Review Article

Bridging and downstaging therapy in patients suffering from hepatocellular carcinoma waiting on the list of liver transplantation

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Abstract: Hepatocellular carcinoma (HCC) is a common primary malignancy worldwide especially in the patients with the background of chronic liver disease. Liver transplantation (LT) is the only curative treatment effective for both malignancy as well as the cirrhosis and portal hypertension. Unfortunately, living donor is not always possible and the deceased graft is scarce. Neoadjuvant therapies, therefore, have been developed as a downstaging treatment to try to downstage the tumor within the transplant criteria, or as a bridging therapy to control the tumor growth in patients while waiting in the transplant list. This paper reviewed the common modalities used as bridging and downstaging therapies for patients suffering from HCC before undergoing LT.

Keywords: Liver transplant (LT); downstaging; radiofrequency ablation (RFA); high intensity focuses ultrasound (HIFU)

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the most common primary liver malignancy worldwide (1,2). Most cases of HCC in Asia are hepatitis B related, which is prevalent in the region (3). It is the third most common cancer causing death in Hong Kong (4). However, the prognosis of majority of HCC patients remained poor due to low resectability rate of 20% (5,6).

Transplant criteria

Liver transplantation (LT) remains the best curative surgical treatment option for patients with HCC and cirrhosis. It removes the tumorous liver as well as corrects the underlying disease liver, and a 5-year post-transplant survival rate of >70% is expected (7-10). The established Milan criteria (11) and the UCSF [University of California, San Francisco] criteria (12) had been well validated and were used as the guideline to list the patients for LT, especially deceased donor LT. Unfortunately, its applicability of LT is limited by the shortage of liver graft supply (13).

Patients, who suffered from HCC with or without poor liver function, who were out of the transplant criteria, remained the most difficult group to be treated. Disease could be downstaged or controlled by various anticancer therapies, which might bring them chance of undergoing a curative treatment such as LT. Local ablative therapies, chemoembolization and/or targeted therapy were used. Some of the tumors showed response to the therapies, however the optimal type of therapy that should be used

and the upper limit of tumor size that should be downstaged were still not clear. A disease-free period of at least three months was recommended after the disease was downstaged (14-17); unfortunately, the optimal waiting time to offer LT remained unclear.

The interval between HCC diagnosis and LT is an important prognostic factor, as drop out rate from the waiting list as a result of tumor progression increases in a time-dependent manner (18). This is particular the case because of the scarcity supply of the liver grafts, hence patients on the LT waiting list have to suffer from a long period of waiting time, result in disease progression and drop out from the waiting list (19-21). A predicted 12% probability of 6-month drop out for patients in whom the tumor is left untreated during the waiting period (19,22).

In view of this, bonus Model for End-Stage Liver Disease (MELD) score are granted for patients for stage 2 HCC (single HCC between 2 and 5 cm or up to three HCCs with none larger than 3 cm). Initial MELD score of 22 points and additional MELD points every 3 months if their tumors remained at stage 2 was given in the United States. In Hong Kong, patients with HCC that remained at stage 2 six months after their tumors had been confirmed as stage 2 HCCs by imaging were assigned an arbitrary MELD score of 18 points. Two MELD points were added every three months. The policy of a 6-month waiting period has benefited HCC patients in the deceased donor LT waiting list who practically have no chance of undergoing living donor LT (23).

Despite the bonus points, the drop out rate was still substantial (24). Increase tumor burden during a long period of waiting time might also adversely affect post-LT survival rate (25). Bridging therapy focused on treating patients within the criteria while they were on the waiting list, in order to avoid tumor progression to more advanced stage and therefore drop out from the waiting list. Bridging therapy was estimated to decrease drop out rate for HCC meeting the Milan criteria to 0–10%. To minimize the number of drop out from the waiting list and reduce the potential risk of recurrent tumor after LT, intervention strategies such as transarterial chemoembolization (TACE) and image guided ablative therapies have been offered to the patients. Effective bridging therapy during the waiting period would help to slow down the disease progression, and therefore, allow them to undergo deceased donor LT. Tumor recurrence rate after LT was found to increase from 12% for patients remaining within Milan criteria, either spontaneously or following bridging therapy, to 45% for those who had a tumor progression beyond the Milan criteria (11,26). Therefore, neoadjuvant therapy to control tumor growth and vascular invasion of the HCC and thereby avoidance of drop out during waiting time is of paramount importance. TACE has been used widely and is the most common bridging therapy.

This review focuses on various bridging and downstaging modalities in the treatment of HCC, in preparing patients for LT.

Diagnostic criteria for hepatocellular carcinoma (HCC) and pre-liver transplantation (LT) work up

The diagnostic criteria for HCC in our center were as follows: (I) typical abnormality with arterial enhancement and contrast washout in the portal venous phase in 3—phases contrast enhanced computed tomography (CT) or magnetic resonance imaging and/or (II) an elevated serum Alpha fetoprotein (AFP) level of greater than 400 ng/mL. Needle tumor biopsy was generally avoided in resectable cases to avoid the risk of needle tract seeding of tumor cells. The diagnosis of HCC was confirmed histologically in the resected or transplanted specimen. Major vascular invasion was defined as tumor thrombosis inside the major branch of the portal vein or hepatic vein macroscopically. In our centre, dual—tracer positron emission tomography (PET) with [^{11}C] acetate and [^{18}F] fludeoxyglucose (FDG) scan, or CT thorax and bone scan, were also used as part of the LT work up. Dual—tracer PET scan with the additional use of [^{11}C] could further improve the sensitivity and specificity in diagnosis of HCC and detection of metastasis to 96.8% and 91.7% respectively (27). Furthermore, PET scan had been used to predict the HCC with poor differentiation as well as presence of microvascular invasion especially by the [^{18}F] tracer (28).

Liver resection

Liver resection can be used as a form of primary treatment for HCC or as a bridging or down staging for LT. Liver resection can potentially control tumor growth with clear resection margin; in addition, it allows assessment of the tumor biology, such as tumor differentiation, presence of microvascular invasion, or capsular effraction, and provides hints for those patients who should be evaluate for earlier LT if possible (29).

Simple liver resection can only be performed in selected patients. Single exophytic or superficial tumor such as subcapsular neoplasms, or tumors in the left lobe are better

tumors to be performed in bridging or downstaging setting. Liver resection can allow salvage LT to be performed as the only curative measure if the tumors are still within the criteria after a period of wait and see. Reports suggested that the post–operative course, complications, and the 3- and 5-year survival rates did not differ significantly between cirrhotic HCC patients undergoing primary LT or secondary LT after the initial liver resection (30), especially those tumors initially submitted to liver resection with the Milan criteria (31,32), or the UCSF criteria (33). In our centre, approximately 80% of patients were still eligible for salvage LT at the time of tumor recurrence (34). However liver resection had risk of surgical complications, and it could only be performed in well-compensated patients without severe portal hypertension. Poor liver function, which was reflected by the high Child-Pugh grading, high indocyanine green retention rate at 15 minutes, i.e., >14% in major resection and 22% in minor liver resection (35), as well as thrombocytopenia were shown to be independent predictor of morality in patients with HCC and cirrhosis (14,36), and therefore, contraindicated for liver resection. Furthermore, the operated abdomen can make the subsequent LT technically more difficult and demanding, with a higher risk of post-operative complications (37).

Transarterial chemoembolization (TACE)

TACE has been proven to improve survival and control symptom (38). It has the advantage of instillation of the chemotherapeutic agent directly into the liver tumor, which was carried by the lipiodol, as well as ischemic necrosis induced by arterial embolization. It has been used for unresectable HCC in patients who are awaiting LT as well as those who are not transplant candidates opted for palliative care (39,40). Adequate tumor necrosis was achieved in the explant liver in the range of 27–57% in patients within Milan criteria (41,42). The use of TACE did not only to affect the features of tumor lesions, but also to impact recurrence rate of HCC after LT (41).

Various reports had suggested some of patients could be bridged as well as downstaged, which resulted in favorable long-term outcome (43-46). Unfortunately, not all patients responded to TACE. AFP level >100 ng/mL and high 3-year calculated survival probability might predict a good response to downstaging therapy after TACE (17). The aim is to achieve 100% necrosis of the tumors, but less than 30% of the cases could achieve complete pathological responds in the histological evaluation (41,45,47,48), hence the reported necrosis rate in the survival benefit after downstaging by TACE remained questionable (41,45,46,49). There was also report suggesting partial necrosis was a risk factor for tumor recurrence after LT (50). A recent study had shown that the significant of to achieve complete or nearly complete pathological response as bridging therapy improved long term survival after LT as it decreased the active tumor load (51). Moreover, a multicenter study suggested that preoperative loco-regional therapy decreased the risk of tumor recurrence in patients with pathologic T2 and T3 HCC (52). In addition, larger degree of tumor necrosis, i.e., >60%, of the largest tumor in the explant resulted in significant better survival than those with less degree of tumor necrosis (15). Afterall, sustained response to TACE would be a better selection criterion for LT than the initial assessment of tumor size or number (53). Majno et al. found a significantly prolonged recurrence-free 5-year survival of 71% in patients successfully downstaged with TACE compared to 29% where TACE did not lead to tumor reduction (41). Decaens *et al.* used TACE as the bridging therapy in a mean waiting time of 4.2 months which resulted >80% of tumor necrosis in the explants without significant difference in the long term survival (46). While another study didn't find significant difference in terms of the recurrent rate, however it attributed the possibility difference in the pathologic characteristic in which TACE group might have larger tumor without presence of the capsules (54). TACE given before LT was found useful for those patients with tumors >3 cm. Despite the controversy, TACE remained one of the commonest bridging and downstaging modalities. However it had to be balanced with the large tumors that were generally considered poor candidates for LT. The low incidence of recurrence for the tumor being downstaged within Milan criteria was similar to the patients with smaller tumors to start with, and therefore should not be excluded from LT (41).

Afterall, TACE is not applicable to every patient with cirrhosis. Patients who suffered from ascites and main portal vein thrombosis resulted from cirrhosis, poor liver function at risk of liver failure, poor renal function at risk of contrast nephropathy, difficult arterial anatomy and difficult cannulation are contraindication from TACE (38,55). These patients are at risk of tumor progression without any intervention. Therefore other forms of bridging therapy must be attempted and developed. Side effects range from post-embolization syndrome, tumor necrosis and rarely liver failure. The judicious use of the TACE would certainly help as a bridging and downstaging modality to LT.

Doxorubicin eluting bead (DEB) transarterial chemoembolization (TACE)

DEB aimed to bind, deliver and elute doxorubicin directly to the tumorous tissue in a sustained fashion (56-58). There are three substantial pharmacokinetic advantages associated with DEB: a continuous elution of the drug for prolonged period of time, a higher concentration locally into the tumor and a lower systematic exposure to the drug in comparison to TACE (56).

Despite reports suggested that there was no significant difference in terms of the safety profile, tumor response, tumor recurrence and overall survival rate for DEB as compared to TACE in non-transplant patients (57,59), DEB was shown to have lower tumor recurrence rate after LT and was identified as an independent predictor of recurrence-free survival in the multivariate analysis (60). Further study should be carried out to confirm the superiority of this technique.

Radiofrequency ablation (RFA)

RFA made use of the radiofrequency (RF) electrode tip, generating alternating electrical current (300–1,000 kHz), inducing temperature of 60–100 ℃. Irreversible damage was resulted by the coagulation necrosis. RF electrode tip could generate an ablative zone of 3–5 cm in diameter (61). An ablative margin of 0.5–1 cm of the peritumoral tissue was necessary as if a clear resection margin achieved during the resection of the HCC, and it should be able to be visualized by the ultrasound for both open and percutaneous procedures. The use of central bile duct cooling during RFA of periductal HCC was effective in preventing thermal injury of bile duct (62). However, the presence of the 'heat-sink effect' may affect the complete ablation of the tumor near the major vessels, and therefore increase the chance of local recurrence after RFA (63,64).

The use of RFA was proven to be safe and effective treatment modality for patients with advanced cirrhosis and non-resectable HCC (65). Majority of the lesions were shown to have high tumor necrotic rate (66), and especially for those HCC less than 3 cm in size (67-69). The drop out rate from the transplant list had decreased after treatment with RFA (67,68). Unfortunately, the remarkable necrotic effect was less than 50% when used in larger tumors (67-69). In fact, tumor size larger than 3 cm was found to be the risk factors for persistent HCC after the treatment (68,69). In addition, the procedure may be associated with a higher rate of satellite nodules occurrence (66). There are some limitations associated with the use of RFA. RFA could not be used in large tumor, preferred less than 5 cm (70), and its greatest effect as bridging therapy was found in patients with tumors 3 cm or smaller who were listed less than 1 year for transplant (71). Whereas higher rate of recurrence exceeding the Milan criteria was found in patients, especially for patient who had a larger tumor size (>2 cm) and/or a higher AFP level (>100 ng/mL) at their initial presentation and early recurrence after initial RFA (72).

Complications of RFA can be classified into collateral thermal damage, direct mechanical injury or other uncommon reported complications, such as haemobilia (73), liver failure (74), cardiac tamponade (75), liver abscess in the presence of bilioenteric anastomosis (76). Tumor seeding could be a potential problem, although rare ~0.3–0.5% (76,77), especially in the setting of bridging therapy, which may render potential LT impossible.

Microwave ablation (MWA)

MWA made use of the electromagnetic energy, creating an electromagnetic field that allowed rapid and homogenous heating of the tissue and resulted in heat-based thermal cytotoxicity from frictional heating from the rapid oscillation of water molecules (78). It also converted kinetic energy into heat through ionic polarization, therefore coagulation necrosis. Similar to RFA, the lesion should be able to be visualized by the ultrasound for proper localization. It created a predictable and reproducible area of tissue necrosis, and it could ablate the tumor capsule as well as surrounding extracapsular invasion. For larger tumors, multiple needle electrode insertions might be needed for complete tumor ablation (79). MVA appeared to be less susceptible to heat sink effects than RFA (80), which might be more effective near the hepatic veins and IVC (81). In general, studies had demonstrated similar complete ablation rate with RFA (82-85), data also showed similar survival rates after RFA and MVA for curative treatment for HCC (82,83,86). While MWA was shown to be a safe procedure use as a bridge for LT, it also allowed complete tumor necrosis (87). Unfortunately, there was higher rate of local tumor recurrence, which was attributed to the potential tumor seeding by the use of larger application (5 mm in diameter) (88). Complications are similar to those RFA, including bile duct stenosis and haemorrhage, with a potential risk of tumor seeding due to

large probe is used (89).

Irreversible electroporation (IRE)

IRE was a non-thermal ablative therapy that used high-voltage, low electrical current to irreversibly increase the permeability of target cells, disrupt cellular homeostasis, and induce apoptosis (90). It also induced complete cell death up to the margin of large vessels bypassing the heat sink effect seen such as in the RFA (91). Up-to-date, there is not much data regarding the use of IRE as bridging therapy, however complete necrosis was achieved in treatment of the tumor <3 cm by IRE (92). There is a potential role of using IRE in management patients waiting for LT.

Transarterial radioembolization (TARE)

Radioembolization involved the transarterial infusion of microspheres containing Y90 loaded microspheres, iodine-131-iodized poppy seed oil, or similar agents into the hepatic artery by transarterial techniques (93). The highly concentrated radioactive substance would be administrated to the tumor, while keeping the level of toxicity affecting the functional liver parenchyma at the minimal and preserving the blood supply (94,95). It was also safe for use in patients with portal vein thrombosis (96).

Candidates with good functional status and relatively adequate liver reserve with relatively normal liver function, low tumor burden without extrahepatic metastasis would be the ideal candidate for radioembolization (97). Reports found a trend towards shorter times to tumor response and longer times to tumor progression were apparent with TARE when compared with TACE (98,99), suggesting a potential advantage as a bridging therapy in patients waiting for LT.

Results of transarterial radioembolization (TARE)

There are limited papers describing downstaging of HCC by means of TARE (96,98,100,101). Downstaging of the tumor had been observed in the rate of around 37% without significant difference as compare to TACE, while the recurrence rate is 26% (102).

However, not all patients could undergo TARE. Pre-treatment mesenteric angiogram and 99Tc macroaggregated albumin scans were required to assess the anatomy and the presence of vascular shunting. This helped to minimize the risk of radiation pneumonitis due to the shunting. (98,99,103)In case of vascular shunting more than >20%, it could be embolized before therapy began. It appeared to be a safe treatment modality. The side effect is usually mild and limited to fatigue and constitutional symptoms (104,105). Nonetheless significant side effects due to non-targeted radiation resulted in cholecystitis, gastrointestinal ulcers, and pneumonitis were reported (43,97,103,106-109).

High intensity focused ultrasound (HIFU)

HIFU was an extracorporeal ablative modality making use of multiple ultrasound (USG) beams. It induced heat generation, produced mechanical effect and radiation forces, aiming at a temperature of 60 ℃ or higher, in order to cause coagulation necrosis and cell death. It allowed minimal thermal damage to tissue located between the transducer and the focal point (110). Clinical results for HIFU ablation of the tumor from China produced some encouraging findings in terms of significant tumor shrinkage and prolonged survival of patients (111-114).

HIFU had been shown to achieve favorable radiological responses for patients suffered from unresectable HCC and Child-Pugh C cirrhosis (115,116). Satisfactory tumor necrosis was also observed according to histological examinations of excised livers in a few transplant recipients (116,117).

HIFU had been shown to be an effective ablative modality in which similar tumor necrosis was achieved in in the explant liver as compared to the TACE. It had the advantage to be offered to the patients who are contraindicated for TACE, i.e., ascites, Child-Pugh C cirrhosis, portal vein thrombosis. It had also proven to improve the percentage of patients receiving bridging therapy in the transplant waiting list (118). In addition the number of drop out rate decreased (119). Nonetheless, whether this converted any survival benefit after the LT remained an area for further research.

Unfortunately, not every HCC could be treated by HIFU. It had to be visualized and localized by the ultrasound before HIFU could be carried out. It was a safe and totally extracorporeal procedure with minimal risk. Minor complications such as skin and subcutaneous tissue injuries occurred in most patients (116), however, more severe complications were reported such as bile duct injury. The patient should be fit to undergo general anesthesia, so to allow momentarily holding of breathing for more precise ablation.

Stereotactic body radiotherapy (SBRT)

SBRT involved the precision delivery of a highly focused dose of radiation to the target tumor over a short number of treatments. With the advancement of the imaging methods for localizing HCC, precise treatment planning facilitated the delivery of targeted radiation with minimal treatment of uninvolved tissue (120). Lesions near the bowels were not ideal for SBRT since there was risk of gastrointestinal perforation and bleeding, however it had the advantage to treat the lesions adjacent to the central biliary system that were not amenable to surgery or ablation (121).

SBRT had been used as one of the bridging therapies and it was found to be effective, safe with low toxicity profile (122-124). The dosage given ranged from 40 to 51 Gy. Complete necrosis in some of the lesions could be achieved at around 27%. Most of the tumors could be decreased in size or remained stable without dropped off (123).

Radiation induced liver toxicity

Radiation induced liver disease (RILD) had been defined as a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes occurring from 2 weeks to 4 months after radiotherapy. The probability of RILD rose up to 50% for a mean dose of 43 Gy given (125). In some severe cases, RILD might result in liver failure and mortality. Hence, careful administration of the radiation and precise planning of the radiotherapy would minimize the complications.

Sorafenib

Sorafenib was an oral multi-kinase inhibitor, which had been shown to have significant efficacy in prolonging the time-to-progression and was the standard treatment for patients with advanced HCC (126,127). Study on the use of sorafenib as bridging or downstaging therapy before LT was limited. A study on this issue, however, was given in patient median times to LT shorter than six months, suggested its cost-effectiveness while comparing to those without any therapy for T2-HCC patients waiting for LT (128). Combination of TACE and sorafenib might be a potential therapeutic approach for both bridging and downstaging HCC before LT. TACE allowed embolization of the tumor feeding vessel with focal chemotherapeutic effect, whereas sorafenib inhibited angiogenesis and retarded the tumor progression. There were clinical trials and studies working on the combination of the sorafenib with other modalities before LT (129).

Combination of modalities

Bridging loco-regional therapies should be sued whenever possible to prevent drop out and to minimize HCC recurrence after LT, particularly when the expected time to LT is longer than six months. TACE had been mostly studied as both bridging and downstaging protocols, especially for multifocal tumors (130). Combinations of various loco-regional modalities seemed to be more effectively downstage the patients than TACE alone (15,131). Given the effects of various modalities, tumor necrotic rate would potentially be increased, however whether this would convert to survival benefit would require confirmation from further studies. The role of the combinations of therapies in the bridging or downstaging setting is still to be determined.

Conclusions

Different modalities had been use as bridging therapies for LT so to decrease the number of drop out rate. At the same time, effective downstaging therapies allowed more patients to be put into transplant waiting list as long as the diseases are remained stable and within the criteria. Combine different modalities could be effective in achieve these goals. However, identification of tumors that would respond to the therapies, and therefore allowed better selection of the patients to be transplanted would benefit a more long term outcome.

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Footnote

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