Review Article

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Current advances made in the surgical treatment of hepatocellular carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is the fifth most common tumor worldwide. Multiple treatment options are available for HCC like curative resection, liver transplantation, radiofrequency ablation, trans-arterial chemoembolization, radioembolization and systemic targeted agent like sorafenib. The treatment of HCC depends on the tumor stage, patient performance status and liver function reserve and requires a multidisciplinary approach. For localized HCC, surgical resection and orthoptic liver transplantation are the gold standard therapies. In the past few years with significant advances in surgical treatments and locoregional therapies, the short-term survival of HCC has improved. Advances in assessment and treatment, including emerging evidence from laparoscopic hepatectomies and combined treatments with newly developed chemotherapies, may lead to expanded indications for liver resection in HCC. 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 investigation and discussion. This review presents and discusses recent studies concerning liver resection and transplantation in HCC patients based on our extensive review of relevant literature.

Keywords: Hepatocellular carcinoma, Trans-arterial chemoembolization, Radiofrequency ablation, Liver transplantation, Laparoscopic hepatectomy

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common form of cancer worldwide and the third most common cause of cancer-related deaths. HCC often occurs in the background of a cirrhotic liver. 1

This makes the treatment of HCC complex and challenging. The parenchyma underlying chronically injured liver tissue can show various histologic changes, including steatosis, inflammation, fibrosis, and cirrhosis. Also there is risk of multicentric carcinogenesis.²

LR is one of the treatments for HCC.^{3,4} Due to considerable progress over the past decade in screening, early radiologic diagnosis, treatment of the underlying liver disease, and surgical techniques has resulted in revision of the indications for LR.² The only staging system currently in use that addresses patients Performance Status (PS) is the Barcelona Clinic Liver Cancer (BCLC) classification. This classification links HCC staging with patient's PS and co-morbidities. This allows for an appropriate treatment strategy and defines the standard of care for each tumor stage. The major advantage of the BCLC system is that it can be used to identify the patients with early-stage HCC, who may

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benefit from curative therapies. This differentiates them from the patients with advanced-stage disease who would benefit more from palliative treatment. American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) have endorsed the BCLC system. 5,6 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. Despite these advances, less than 30% of HCC patients are eligible for LR.^{3,4} However, recent evidence from laparoscopic hepatectomies⁸ and the use of combined treatments with newly developed chemotherapies may lead to expansion of the indication for LR.

Liver Transplantation (LT) is a potentially curative treatment and the best treatment option for the patients with decompensated cirrhosis. However, LT is restricted to patients with minimal risk of tumor recurrence under immunosuppression. Expansion of criteria for LT in HCC patients is still under investigation and discussion. The limited availability of donors for LT, has led to considerable interest for expansion of the donor pool and living donor-related transplantation, and combined treatments involving LR and LT. 9,13

This review presents and discusses recent advances in the surgical treatment of HCC. Advances in the assessment of liver function are also described, along with discussion of patient management.

LIVER RESECTION

Liver resection is the preferred treatment for noncirrhotic patient with HCC. These patients generally have normal liver function, no portal hypertension, and can tolerate major liver resections with acceptable morbidity and low mortality. Liver cancer study group in Japan, has the largest study of liver resections for HCC which involved 27062 resected HCC patients treated between 1992 and 2003. 14 This study reported 1-, 3-, 5-, and 10-year survival rates of 87.8%, 69.2%, 53.4%, and 27.7%, respectively, which are almost similar to survival data reported by other groups worldwide. Surgical resection has an increased risk of hepatic decompensation in the patients with cirrhosis. 15,16 Thus, only patients with wellcompensated cirrhosis, Child-Pugh class A, are considered the ideal candidates for surgical resection. Survival rates as high as 60% at five years could have been achieved in Child-Pugh A patients with wellencapsulated 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.

Patients with severe CLD can present with various signs, such as (a) deterioration of protein synthesis and metabolism; (b) gastrointestinal tract congestion, ascites, pancytopenia due to portal hypertension and hypersplenism; and (c) susceptibility to infectious diseases and hepatopulmonary syndrome (hypoxemia) due to increased shunt vessels.¹⁷ These patients with underlying cirrhosis have high morbidity and mortality following anesthesia and surgery¹⁸ and the risk from abdominal operations increases according to the preoperative Child-Pugh classification¹⁹ of the patients.²⁰

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. 13,21 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.²² 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.²³ 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.

Portal hypertension in cirrhotic patients is considered a relative contraindication for surgical resection according to EASL/AASLD guidelines. In earlier studies Bruix et al.5,24 reported that in Child-Pugh A cirrhotic patients undergoing hepatic resection, the presence of portal hypertension based on Hepatic Venous Pressure Gradient (HVPG) ≥10 mmHg, to be the best predictor of postoperative liver decompensation and poor long-term outcomes. As the measurement of HVPG is an invasive procedure and requires trained expertise, some studies used other surrogate markers of portal hypertension like the presence of esophageal varices or splenomegaly (major diameter >12 cm) with a platelet count of <100000/mm³. Even few recent studies have reported comparable postoperative and long-term outcome in patients with and without portal hypertension using these surrogate markers of portal hypertension. These studies demonstrated that cirrhotic patients with both clinically significant portal hypertension and well-preserved liver function have similar short- and long-term outcomes compared with patients without portal hypertension. Overall surgical results depend not only on the presence of portal hypertension but also on the residual liver function, size of segmental resection and the remnant liver volume. ^{25,26} Prognostic relevance of clinically significant portal hypertension after hepatic resection in

patients with HCC is still a matter for debate as with improvement in anesthesia and surgical techniques, specifically laparoscopic resection, results of surgery are much superior.²⁷ The recent study by Santambrogio et al.28 reported that the presence of clinical portal hypertension alone does not influence the post-operative course of cirrhotic patients who undergo hepatic resection. If strict preoperative selection criteria are met (i.e., Child-Pugh class A patients undergoing resection with a laparoscopic approach and limited segmental hepatic resection) the post-operative mortality rate is very low. Patients without portal hypertension or with clinically significant portal hypertension and preserved liver function (Child-Pugh A5 class) can undergo hepatic resection without hepatic decompensation and good longterm survival, if limited hepatic resection with enough remnant liver volume is done with laparoscopic approach. Recurrence rate correlates with the presence of microscopic vascular invasion, which is present in more than 30% of HCC patients without there being any evidence of macroscopic vascular invasion. 29,30 Early tumor recurrence within two years of surgery is mainly related to local invasion and intrahepatic metastasis. Late recurrence, occurring after two years of surgery, is mainly related to de novo tumor formation. Some studies have shown benefit of adjuvant therapies in decreasing the postoperative recurrence rate. 31-33 Some of the biomarkers (gene signatures or molecular biomarkers) are promising in predicting the late recurrence.³⁴ These biomarkers are likely to improve selection of candidates for surgical resection with lower risk of recurrence. At present, surgical resection is recommended in the patients with early-stage disease and preserved liver function.

ASSESSMENT AND MODULATION OF REMNANT LIVER FUNCTION

A low remnant liver volume is associated with poor postoperative liver function and mortality/morbidity after LR.35 The safety limit for the remnant liver volume in patients with normal liver is approximately 30% of the Total Liver Volume (TLV), but remnant liver volume of 40%-50% should be preserved in patients with CLD. 36 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. The aim of preoperative assessment of liver function is to prevent postoperative liver failure but to determine the postoperative function of a reduced-volume FLR and its capacity to regenerate is difficult. 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.³⁷ Resection is

contraindicated in grade C cirrhotic patients and restricted to very limited resection in grade B cirrhotic patients. ³⁸ It was necessary to develop 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. ^{39,40} A normal ICG rate in healthy patients is approximately 10%, and cutoff values predictive of safe major hepatectomies range from 14% to 17%. ^{41,42} Minor resections can be performed for ICG clearance rates of up to 22%, ⁴³ limited hepatectomies (without sacrifice of non-tumorous liver) for values up to 40%, ²³ and limited wedge laparoscopic resections can possibly be tolerated for even higher values. ^{44,45}

Preoperative Portal Vein Embolization (PVE), first introduced by Makuuchi et al.,46 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. 35,47 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. 48 It has been that sequential selective transarterial shown chemoembolization (TACE) before PVE can increase the rate of hypertrophy, 48,49 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, 50,51 and to determine the hypertrophy rate from the FLR/TLV ratio.⁵²

ANATOMIC RESECTION

There are reports which show significantly better overall and disease-free survival rates achieved with anatomic LR for small solitary HCC compared to limited resection, without increasing the postoperative risk. The basis for anatomic LR is Intrahepatic metastasis of HCC along the portal vein and the presence of satellite nodules within 2 cm of the main nodule, 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 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. 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, though other studies report no difference between margins smaller or larger than 1 cm. However, an adequate margin of LR also depends on the tumor type (with/without capsules, with/without invasion outside the capsule), and is still under discussion.

Three-dimensional CT-assisted preoperative surgical planning allows for To determine the resectability threedimensional CT-assisted preoperative surgical planning is must and it also helps to assess 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).⁵⁹ These imaging are 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 subsubsegment anatomic LR for small tumors in highly injured liver and anatomic LR of combined territories for deep centrally-located tumors.

LAPAROSCOPIC LIVER RESECTION

Laparoscopic LR is a less invasive procedure than conventional open LR for the treatment of hepatic lesions. 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. The advantages associated with laparoscopic LR are, 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. Expansion of the indication for laparoscopic LR.

The safety and feasibility of the laparoscopic approach and its short-term benefits for HCC patients with CLD have been demonstrated by many studies. Tranchart et al. Tranchart

disadvantages of laparoscopic hepatectomy, such as the motion restriction of the forceps on manipulation, the lack of sensation and 3-dimentional 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.

Reduction of surgery-induced injury with laparoscopic LR should lower the surgical stresses as compared to open LR for HCC patients with severe CLD. Laparoscopic LR also results in improved vision and manipulation in a small operative field under the proper conditions, adhesions.⁶⁷ including repeat hepatectomy 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 LIVER RESECTION

Recurrence occurs in up to 80% of patients five years after LR.⁶⁸ Two-thirds of these are early recurrences, occurring within two years, which is considered as dissemination from the original tumor.⁶⁹ 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.⁷⁰ Delayed recurrences are associated with the presence of cirrhosis (F4), hepatitis activity, and multi nodularity, in addition to vascular invasion, and moderately or poorly differentiated HCC.⁶⁹

Several strategies have been tested to prevent recurrence, such as preoperative chemoembolization, 71 chemotherapy, internal radiation, 72 adoptive immunotherapy, 73 and treatment with retinoids. 74

Several clinical trials are currently underway to further evaluate this combination therapy.

LIVER TRANSPLANTATION

Theoretically, liver transplantation is the ideal therapy for HCC in cirrhotic patients because it treats both the cancer as well as the underlying parenchymal disease. However, early experience with transplants produced dismal results. Bismuth et al. was one of the first groups to consider that, in advanced disease, the likelihood of systemic disease was so high that recurrence rates, and therefore long-term outcomes, were unacceptably poor. They demonstrated that patients with limited disease (uninodular or binodular

<3 cm tumors) had much better outcomes with transplant than resection (83% 5-year versus 18%).⁷⁵

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. Furthermore, an international consensus conference (involving 300 experts from five continents) was recently held in order to develop internationally accepted standards and guidelines. 77

CRITERIA FOR LISTING CANDIDATES

Germani et al. 78 conducted a meta-analysis and 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 which fall within the Milan criteria (MC; solitary HCC ≤5 cm or up to three nodules of ≤ 3 cm)⁷⁹ had a 5-year survival of 70% after LT, which matches survivals for other indications, with recurrence in less than 10%. The landmark works of Mazzaferro et al. 80 recently have defined the most commonly used criteria for selection of patients with HCC for transplantation and showed that the MC is an independent prognostic factor for outcome after LT. The suitability of MC for selection of patients for transplantation and being recommended by international consensus conference as the current benchmark for the selection of HCC patients for LT and forms the basis for comparison with other suggested criteria.77

The excellent outcomes of HCC patients within the Milan criteria led many to explore more expansive and inclusive criteria. The most accepted of the expanded criteria is that from the University of California, San Francisco (UCSF), which includes single tumors ≤6.5 cm or two to three tumors ≤4.5 cm, with a total tumor diameter ≤8 cm (UCSF criteria). 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. S1.83

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.⁸⁴

The largest experience to date using transplantation for HCC was reported from the University of California, Los Angeles (UCLA), showed the overall 1-, 3- and 5-year survivals of 82%, 65%, and 52% respectively. 85 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. 11

LIVING DONOR LIVER TRANSPLANT

Because of the shortage of cadaveric livers, Living Donor Liver Transplant (LDLT) has become an increasingly utilized modality for the treatment of patients with decompensated cirrhosis. In many Asian countries, where prevalence of HCC is high, living related transplants are the most common liver transplants performed. Survival outcomes for all patients undergoing LDLT are compatible to the results with deceased donors. 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. See

MULTIMODALITY MANAGEMENT WHILE ON 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 months after enrollment as determined by two reports from the late 1990s[87,88]. 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.^{89,92} 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.⁹³ The 22 threshold was set to offer HCC patients the same dropout probability as patients without malignancy.⁹⁴

For HCC patients listed within the MC, a delay of over six to 12 month 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. 87,88,94 If a longer wait-time is needed, the use of bridging treatments is recommended in many guidelines. 76,77 However, there is no evidence that bridging treatments are useful in patients with early stage HCC. 77

To reduce the likelihood of tumor progression while on the wait list, many local treatments are used, including TACE, percutaneous radiofrequency ablation, or percutaneous ethanol injection.⁷⁵

Although no specific nonsurgical bridging therapy is recommended over another, ⁷⁷ 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. Shown in more than 50% of cases. Mazzaferro et al. reported no dropout for their patients treated with RFA as bridge to transplant, with 3-year survival of 83%. 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. TACE limits wait list dropout, decreases posttransplant recurrence, and can downstage HCC that is beyond transplant criteria. Multimodal treatment strategies, including sequentially applied TACE and RFA, are also likely to be effective.

Belghiti et al.⁹⁷ 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 longterm survival when HCC recurrence is limited.⁹⁷ 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. 97

"Salvage transplantation" was first proposed by Majno et al. 98 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. 97 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.

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