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Neoadjuvant Chemotherapy for Hepatocellular Carcinoma

Xin-yu Huang, Qi Zheng and Zhou Yuan

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1. Introduction

Hepatocellular carcinoma (HCC), a primary fatal malignancy of the liver, is the sixth most common cancer and the third most common cause of cancer death worldwide [1]. The estimated incidence of HCC is about 500,000–1,000,000 per year worldwide, causing 600,000 deaths globally per year [2]. It varies widely according to geographic location, with the highest incidence in sub-Saharan Africa and China, where chronic hepatitis B virus (HBV) infection remains the leading cause [3]. In the United States and Europe, the incidence of HCC is on the rise and is expected to increase over the next two decades because the number of patients with chronic hepatitis C virus (HCV) infection gradually increased in the past two decades [4]. Liver cirrhosis, especially after chronic infection with hepatitis B or C virus, remains the main risk factor that predisposes to the development of HCC, although rarely can HCC develop in a patient without cirrhotic liver. Despite of major progress in diagnosis and therapeutic options of HCC in the past two decades, the prognosis of HCC is still dismal and 5-year survival rate is less than 5%.

Of the therapies aiming at cure, surgical resection or liver transplantation are the optimal treatments with better outcomes in well-selected patients HCC. Unfortunately, more than 50% of all HCCs are diagnosed at locally advanced tumor stage or extrahepatic metastasis and therefore not eligible for potentially curative therapy such as surgical resection and liver transplantation [5]. In addition, some patients with early HCC are not eligible for curative hepatic resection because of poor liver function. Thus, only 10%-30% of patients with early HCC at diagnosis are amenable to curative surgical treatment and the rest of patients with have to receive non-curative treatment. Furthermore, after curative resection, tumor recurrence rates can be as high as 25% per year and 50-90% of postoperative death is due to recurrent disease. Therefore, despite curative treatment options for patients with early stage HCC, survival rate after curative treatment has been as low as 50% at 3 years and 20-30% at 5 years

[6-8]. Tumor recurrence is the main drawback of resection and intra-hepatic recurrence is frequently the only site of recurrence. HCC commonly arises from chronic hepatitis viral or alcoholic liver diseases, which are likely to harbor multiple and independent clones of premalignant cells. When these clones are further exposed to continuous carcinogenic insults, multicentric carcinogenesis follow. Thus, intra-hepatic recurrence may represent either “de novo” tumor formation in a cirrhotic liver, or intra-hepatic metastasis from a clonally identical neoplasm. In other word, recurrent HCC can result from intrahepatic dissemination of the primary tumor (true recurrence) or by new “de novo” carcinogenesis. No matter how the recurrence happens, it is generally believed that recurrences arise not because of inadequate resection but because of pre-existing microscopic tumor foci that are undetected by imaging modalities, or because malignant cells have been disseminated during surgical manipulation[9-10]. Therefore, neoadjuvant or adjuvant therapy could potentially delay or decrease the incidence of intrahepatic recurrence, which could improve patients’ prognosis after hepatic resection.

Liver transplantation is an optimal treatment to manage end-stage liver disease with HCC, because this procedure cures not only the tumor but also the underlying cirrhosis. Liver transplantation achieves excellent results in selected patients with HCC. Patients with solitary HCC of less than 5 cm or with up to three nodules of less than 3 cm with no macroscopic vascular invasion (the Milan criteria) have a 5-year survival of 70% after liver transplantation, with recurrence in less than 10% [11]. Compared with surgical resection, liver transplantation is associated with better overall and disease-free survival in well-selected patients [12]. Unfortunately, the majority of HCC patients are diagnosed at a late stage and therefore not eligible for liver transplantation. Furthermore, patients drop off the transplant list owing to tumor progression during the long waiting time, resulting from shortage of liver donor worldwide. Thus, it is pivotal to decrease the rate of dropout by using neoadjuvant therapy for those patients during the waiting time. In addition, neoadjuvant therapy for HCC beyond the Milan criteria may downstage HCC tumors within the Milan criteria to expand liver transplantation candidates.

Neoadjuvant therapy is used preoperatively with the aim to reduce tumor recurrence in the past two decades. The aims of neoadjuvant therapy are to reduce the tumor mass thus making curative surgery more feasible and to reduce postoperative recurrence. Thus, the administration of neoadjuvant chemotherapy may offer several theoretical advantages. First, neoadjuvant therapy can reduce the tumor burden and shrink the tumor so patients are amenable to curative and negative-margin resection. Second, it can potentially eliminate “circulating cancer cells” or “disseminated cancer cells”, which is regarded as the source of tumor recurrence. Third, neoadjuvant chemotherapy potentially reduces intraoperative tumor cells spread. Fourth, the delivery of treatment agents before surgical manipulation may provide better tissue oxygenation, facilitating the distribution of chemotherapy agents into the tumor, and increasing normal tissue tolerance. Fifth, the administration of chemotherapy before surgery allows an in-vivo assessment of tumor chemo-sensitivity through analyzing resected tissue samples. Finally, neoadjuvant chemotherapy may also lead to more definitive surgical resections by reducing the risk of tumoral infiltration of lymph nodes and of resection margins in the surgical specimen.

However, neoadjuvant therapy has the disadvantage of delaying the surgery. This can be detrimental if the tumor fails to respond to the therapy and continues to grow and becomes inoperable. Moreover, neoadjuvant therapy also has the potential to adversely affecting the liver function, with an increased risk of liver failure after partial hepatectomy [13-14]. In recent decades, more light has been shed on the role of neoadjuvant or adjuvant therapy for HCC.

2. Neoadjuvant therapy for resectable hepatocellular carcinoma

Surgical resection offers the only hope for cure and is the preferred option for patients with HCC. For those noncirrhotic HCC patients, surgical resection is the optimal curative treatment. They are likely to tolerate extended hepatic resection without liver failure. Moreover, the noncirrhotic residual liver is less likely to develop de-novo HCC. Unfortunately, the majority of patient develops HCC in the context of cirrhosis, so the selection criteria of liver resection depend not only on tumor-related parameters (tumor size, numbers, location and vascular invasion) but also on preserved liver function. Meanwhile, the long-term survival remains poor owing to high incidence of recurrence and metastasis after hepatectomy. Recurrences, in particular, intrahepatic recurrences are the most common and are found in up to 68-96% of patients undergoing resection [15-16]. Therefore, neoadjuvant HCC therapy, which can decrease or delay the incidence of intra-hepatic recurrence, may improve the results of liver resection.

Large HCC, tumor with a diameter of 5 cm or more, are relatively common, especially when HCC screening is not a routine practice in patients at risk. Generally speaking, patients with large HCC are not eligible for liver transplantation or ablation. Hepatic resection thus remains the only surgical treatment option for these patients. Despite improvements in preoperative assessment and intraoperative techniques in liver resection over the past 10 years, major liver resection in diseased liver is still considered a risky procedure [17-18], because of the potential risk of developing liver dysfunction after hemihepatectomy or hepatic trisegmentectomy. Thus, portal vein embolization (PVE) is used prior to extended hepatectomy to increase future remnant liver volume and to prevent postoperative liver dysfunction.

The primary goal of neoadjuvant HCC therapy is to eradicate residual microscopic HCC foci and to reduce the incidence of a second HCC from developing within the live remnant after partial hepatectomy and thus to reduce death from recurrent HCC. Recently published reviews concluded that there are little or no evidence to show that neoadjuvant therapy added benefit after curative hepatectomy for HCC so far. However, neoadjuvant therapy is continuously evolving and gaining importance in the treatment of HCCs. At present, the most popular techniques include transarterial chemo-embolization (TACE), portal vein embolization (PVE), and target therapy. Herein, we review the rationale behind each strategy and the studies on neo-adjuvant treatments for HCC before partial hepatectomy.

2.1. TACE

Since transarterial chemoembolization (TACE) was introduced during the late 1970s as a palliative treatment for patients with unresectable hepatocellular carcinoma (HCC), it has been

applied more frequently in patients with unresectable HCC. In contrast to the normal liver which has dual blood supply, mainly from the portal venous system, hepatocellular carcinoma tumor is supplied almost exclusively by arterial supply. By direct infusion of the lipiodol and chemotherapy through the hepatic artery, it allows a high dose of chemotherapy to be delivered directly to the tumor. This provides the rationale for therapeutic local chemotherapy and hepatic artery selective obstruction of HCC via TACE. The embolization of the hepatic artery reduces the blood flow of tumor, creates ischemia and increases the contact time between the chemotherapeutic agent and the tumor cells, resulting in synergetic effect and complete tumor necrosis.

A meta-analysis including seven randomized clinical trials was undertaken in the late 1990s to investigate the usefulness of TACE for treating unresectable HCC, which demonstrated an improvement in 2-year survival ($P = 0.017$) compared with control patients who were treated conservatively or received suboptimal management [19]. According to the guidelines published by the American Association for Study of Liver Diseases (AASLD) [20] and the European Association for the Study of the Liver (EASL) [21], TACE is recommended as first-line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (level I). Given the promising results in its palliative role, TACE has been evaluated as a neoadjuvant therapy with the hope of reducing tumor size, inducing tumor necrosis, and preventing tumor dissemination. Preoperative TACE is not only intended to prevent recurrence by controlling intrahepatic spread via the portal system, but also to facilitate surgery by reducing tumor bulk. The use of TACE as a neoadjuvant treatment for HCC was first described in the early 1990s, where its use was proposed in a variety of settings; palliatively for unresectable recurrent HCC, to increase the rate of resectability of unresectable HCC, and to downstage the primary tumor for liver transplantation [22].

Whether preoperative TACE is beneficial for survival of patients with resectable HCC remains a controversy owing to the numerous conflicting reports. A few studies suggested that preoperative TACE may be beneficial for overall survival and/or disease-free survival in patients with resectable HCC [23-24]. In contrast, several studies have shown that neoadjuvant TACE had no significant influence on postoperative survival [25-26]. A randomized controlled trial from China indicated that preoperative TACE did not improve surgical outcome and five patients lost the chance of undergoing a curative liver resection owing to disease progression and hepatic failure [27]. Furthermore, several studies have found that preoperative TACE negatively affected survival of patients postoperatively [28-29]. A meta-analysis including three randomized clinical trials is undertaken to evaluate the definitive effect of preoperative TACE on both disease-free survival rate and overall survival rate following curative resection in resectable HCC patients, which demonstrated no significant benefits for 5-year overall survival and disease-free survival [30]. However, the number of patients was small in these trials, which limited the ability to draw firm conclusions. Another systemic analysis indicates that there appears to be no DFS advantage by using TACE as a neoadjuvant therapy for resectable HCC, although it is a safe procedure [31].

Can we predict which kind of HCC will develop necrosis after neoadjuvant TACE owing to its heterogeneity or does it benefit the subgroup of patients according to tumor size, tumor stage, frequency of TACE, the interval between TACE and operation, etc.? The answer to these

questions is very important to evaluate the role of neoadjuvant TACE. In conclusion, current evidence indicates that there appears to be no DFS advantage despite its safety and feasibility. In future, a well-designed prospective multi-institutional randomized controlled trials (RCTs), with a clearly defined protocol for concealed allocation, eligibility criteria, TACE intervention regimen and endpoints will be potentially meaningful.

2.2. PVE+TACE

Hepatic resection is considered to be the only curative treatment for patients with large HCC and preserved liver functions, because these patients are not amenable to liver transplantation or ablative therapy. For these patients, major hepatic resection is feasible in theory and technique to achieve complete resection and provide the possibility of cure, but, most of them will develop postoperative liver failure, a fatal complication, owing to not enough remnant liver volume. In addition, most patients with hepatitis B or C virus-associated liver cirrhosis increase the risk of postoperative liver failure.

Preoperative portal vein embolization (PVE), first reported by Makuuchi, is a technique to induce atrophy of the embolized lobe to be removed with compensatory hypertrophy of the nonembolized future liver remnant (FLR). This technique was first applied to patients with hilar bile duct tumors (Klatskin tumors) [32], then has been introduced in major hepatic resection. The aim of PVE is to preserve enough remnant liver volume and to prevent post-hepatectomy liver failure, which is the predominant cause of death in cirrhotic patients. However, the major limitation of PVE is a compensatory increase in the hepatic arterial flow to the embolized segments, thus resulting in insufficient nonembolized liver hypertrophy or rapid tumor growth because most HCCs are hypervascular tumors fed mainly by arterial blood flow [33]. To overcome the shortcoming of PVE, sequential preoperative TACE combined with PVE has been evolved. The new technique has recently shown promising results for increasing the rate of hypertrophy in HCC patients with chronic liver disease, as it decreases arterial flow and thus increases parenchymal damage in the embolized liver and suppresses arterioportal shunts [34]. In addition, it may have a strong anticancer effect by obstructing tumor feeding vessels and suppressing intrahepatic spread by portal vein invasion from HCC and arterioportal shunts in HCC patients. Thus, preoperative TACE+PVE may increase the probability of resectability for major hepatectomy and may decrease the risk of postoperative hepatic failure. However, sequential TACE and PVE may have the theoretical drawback of increased risk of liver damage caused by double occlusion of the blood supply. The data from Yoo shows that incidence of hepatic failure is higher in the PVE-only group than in the TACE + PVE group ($P = 0.185$) after operation and overall ($P = 0.028$) and recurrence free ($P = 0.001$) survival rates are significantly higher in the TACE + PVE group than in the PVE-only group [35]. Other studies also show that preoperative sequential TACE and PVE is a safe and feasible technique and the short and long-term survival outcomes are satisfactory [36-37].

2.3. Sorafenib

Sorafenib is an oral multi-kinase inhibitor, which simultaneously inhibits molecular components of the Raf-MEK-ERK signaling pathway, abrogating tumor growth and VEGFR-1,

VEGFR-2, VEGFR-3, and PDGFR- β , thus inhibiting neoangiogenesis [38]. By targeting two key pathways that are reported to play an important role in the pathogenesis of hepatocellular carcinoma, sorafenib is likely to delay disease progression [39]. Furthermore, sorafenib exhibited growth-inhibitory effects, induction of apoptosis, and down-regulation of the anti-apoptotic proteins in a wide range of tumor models.

Recently, Sorafenib was approved and regarded as the first and so far the only drug which shows an increase in overall survival in patients with advanced, unresectable HCC. In the large randomized phase III study (SHARP), median overall survival (OS) increased from 7.9 months in the placebo group to 10.7 months in the sorafenib group. Sorafenib showed a significant benefit also in terms of time to progression (TTP), with a median of 5.5 months in the sorafenib group and 2.8 months in the placebo group. On the basis of these findings, FDA has approved sorafenib for advanced HCC treatment [40]. Thus, for patients with unresectable HCC, sorafenib is the first systemic therapy to significantly prolong survival and is now considered standard of care for patients with Child A cirrhosis and good performance status. Could sorafenib downstage HCC and thus represent a bridge to surgery, as a neoadjuvant therapy for advance HCC? The phase III SHARP study reported a partial response of only 2% with complete remission given the cytostatic nature of sorafenib effect. However, Irtan et al reported two cases of locally advanced HCC with portal vein tumor thrombosis (PVTT) who complete regression by sorafenib treatment allowed curative resection with good long-term outcome [41]. Another study also reports two cases with large HCC in the right liver with venous neoplastic thrombi undergo curative resection after sorafenib treatment [42]. However, no large clinical experiences have been reported in neoadjuvant therapy with the use of sorafenib. Thus, large scale RCT clinical trials should be undertake to investigate the role of sorafenib as a neoadjuvant treatment in advanced HCC, preferably in combination with local therapy modalities to increase the chances of down-sizing.

In summary, further randomized controlled studies need to be carried out. Currently, there is no consensus on a standard neoadjuvant therapy in partial hepatectomy for HCC.

3. Neoadjuvant therapy for hepatocellular carcinoma before liver transplantation

Liver transplantation is a potentially curative treatment for HCC for those patients with early HCC in the setting of cirrhosis. It has two principle advantages to remove the tumor as well as the underlying liver cirrhosis, restoring both liver function and decreasing the risk of de novo HCC. Compared with surgical resection, liver transplantation is associated with better overall and disease-free survival in well-selected patients (5 year-DFS >75% vs. 50%) [43]. Patients with solitary HCC of less than 5 cm or with up to three nodules of less than 3 cm, with no macroscopic vascular invasion (the Milan criteria) have a 5-year survival of 70% after liver transplantation, with recurrence in less than 10% [11]. In addition, the survival matches post-transplant survival of most other indications for liver transplantation, such as end-stage liver cirrhosis disease. As evidence accumulated of good outcomes in some patients outside the

Milan criteria, there was a drive to identify expanded criteria and to increase the number of eligible candidates for liver transplantation. Among the many proposals, only the University of California San Francisco (UCSF) criteria (one tumor ≤ 5 cm, three nodules at most with the largest ≤ 4.5 cm, and total tumor diameter ≤ 8 cm) have been prospectively validated with long-term survival comparable to patients with Milan criteria [44]. At present, the Milan criteria have been adopted as the guideline of liver transplantation for HCC worldwide. Unfortunately, the majority of HCC patients are diagnosed in a late stage and therefore not eligible for liver transplantation. Meanwhile, shortage of available graft is still a very stringent problem worldwide so that many patients will drop off the transplant list owing to tumor progression during the long waiting time. Historical data suggest that the median doubling time in HCC is about 3 to 6 months, but the waiting time for live transplantation continues to increase and is up to 24 months in the United States [45]. So, many eligible patients with HCC will drop out if they are not given some effective therapy to stop tumor progression during the waiting time. Thus, neoadjuvant therapy has been proposed as a strategy to treat HCC before liver transplantation.

Neoadjuvant therapy for HCC beyond the Milan criteria has been performed with the purpose of downstaging HCC to parameters within the Milan criteria. This enables substantially the expansion of liver transplantation candidates with potential good outcomes after transplantation. It is defined as 'downstaging therapy'. Another aim of neoadjuvant therapy is to delay tumor progression and decrease dropout for those patients within Milan criteria HCC. It is defined as 'bridging therapy'. The last aim of neoadjuvant therapy can decrease or even eliminate circulating cancer cells, which are the mainstay source of recurrence and metastasis. Although associated with good results, around 10% of within Milan criteria HCC patients will exhibit post-transplant recurrence. Recurrence is either due to the growth of occult metastases or to the engraftment of circulating tumor cells. Thus, pre-transplant neoadjuvant therapy may serve a pivotal role in improving survival following liver transplantation. At present, neoadjuvant therapy is gradually evolving and gaining importance in the treatment of HCC patients undergoing liver transplant.

Locoregional therapy, such as TACE, transarterial radio-embolization (TARE) and radiofrequency ablation (RFA), and systemic chemotherapy are most common used as neoadjuvant therapy for patients with HCC before liver transplantation. Herein, we evaluate the rationale of each strategy for HCC before liver transplantation.

3.1. TACE

The rationale for using TACE as a neoadjuvant therapy prior to liver transplantation is to control tumor growth while the patient awaits an organ and to cause significant tumor necrosis, which may reduce tumor dissemination during surgery. In addition, TACE can be used to downstage tumor and make them eligible for transplantation[46]. In a case-control study, researchers showed that the high rate of tumor necrosis observed in the pretransplant TACE group was not associated with difference in overall survival [47]. In the French multicenter case-control study, the patients in the TACE group in which more than 80% of the tumor was necrotic at the time of transplantation and their matched controls had 5-year survival rate

of 63% and 54%, respectively ($p = 0.9$) [48]. Thus, although preoperative TACE can lead to tumor necrosis in about one third of cases and reduces tumor size in half of the patients, there was no sufficient evidence to support the concept that it can improve long-term survival for patients with within Milan criteria HCC after transplantation.

Success in downstaging has been reported in many studies, although most of these are uncontrolled observational studies. As a downstaging tool in his study, Graziadei et al. included 15 advanced HCC patients not eligible for transplantation received TACE (range, 2–12). 11 patients had a partial response with $>50\%$ necrosis and $1 < 50\%$. 10 patients underwent OLT and found to have 30% HCC recurrence rate. Thus, despite successful downstaging before OLT, patients with primarily advanced HCC had a significantly less favorable outcome in the intent-to-treat analysis as well as in the post-transplantation survival compared with patients with early-stage HCC (31% vs. 94% at 5 years, $p < 0.001$ and 41% vs. 94% at 5 years, $p < 0.001$) [49]. Downstaging of HCC by TACE is possible in most of candidates; however, these patients tend to have higher dropout rates, higher recurrence rates, and unfavorable outcomes compared with early stage patients. Therefore, there is currently no sufficient evidence that pretransplant TACE may delineate the possibility of expanding current selection criteria for liver transplantation in patients with HCC.

3.2. RFA

Radiofrequency ablation appears to be equivalent to surgical resection inducing total tumor necrosis in tumor < 3 cm [50]. Subsequently, RFA is used as the second most popular neoadjuvant therapy before liver transplantation after TACE. In transplant candidates, RFA has been used mainly as a bridge therapy rather than for downstaging before transplantation owing to its limited efficacy for large tumors. However, RFA can have severe side effect, including tumor dissemination in subcapsular HCC. Pretransplant RFA for HCC as a strategy to reduce dropout has been addressed in some studies [51]. More than 80% of patients were in the Milano criteria treated by RFA with approximately 1 year on the waiting list. The dropout rate ranged from 0 to 14%. However, the effect of preoperative RFA should be carefully evaluated by more randomized clinical trials

In summary, the lack of controlled clinical trials, some uncontrolled studies support the use of RFA as a safe and effective bridge therapy in patients who meet the Milan criteria.

3.3. Transarterial Radio-Embolization (TARE)

Radioembolization involves the transarterial administration of embolic microspheres labeled with Yttrium-90 (Y90). TARE has been used as a primary therapy for unresectable HCC. For patients with unresectable HCC, retrospective studies found similar efficacy and toxicity between radio embolization and TACE. For patients with main portal vein thrombosis, radioembolization may be considered advantageous over TACE, owing to its relatively decreased embolic effect. Radioembolization has also demonstrated favorable outcomes for downstaging tumors to meet the Milan criteria. Lewandowski et al retrospectively compared transarterial radioembolization with Y90 (TARE-90) with TACE in patients with T3 disease. The

TARE-90 group demonstrated a trend toward higher partial response and higher percentage of downstaging from T3 to T2 (58 vs. 31%, $P < .028$), thus falling within the Milan criteria [52].

3.4. Sorafenib

HCC is highly refractory to traditional cytotoxic chemotherapy, with no evidence to date of a survival benefit from its use. Sorafenib, a small molecule multi-kinase inhibitor acting via inhibition of tumor-cell proliferation and tumor angiogenesis, has been widely used in most solid tumor. Recently, Sorafenib is regarded as the first and so far the only drug which shows an increase in overall survival in patients with advanced, unresectable HCC. Can sorafenib be used as a tool to bridge or downstage HCC for patients before transplantation? At present, there are no reported randomized clinical trials in this setting. However, a few case reports show a promise of HCC tumor response to neoadjuvant sorafenib therapy, with effective downstaging to allow for liver transplant listing [53].

3.5. How to select neoadjuvant therapy?

Patient-individualized treatment strategy should be based on the performance status, hepatic reserve, tumor burden and tumor vascularity pattern. Generally speaking, for single HCC <3 cm, RFA may be appropriate. For larger or multifocal HCC, TACE would be indicated. In cases of thrombosis of the main or large branches of the portal vein, TARE appears to be better tolerated because of its less embolic nature. Moreover, these therapies might be implemented alone or via a combined approach. In addition, the benefit of the thoughtful concept of combining locoregional therapy with systemic therapies such as sorafenib has to be proven. In addition, the combination of locoregional therapy strategy, such as TACE+RFA and TACE +sorafenib, has been used in some transplantation communities and the outcome is promising. However, due to the lack of prospective data, the most appropriate treatment protocol has not yet been defined.

In summary, more light has been shed on the role of neoadjuvant therapy for HCC in recent decades, although the benefits of the therapy remain marginal so far. One of the possible reasons is tumor heterogeneity. Who will benefit from neoadjuvant therapy? The outcome after neoadjuvant therapy will be better if we can predict who will respond to the neoadjuvant therapy before the treatment.

4. Role of circulating tumor cells in recurrence

The term circulating tumor cells (CTC) defines specifically the tumor cells spontaneously disseminating from primary or metastatic sites and invading into peripheral blood or lymphatic vessels. They are also called disseminated tumor cells (DTCs). CTC may remain silent, in a dormant state, for variable periods of time, or grow into clinically detectable metastases. The presence of CTC reflects the aggressiveness characteristic feature of a solid tumor. The major difficulty in the CTC studies is that an extremely small number of CTCs exists in the bloodstream [54] and common serological, imaging and pathological approaches are not

sensitive enough to effectively capture CTC. Approximately less than 10 CTCs may be found among one billion blood cells in early stage cancers; therefore highly sensitive methods are required to detect and isolate these cells from the bloodstream. Although CTC detection has been applied and well documented in different types of cancer, especially in breast cancer [55], CTC detection is not routinely performed in HCC and remains in the experimental field. The clinical results suggest CTC detection and identification can be used to evaluate prognosis and may serve as an early marker to assess antitumor activity of treatment [56]. In addition, CTC detection might bring new interesting information of metastatic process and might be used as diagnostic tool of early recurrence after HCC resection or transplant, and may allow a better patient selection.

A major factor in tumor recurrence after a potentially curative treatment for HCC is CTC. Although tumor recurrence in the liver after tumor resection or transplantation may be explained by either intrahepatic tumor cell spreading or de novo tumor development, intrahepatic tumor recurrence after liver transplantation can be explained only by the homing of systemically disseminated and circulating tumor cells. CTC have the potential to migrate and engraft in multiple organs, including the newly implanted liver, where significant recurrences are observed. The tumor response to preoperative treatment might be predictable prior to surgery by a drop in CTC count and this allows improved choice of the best timing of surgery. After surgery, CTCs can be examined in terms of pharmacodynamic biomarkers to choose the most sensitive chemotherapy agents and assist in deciding the duration of adjuvant therapy.

There are so many questions to answer in future. Is CTC a transient or recurrent phenomenon? Does locoregional therapy in HCC affect the number of CTC? Can the number of CTC be used as criteria of liver transplantation? Which pharmacological and/or surgical protocols might be successful in eliminating or restricting tumor-cell circulation and spread? Thus, the detailed analysis and characterization of CTC in HCC patients may give us new insights into their biology and may lead to new therapeutic strategies for their elimination.

Author details

Xin-yu Huang, Qi Zheng and Zhou Yuan*

*Address all correspondence to: zhouyuan851@163.com

Department of General Surgery, The Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China

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