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# Management of Hepatocellular Carcinoma in the Setting of Liver Cirrhosis

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## Abstract

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being the 14th most common cause of death worldwide. Hepatocellular carcinoma (HCC) consists a significant health issue worldwide, responsible for more than 1 million deaths annually. The incidence and mortality rates vary across different geographical areas. Between 60 and 90% of HCC patients already have liver cirrhosis, attributed mainly to chronic hepatitis B and C, alcohol abuse, and non-alcoholic fatty liver disease (NASH). The surgical management of HCC in the setting of liver cirrhosis with curative intent includes liver resection, ablation or microwave coagulation, and liver transplantation (LT). Liver resection in a cirrhotic liver with HCC is associated with lower survival rates compared with liver transplantation (LT), depending on the diseases' stage but on the contrary liver resection could be potentially offered in a larger population compared to liver transplantation. One of the biggest limitations of liver resection is the risk of tumor recurrence, which is high, and it may exceed 70% 5 years after the procedure. Liver transplantation is considered the best treatment for hepatocellular carcinoma at early stages because it removes the tumor as well as the underlying cirrhotic liver.

**Keywords:** liver resection, liver transplantation, HCC, cirrhosis, RFA, TACE

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## 1. Introduction

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being the 14th most common cause of death worldwide. The natural history of cirrhosis is initially compensated and is asymptomatic progressing into decompensated cirrhosis

with portal hypertension and liver dysfunction and in the development of hepatocellular carcinoma (HCC).

Hepatocellular carcinoma consists a significant health issue worldwide, responsible for more than 1 million deaths annually. The incidence and mortality rates vary across different geographical areas [1, 2]. Between 60 and 90% of HCC patients already have liver cirrhosis, attributed mainly to chronic hepatitis B and C, alcohol abuse, and non-alcoholic fatty liver disease (NASH). In the past, HCC was usually diagnosed late during the course of the liver disease, and consequently, the vast majority of patients had a poor prognosis at diagnosis. Survival is poor, and high recurrence rates after treatment were exhibited regardless of treatment. Currently, the implementation of screening programs especially for chronic virus hepatitis, and advances in radiological assessment, leads to an increasing proportion of patients being diagnosed within early stage of HCC. The surgical management of HCC in the setting of liver cirrhosis with curative intent includes liver resection, ablation or microwave coagulation, and liver transplantation (LT).

## 2. Hepatocellular carcinoma staging

Cancer staging should serve to select the appropriate primary and adjuvant therapy, to estimate the prognosis, and also to assist in the evaluation of the results of treatment and this is also applicable in HCC [3, 4]. The EASL panel of experts recommended the consideration of four-related aspects: tumor stage, degree of liver function impairment, general condition of the patient, and treatment efficacy [5]. In the past, the Okuda classification [6] has been widely applied in HCC patients, and it included parameters related to the liver functional status like albumin, ascites, and bilirubin. The Cancer of the Liver Italian Program (CLIP) score [7] was proposed and validated [8]. It combines four variables that provide a seven-stage classification system and was more discriminatory compared with Okuda stage and TNM. Groups from Asia published different survival rates compromising its external validation [9]. The Barcelona-Clinic Liver Cancer (BCLC) staging system [10] was proposed by the Barcelona group on the basis of the results obtained from cohort and RCT studies. It consists a staging classification that uses variables related to performance status, tumor stage, liver functional status, characteristic of the tumor, vascular invasion, and the presence of portal hypertension (PH). This BCLC classification system has become a widely accepted algorithm for all HCC patients in earlier disease, linking their current status prognosis with treatment recommendations. Recently, a new staging system was proposed from the Hong Kong group [11]. The Hong Kong Liver Cancer (HKLC) used four prognostic factors in the treatment of HCC, the Eastern Cooperative Oncology Group performance status (ECOG PS), Child-Pugh grade, liver tumor status, and presence of extrahepatic vascular invasion/metastasis. Liver tumor status was a composite factor of the size of the largest tumor in the liver, number of tumor nodules, and the presence or absence of intrahepatic vascular invasion. The authors support that the HKLC staging classification has the potential to provide better prognostic classification than BCLC staging and may be more effective in identifying patients suitable for more aggressive treatments, hence yielding a better survival outcome.

### 3. Liver resection vs. TACE and RFA

Liver resection when it is feasible, in a cirrhotic liver with HCC, is associated with lower survival rates compared with liver transplantation (LT), varying from 35 to 62% at 3 years and from 17 to 50% at 5 years, depending on the diseases' stage but on the contrary liver resection could be potentially offered in a larger population compared to liver transplantation. One of the biggest limitations of liver resection is the risk of tumor recurrence, which is high, and it may exceed 70% 5 years after the procedure. Hepatic resection tends to be applicable only in patients with cirrhosis that is classified as Child-Pugh class A or B and with mild portal hypertension. The application of palliative therapies like radiofrequency ablation (RFA), microwave coagulation (MC) and transarterial chemoembolization (TACE) is frequently limited by impaired hepatocellular function, severe portal hypertension, or multiple tumor nodules.

Huang et al. [12] in a large randomized trial of 230 patients within the Milan criteria (BCLC stage A) compared surgical resection and radiofrequency ablation for HCC patients indicating a favorable outcome for surgically treated patients. Wang et al. in their meta-analysis evaluated three randomized and 25 nonrandomized trials, and they confirmed the long-term superiority of surgical treatment [13]. In another meta-analysis by Kapitanov et al. and taking into account the limited available literature and prospective studies, they concluded that liver resection shows significantly improved long-term survival compared to TACE in cirrhotic patients with BCLC stage A and B HCC. T. Utsunomiya et al. conducted a large prospective multicenter trial and demonstrated clear superiority for hepatic resection when compared to TACE and RFA for patients with Child-Pugh stage A and B liver cirrhosis and stage II HCC (JIS scores 1 and 2) [14]. Peng et al. [15] showed that even for patients with portal venous tumor, thrombus liver resection improves long-term survival compared to TACE as long as tumor thrombosis was confined to the liver. This effect vanished in the presence of extensive tumor thrombosis into the portal venous confluence and the superior mesenteric vein. Zhong et al. [16] demonstrate clear superiority for hepatic resection versus TACE in terms of patient survival. They analyzed an impressive total number of 1259 of patients with the vast majority of cases being hepatitis-B positive. Limitations of the study were a rather heterogeneous patient collective and a mean patient age and tumor size being both greater in the TACE group. For this reason, matched-pair analysis was performed between TACE and resection patients with identical demographics confirming the positive overall results for surgically treated patients.

Laparoscopic liver resection (LLR) consists a contemporary surgical approach in the management of hepatocellular carcinoma with or without liver cirrhosis. The indications for LLR have changed substantially since its introduction. In the beginning, it was limited to benign diseases, while gaining increased knowledge and experience of the procedure, its indications have expanded to malignant diseases, including HCC and colorectal liver metastasis [17]. However, laparoscopy has been limitedly used for liver resection due to the risk of air embolism and the difficulty of parenchymal dissection and bleeding control [18]. Therefore, LLR has been frequently performed for tumors superficially located in the anterolateral segments

[19]. Liver cirrhosis consists a substantial risk factor for developing postoperative complications following hepatectomy. Severe blood loss or prolonged ascites after major hepatectomy, especially by open surgery, can occur by interruption of collateral circulation in the parietal wall and surrounding ligaments in patients with liver cirrhosis [20] and may prolong the postoperative hospital stay or induce hepatic failure in some patients. However, LLR may minimize the reduction in collateral and lymphatic flow caused by laparotomy and mobilization [21, 22]. The benefits of LLR in liver cirrhosis include enhanced recovery, less postoperative pain, and potentially less postoperative complications. Other important advantages of LLR in patients with liver cirrhosis are the lower incidences of postoperative liver failure and ascites due to minimal invasiveness of LLR, which helps to preserve collateral circulation. Therefore, laparoscopic hepatectomy may be a good option in patients with cirrhosis [23].

## 4. Down-staging and bridge therapies

### 4.1. TACE

Down-staging in HCC patients includes but not limited to TACE, radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), microwave coagulation (MC), resection, and radiation [24]. The objective of down-staging is to decrease the tumor size and/or number of nodules in those patients that initially are presenting with tumors beyond the acceptable criteria for liver transplantation in different centers. The response to different DS treatment has to be based on radiological measurement of tumor characteristics. The EASL HCC guidelines suggested, and this was also endorsed by the AASLD guideline, that assessment of tumor response should consider only the area of viable tumor [25], defined by arterial enhancement on a radiological contrast study modified response evaluation criteria in solid tumors (mRECIST).

Prospective studies showed that survival after liver transplantation in patients with large tumor burden successfully treated by down-staging was similar to survival in patients who initially met the criteria for transplantation [26]. There is currently no well-defined upper limit for size and number of lesions as eligibility criteria for down-staging, although the presence of vascular invasion and extrahepatic disease is generally considered absolute contraindications.

The role of DS has been ambiguous concerning the overall and recurrence-free survival post-transplantation. In the case that complete tumor necrosis with locoregional therapy is achieved, this is associated with better survival. A multicenter case-control study compared matched patients with TACE (100) and without TACE (100) [27] showed that survival rates 5 years after OLT were similar 59.3% versus 59.4%, respectively. In addition, there were fewer recurrences in the TACE group although this was not statistically significant. Moreover, the waiting times were short, and the median number of TACE procedures was only 1, and this may impact negatively the detection of any advantage for TACE.

Comparisons of the dropout rates of treated and untreated patients are limited with the existing data. Yao et al. from the UCSF analyzed 70 patients a proportion of them having pretransplant therapy either TACE or ablation, and this was associated with a significantly lower risk



of dropout. Disadvantage of the study was that the population was heterogeneous regarding the disease stage, and the criteria for treatment were influenced by external factors [28]. Another study from Toronto including 74 patients identified a difference in tumor-related dropout that became apparent only after 300 days [29].

Drug-eluting beads loaded with chemotherapy agents are delivered into the tumor through the feeding artery. Chemotherapy agents are released gradually, so systemic side effects are reduced, and tumor drug delivery is enhanced. The PRECISION study compared conventional TACE with DEB for the treatment of 212 patients with Child-Pugh A or B cirrhosis and unresectable HCC [30]. Subpopulation analysis revealed that patients with Child-Pugh B cirrhosis or bilobar tumor disease showed a better response to DEB. In addition, the overall DEB was better tolerated than conventional TACE. While it appears that DEB might be better tolerated than conventional TACE, more extensive data are needed.

#### 4.2. RFA

The use of RFA as a bridge to transplantation in HCC patients is also applicable. It has been reported complete tumor necrosis at pathological evaluation of the explanted liver in 47–75% of cases, with a mean value of 58% [31–35]. Different rates of complete necrosis ranges have been observed between 50 and 78% in HCCs up to 3 cm and between 13 and 43% in larger neoplasms, respectively [31–33]. Furthermore, in two studies, a tumor size larger than 3 cm was the only risk factor found for HCC recurrence after treatment [31–33]. Analysis of the largest available series of HCC patients awaiting LT regarding RFA-related complications showed the safety of the procedure. From five large series, we could see that the mean rate of post-ablation major complications was below 5% [31–36], and in addition, the risk of tumor seeding at the level of the abdomen wall appears to be low.

#### 4.3. Liver resection

Belghiti [37] proposed that resection can be used as an alternative treatment option for HCC or before LT as “down-staging” procedure. Liver resection can be used as a primary therapy in patients with HCC and well-preserved liver function, with LT reserved as a “salvage” therapy for patients who developed recurrence or liver failure. Moreover, resection can be used as an initial therapy in order to select patients whose explants pathology would be favorable for LT. Resection could also be used as a “bridge” therapy for patients who have been already enlisted for LT. Whether resection or LT should be the treatment of choice for small HCC in patients with preserved liver function is a hot issue and still in debate. Long-term overall survival after resection or transplantation appears comparable in a well-selected population with HCC within the Milano criteria [37–39]. LT has the advantage of increased disease-free survival compared with liver resection, but its use is limited by shortage of liver organs. It has been proposed by the group of Belghiti but also from other groups that resection as the first-line treatment for patients with small HCC with preserved liver function, followed by salvage transplantation only for recurrence or liver failure, would be feasible in a large proportion of HCC patients [37–39].

Considering emergency LT after resection as center, policy would require a strict selection of the candidate with clear and strong indicators of irreversible postoperative liver insufficiency. Patients with liver failure due to massive necrosis of the remnant liver or those with uncontrollable bleeding are easy to be identified, but it is unclear and very difficult to ascertain the irreversibility of liver insufficiency in all settings. A significant increase in international normalized ratio (INR) and serum bilirubin within the first postoperative days is a common characteristic of extended resection making identification and selection of patients in need for early liver transplantation tricky. It is documented that, in the absence of any treatable complication, the lack of significant improvement on postoperative day 5 may lead to strongly considering rescue transplantation [40].

Poon et al. [38] proposed liver resection for HCC lesions in selected patients eligible for LT and to reserve LT for those who develop recurrence or deterioration of liver function. This approach, which proposes resection as a bridge treatment to prevent tumor progression during the waiting period, looks attractive but has not been studied well, especially with prospective studies and needs external validation of published data from the various transplant centers. As major concern from transplant surgeons is that prior liver resection especially if done in no-specialized centers could complicate the operative transplant procedure, increase the risk of postoperative complications, and finally compromise results and impair the survival advantage of transplantation over resection alone.

## 5. Liver transplantation

Liver transplantation is considered the best treatment for hepatocellular carcinoma at early stages because it removes the tumor as well as the underlying cirrhotic liver. However, as a result of organ shortage, it is anticipated that transplantation to HCC patients will be performed with an expected five-year post-transplantation survival of greater than 50%, and, in most programs, an expected five-year post-transplantation survival similar to survival achieved after liver transplantation for benign liver diseases (i.e., 70%).

In 1996, Mazzaferro et al. [41] conducted a prospective cohort study defining restrictive selection criteria (Milan Criteria (MC)) that led to improved survival for transplant patients compared with any other previous experience with transplantation for HCC. Adopting the MC demonstrated a five-year survival of 70% after LT [41]. The survival outcome of MC is comparable to LT in benign diseases and given that this excellent outcome MC has been established from most liver societies (EASL and AASLD guidelines) as the golden standard in selecting HCC patients for liver transplant [42, 43].

In 2001, Yao et al. from University of California San Francisco (UCSF) [44] demonstrated a tumor recurrence rate of little more than 10% and survival rates exceeding 70% in T1, T2 and T3 tumors. The new criteria included solitary tumors smaller or equal to 6.5 cm in size or three or fewer tumors with the largest diameter not exceeding 4.5 cm and the total tumor diameter being less or equal to 8 cm and became known as the UCSF criteria.

Alternative criteria have been proposed by other centers. These include criteria from the Asan Medical Center in Korea [45], from Hangzhou, China [46], the University Clinic of Navarra in Spain [47], Kyoto, Japan [48]. All use different criteria in terms of number of nodules and size and in addition try to implement some biological criteria like  $\alpha$ -FP, protein induced by vitamin K absence II (PIVKA II) and other. Unfortunately, none of these criteria have been externally validated in order to get wider acceptance.

In 2009, the Metroticket was introduced by Mazzafero et al. [49]. The Metroticket introduced the logic that the further you expand HCC staging criteria for LT, this would impact negatively the outcome in terms of higher recurrence rates and poorer overall survival. This model potential could be a simple predictive model for estimating the survival of patients undergoing LT with tumors excising the Milan criteria in number and size of the tumors.

High  $\alpha$ -fetoprotein (AFP) levels are predictive of poor prognosis in non-transplant patients, and AFP levels greater than 1000 ng/mL have been associated with a high risk of recurrence in the University of California, San Francisco (UCSF), experience [44] after liver transplantation.

AFP value is proposed as a good indicator in selecting HCC patients for LT [50, 51]. In the non-transplant patients, an elevated AFP is a marker of advanced disease. It has been proposed that an increase in AFP levels might be an indicator of tumor aggressiveness including differentiation degree and vascular invasion and, consequently, lead to a higher risk of tumor recurrence. Toso et al. [52] analyzed adult recipients in the Scientific Registry of Transplant Recipients. In the multivariate analysis, it was shown that high AFP levels and TTV >115 cm<sup>3</sup> were associated with poor long-term survival.

Duvoux et al. [53] in a French multicenter study showed that AFP levels strongly correlated with the pathologic features of HCC. Based on the analysis of 453 explanted livers, they found that increased AFP levels were associated with vascular invasion and loss of differentiation.

Living Donor Liver Transplantation (LDLT) consists of an alternative option to Deceased Donor Liver Transplantation (DDLT). Special consideration regarding LDLT for HCC is required, since patients for LDLT are not dependent of the cadaveric donor pool, but bring their "own" liver graft. It is important to stress that the application of strict eligibility criteria similar the one required with cadaveric grafts for patients with HCC might not be necessary. However, survival benefit to the recipient should be substantial, and the risk to the donor must be incorporated into the centers policy, since it is clearly unethical to expose a donor to a significant risk of morbidity or mortality. Generally, similar criteria apply to patients undergoing DDLT or LDLT. For patients subjected to either DDLT or LDLT for HCC within MC, similar outcomes have been documented [54, 55]. Asian groups have proposed different policies concerning different criteria for LDLT in the setting of HCC. The Tokyo group applies the 5–5 rule (number of tumors not exceeding 5 and maximum tumor diameter not exceeding 5 cm); the Kyoto group the 10–5 rule (number of tumors not exceeding 10; each tumor not exceeding 5 cm) in combination with the biological tumor marker PIVKA (or DCP) (not exceeding 400 mAu/ml), and finally, the Seoul group adopts an intermediate policy with limiting the number of tumors not exceeding 6 and the maximum tumor diameter not exceeding 5 cm. All three groups obtained around 85% 3–5 years disease free survival (DFS) survival rates.



In the West, LDLT is often stretched in patients who do not strictly meet the Milan criteria for MELD exception points and have tumors with a probable worse prognosis. Updated re-analyzed data of the A2ALL cohorts concluded that “differences in tumor characteristics and management of HCC in patients who received LDLT likely accounted for the higher HCC recurrence rates observed in their LDLT group.”

Systematic review analysis by Grant et al. [56] suggests that DFS is worse after LDLT compared with DDLT for HCC. Decreased DFS may eventually translate to decreased OS, and it is advisable that the increased risk of recurrence should be communicated to all potential donors and recipients who are considering LDLT for HCC.

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