of post-transplant recurrence and survival. Patients with HCC within the Milan criteria (MC; solitary HCC \leq 5 cm or up to three nodules of \leq 3 cm)^[80] had a 5-year survival of 70% after LT, which matches survivals for other indications, with recurrence in less than 10%. Mazzaferro *et al*^[97] recently showed that the MC is an independent prognostic factor for outcome after LT. The MC was recommended by the international consensus conference as the current benchmark for the selection of HCC patients for LT and the basis for comparison with other suggested criteria^[95]. However, evidence suggesting good outcomes in some patients outside the MC has led to attempts to expand the criteria. At the University of California, San Francisco (UCSF), one of the first attempts was made to include single tumors \leq 6.5 cm or two to three tumors \leq 4.5 cm, with a total tumor diameter \leq 8 cm (UCSF criteria)^[9]. Although the study was retrospective and used post-transplant pathologic staging instead of pre-transplant image staging, retrospective analyses by the authors and others showed survival rates were equivalent to those of patients who underwent LT within the MC^[98-100]. An additional multicenter study that used pre-transplant image staging found that survival rates were lower in patients within the UCSF criteria compared to those meeting the MC, though the difference was not statistically significant^[101]. Independent

Table 3 Summary of recent advances in liver transplantation for hepatocellular carcinoma

	Established	Under discussion	Under trial or proposal
Criteria for listing candidate	The Milan criteria: Solitary tumor of ≤ 5 cm or up to 3 nodules ≤ 3 cm 5-yr survival of 70% with recurrence in less than 10%	The UCSF criteria: Single tumors ≤ 6.5 cm or 2-3 tumors ≤ 4.5 cm, with a total tumor diameter ≤ 8 cm	Add parameters for biologic features of tumors related to risk of recurrence (AFP, PIVKA-II, <i>etc.</i>) Expansion of criteria for living donor-LT
Management on the waiting list (about 40% dropout rate at 12 mo)	Local ablation therapy and TACE are performed without solid evidence	Different models have been developed to quantify the risk of death in neoplastic and non-neoplastic patients Association with liver resection: "bridging resection" to transplantation and "salvage transplantation" following resection	Application of living donor-LT to shorten the waiting time Candidate selection with information from precedent therapy (histologic specimen, response to locoregional therapy, <i>etc.</i>)

AFP: α -fetoprotein; PIVKA: Protein induced by vitamin K absence; LT: Liver transplantation; TACE: Transarterial chemoembolization; UCSF: University of California, San Francisco; HCC: Hepatocellular carcinoma.

studies from the UCSF group and a group from the University of California at Los Angeles found similar results of LT in HCC cases, with 5-year survival rates of 80.9% (median follow-up: 26 mo) and 64% (mean follow-up: 6.6 years), respectively^[102,103]. Although most studies have proposed expanded criteria based on tumor number and size as an estimate of tumor load, additional parameters concerning tumor biologic features related to risk of recurrence have also been proposed^[10] (Table 3).

In addition to expanding the criteria for recipients of LT, the acceptance of marginal livers (advanced age or steatotic organs, non-heart beating, hepatitis C virus-infected) and domino or split LT have been considered. Living donor-LT has emerged as the most feasible alternative to cadaveric-LT for early HCC in patients with waiting times exceeding seven months^[11]. However, a massive expansion of the criteria to include patients with larger tumor loads may significantly constrain the outcomes of transplantation. With the certain morbidity/mortality of the donor, it is of concern to put a donor at risk for an uncertain recipient prognosis^[104].

Management on the waiting list

While on the waiting list for LT, HCC patients can experience tumor growth beyond the LT criteria resulting in a high cumulative probability of dropout from the waiting list. This probability ranges from between 7% and 11% at six months to approximately 38% at 12 mo after enrollment as determined by two reports from the late 1990s^[105,106]. Accordingly, strategies to increase the donor pool and diminish the dropout rate due to tumor progression became a priority in many centers. Allocation policies for HCC patients awaiting LT remain controversial in the era of the MELD score. Different models have been developed to quantify the risk of death in neoplastic and nonneoplastic patients^[107-111]. As the neoplastic risk assessment is not considered in MELD scoring, patients with unresectable HCC within the MC have been considered exceptions in the American allocation system. Patients with HCC fulfilling the MC enter the waiting list with a MELD score equal to 22 and receive incremental points for every three months spent on the waiting list^[112,113].

The 22 threshold was set to offer HCC patients the same dropout probability as patients without malignancy^[114].

For HCC patients listed within the MC, a delay of over six to 12 mo for LT without bridging treatment is a well-recognized risk factor for tumor progression and dropout from the list, or interval dissemination with post-transplant tumor recurrence^[105,106,114]. If a longer wait-time is needed, the use of bridging treatments is recommended in many guidelines^[94,95,115]. However, there is no evidence that bridging treatments are useful in patients with early stage HCC^[95]. Although no specific nonsurgical bridging therapy is recommended over another^[95], RFA could be the first-line treatment for lesions up to 3 cm, in which complete tumor necrosis has been shown in more than 50% of cases^[116]. Percutaneous ethanol injection appears to show lower efficacy and can be reserved for small lesions located in sites considered "dangerous" for RFA (*e.g.*, near the gallbladder or bowel loops). TACE may be preferred for treating lesions > 3 cm, as it may be more effective in well-vascularized large tumors with thick feeding arteries. Multimodal treatment strategies, including sequentially applied TACE and RFA, are also likely to be effective^[117].

Belghiti *et al.*^[118] demonstrated that surgical resection before LT does not increase the surgical risk nor impair survival and stated that resection and transplantation could be associated rather than considered separately. The authors proposed that resection could be used as a bridge to transplantation, especially for tumors located in the upper part of the right liver, which can be easily and completely removed through a transthoracic incision. Similarly, some superficial tumors that are not easily accessible by a percutaneous approach could be resected through a laparoscopic approach. Additional studies have confirmed that LT for recurrence after LR does not increase the operative risk and offers a chance of long-term survival when HCC recurrence is limited^[118-120]. Initial LR of HCC as a primary therapy in patients who otherwise would have received transplants offers a good quality of life and is less demanding than LT. Patients do not need long-term immunosuppression, and grafts can be re-allocated to patients with no alternative to LT^[8,118,119]. "Sal-

Table 4 Overview of current outcomes of liver resection and liver transplantation for hepatocellular carcinoma

Liver resection			
Overall survival after liver resection			
1 yr	3 yr	5 yr	
87.8%	69.2%	53.4%	(Japanese registry, <i>n</i> = 27062) ^[16]
			90% 72% 56% (Multi-center study of the HCC East-West Study Group, <i>n</i> = 2046) ^[5]
Disease free survival after liver resection			
67%	38%	23%	(Multi-center study of the hepatocellular carcinoma (HCC) East-West Study Group, <i>n</i> = 2046) ^[5]
90 d mortality rate: 2.7% Morbidity rate: 42% (Multi-central study of the HCC East-West Study Group, <i>n</i> = 2046) ^[5]			
Overall survival of the patients with massive portal vein invasion after liver resection			
50.4%	25.8%	18.4%	(Japanese registry, <i>n</i> = 976) ^[16]
Liver transplantation			
Overall survival after liver transplantation			
1 yr	3 yr	5 yr	
Within Milan			
91%	85%	79%	(72% of 5 yr DFS, UCLA, <i>n</i> = 467)
		60.1%	(Multi-center study of 14 French institutes, <i>n</i> = 479)
Beyond Milan and Within UCSF			
88%	74%	64%	(64% of DFS, UCLA, <i>n</i> = 467)
		45.6%	(Multi-center study of 14 French institutes, <i>n</i> = 479)
Beyond UCSF			
71%	49%	41%	(UCLA, <i>n</i> = 467)
		34.7%	(Multi-central study of 14 French centers, <i>n</i> = 479)
30 d mortality rate: 5.3% Re-transplantation rate: 4.2% (UCLA, <i>n</i> = 467)			

DFS: Disease free survival; Milan: Milan criteria = Solitary tumor of ≤ 5 cm or up to 3 nodules ≤ 3 cm; UCSF: University of California: San Francisco Criteria = Single tumors ≤ 6.5 cm or 2 – 3 tumors ≤ 4.5 cm, with a total tumor diameter ≤ 8 cm; UCLA: Single center study from University of California, Los Angeles.

vage transplantation” was first proposed by Majno *et al.*^[121] for tumor recurrence or deterioration of liver function in patients after LR as a primary therapy. This concept is applicable to a significant proportion of patients, with long-term survivals similar to those of patients who undergo LT as a primary treatment^[118-120]. Moreover, the response to pre-LT locoregional therapies, including LR, and histologic analysis of specimens (from LR), either in “bridging” or “salvage” settings, can aid in the selection of patients who could most benefit from subsequent LT.

NONSURGICAL TREATMENTS

In addition to surgical treatments, local ablation therapies play important roles in HCC treatment, either alone or combined with surgical approaches. RFA is effective for treatment of early stage (small in number and size) HCC, with complete ablation of lesions smaller than 2 cm in more than 90% of cases^[13]. The advantage of RFA treatment for HCC in cirrhotic patients is that it allows selective destruction of the tumor, sparing the surrounding parenchyma, and can be easily repeated in case of recurrence. In addition to tumor size, the use of RFA is limited in cases where the tumor is adjacent to a major blood vessel, or with subcapsular lesions that can undergo rupture and/or injure adjacent organs. However, the benefit of RFA in the treatment of HCC has been well demonstrated, with overall 5-year survival rates between 33% and 55%^[122]. Rather than competing techniques, RFA and LR are effective therapeutic options that can be chosen based on the severity of CLD as well as the size and location of the tumor. Microwave coagulation thera-

py (MCT) also has been shown to be an effective thermal ablation procedure for the percutaneous treatment of HCC. Compared to RFA, this technique could theoretically provide a larger volume of necrosis and be more effective when treating nodules adjacent to large vessels; however, a clear advantage of MCT with respect to RFA has not been demonstrated^[123,124] (Table 4).

There are also promising results involving the use of transarterial radioembolization with radioactive substances such as ¹³¹iodine-labeled Lipiodol^[14] or microspheres containing yttrium-90^[15], which has been shown to be safe and feasible for the treatment of HCC in cirrhotic patients^[125,126]. This treatment involves the delivery of high-energy and low-penetration radiation to the tumor area. Radioembolization can be safely performed in patients with VTT due to the minimally embolic effect of yttrium-90 microspheres^[127]. The reported rate of complete tumor necrosis is 90% for patients with HCC < 3 cm^[128], whereas the rate of complete necrosis after TACE varies widely in the literature, from 15% to 70%^[129]. However, Y90 is contraindicated in patients with significant hepatopulmonary shunting because it could result in very high levels of pulmonary radiation exposure^[130]. This new and promising treatment should be further examined and the 2010 Clinical Practice Guidelines from the AASLD state that radioembolization cannot be recommended as standard therapy for advanced HCC outside of clinical trials.

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