Transjugular Intrahepatic Portosystemic Shunt in Hepatocellular Carcinoma Patients

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Liver cancer is very frequent, and hepatocellular carcinoma (HCC) accounts for the majority of liver cancer cases. Its growing incidence has been greatly affected by the increasing prevalence of metabolic-associated fatty liver disease (MAFLD). The latter is a new epidemic in the era. In fact, HCC is often generated from noncirrhotic liver and its treatment benefits from surgical and nonsurgical approaches, potentially bridged by transjugular intrahepatic portosystemic shunt (TIPS) use. TIPS use is an effective treatment for portal hypertension complications, but its application in patients with HCC and clinically significant portal hypertension (CSPH) remains controversial due to concerns about tumor rupture, dissemination, and increased toxicity.

Keywords: transjugular intrahepatic portosystemic shunt ; hepatocellular carcinoma ; locoregional therapy ; systemic therapy ; liver surgery

1. Introduction

Liver cancer is the seventh most frequent cancer worldwide and the second most frequent cause of cancer-related mortality [1]. Hepatocellular carcinoma (HCC) accounts for about 75% of the total cases; interestingly, it is one of the main contributors to the world's cancer burden [2]. The most important risk factors for HCC development are hepatitis B virus (HBV)/ hepatitis C virus (HCV) chronic infections, alcohol intake, and aflatoxin exposure [3]. However, increasing evidence supports the idea that metabolic syndrome, diabetes, and obesity may also play an important role in HCC development [4]. Moreover, the incidence of HCC is greatly increased in cirrhosis, regardless of the underlying etiology [5]. Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for portal hypertension complications. Typical indications for TIPS are refractory ascites and secondary prevention of variceal bleeding. Indeed, more recently, its application has also been used to treat acute refractory variceal bleeding, hepatorenal syndrome, and hepatic hydrothorax [6] (**Figure 1**). Although TIPS use can effectively reduce portal hypertension and may improve survival in some cirrhotic patients [7], to date, there is no clear consensus on the best treatment strategy in patients with HCC and clinically significant portal hypertension (CSPH). In fact, TIPS positioning in patients with HCC involves specific concerns: the possibility of tumor rapture and bleeding [8], tumor dissemination [9], increased toxicity, and complications of locoregional therapy [10]. On the other hand, TIPS use may play as critical role in some patients with CSPH, allowing the possibility of systemic therapy [11] and/or surgery [12][13].

TIPSS RECOMMENDATIONS	
Variceal bleeding	Gastro- oesophageal variceal bleeding refractory to endoscopic and drug therapy
	Child's C or MELD ≥19 bleeding from oesophageal varices or GOV1 and GOV2 gastric varices and are haemodynamically stable, early or pre- emptive TIPSS should be considered within 72 hours
	Secondary prevention of oesophageal or gastric variceal bleeding
	Bleeding from ectopic varices refractory to local and pharmacological therapies
	Bleeding from portal hypertensive gastropathy (PHG) refractory to NSBB and iron therapy,
Refractory or recurrent ascites	Except patients with bilirubin >50 µm/L and platelets<75×109, pre-existing encephalopathy, active infection, severe cardiac failure or severe pulmonary hypertension
Hydrothorax	Refractory hepatic hydrothorax
Hepatorenal syndrome	Renal function may improve following TIPSS, but it is still experimental
Budd–Chiari syndrome	When fail to respond to medical therapy with anticoagulation or hepatic vein interventions
Curative surgery for cancer	Insufficient data, there may be a role ?

Figure 1. Summary of main TIPSS recommendations.

2. Technical Feasibility and Safety of TIPS Use in HCC Patients

The presence of extensive hepatic malignancy is considered a relative contraindication to TIPS use. In addition, one of the factors limiting the application of TIPS placement in patients with portal hypertension and liver cancer is its feasibility and safety. The major concern linked to this procedure is the development of intraprocedural complications (e.g., liver failure, tumor rupture, or bleeding) [8]. However, in one of the largest retrospective studies accounting for 209 cases of TIPS placement in HCC patients, Qui et al. [14] showed that 97.69% of the TIPS procedures were successfully completed, with no serious procedure-related complications. Another issue may be linked to HCC dimensions: it was reported that large liver tumors are prone to rupture. Nevertheless, there was no evidence of an association of rupture with tumor size during TIPS placement in this enrolled cohort [14]. On the other hand, Liu et al. [15] reported tumor rupture in 8.6% of patients. Indeed, this was reported mainly in tumors bigger than 10 cm, and the cohort was significantly smaller than the previous one.

In particular, stent dysfunction and hepatic encephalopathy (HE) are recognized as common major complications of TIPS. In a recent meta-analysis, TIPS dysfunction was defined as the need for reintervention or clinical relapse, and its pooled incidence was 23% [16]. A possible cause of the increasing incidence of shunt dysfunction might be related to bare stent placement; there is significantly lower incidence in patients with polytetrafluoroethylene (PTFE)-coated stents.

Another anecdotal issue related to TIPS placement in the setting of HCC remains debated: the fear of HCC progression and tumor spread, which can occur, especially in centrally located nodules, because the creation of a connection between the portal vein and the hepatic vein could provide a route for cancer cell metastasis. However, the evidence of the risk of tumor dissemination after TIPS placement is limited.

3. TIPS and Locoregional Treatments: Transarterial Chemoembolization (TACE) and Transarterial Radioembolization (TARE)

According to Barcelona Clinic Liver Cancer (BCLC) staging, the Child–Pugh score influences HCC treatment choice. In fact, the Child–Pugh score predicts the outcomes of locoregional treatment in terms of liver decompensation and death. Because decompensated liver cirrhosis is usually a contraindication to locoregional treatments, TIPS use may offer the possibility to reach the goals through the resolution of refractory ascites and, in general, of decompensated liver function [17]. However, considering the changes in venous and arterial flow before and after the TIPS procedure, the efficacy and toxicity of TACE in combination with the TIPS procedure require special attention by physicians [18].

In a multicentric study, Huzheng Yan et al. [19] enrolled 68 patients with HCC and portal-hypertension-related refractory ascites. After TIPS implantation, patients were reassessed with the Child–Pugh score and evaluated for anti-HCC treatment. Of the patients, 14.7% received TACE alone, 30.9% received TACE combined with microwave ablation, and 14.7% received TACE combined with systemic therapy. The latter had a median OS of 8.7 months. Importantly, the authors estimated that TIPS use may have increased the chance of achieving locoregional treatment by at least 16.2%, explaining the improved survival rate.

Bin Qiu et al. [14] analyzed 261 patients with HCC and portal hypertension undergoing TIPS placement together with other interventional treatments. Within this cohort, 185 patients received TACE/transarterial embolization (TAE), and 113 received percutaneous radiofrequency ablations (RFAs) alone or in combination with other treatments. No procedure-related deaths or serious complications (e.g., abdominal bleeding, hepatic failure, or distant metastasis) were recorded.

Another retrospective study enrolled 50 patients undergoing TACE for HCC treatment. These patients were divided in 2 groups (25 patients with preexisting TIPS vs. 25 controls). Patients showed only one severe adverse event (namely, severe bilirubin increase) in the TIPS group, although the TIPS group had worse baseline liver function than the controls [20].

Specifically, only a few studies have evaluated the safety and efficacy of multihit TACE in patients with a TIPS. Ji-Won Kang et al. [21] studied 20 patients each undergoing single or multiple TACE for HCC treatment after TIPS placement. After the TACE procedure, 70% of patients showed tumor reduction, with a median survival period of 23 months. Only one patient experienced a major complication (namely, spontaneous bacterial peritonitis). From multivariate Cox regression analysis, it was shown that tumor stage only was the independent prognostic factor affecting patient survival ($p = 0.049$).

4. TIPS Use as a Bridge to Systemic Therapy

Since 2008, the prognosis of HCC patients with BCLC stage C has improved due to the introduction of the oral multikinase inhibitor sorafenib, which has increased the OS time by 2.8 months [22]. More recently, other treatments such as lenvatinib (an inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor (FGF) receptors 1–4, and platelet-derived growth factor (PDGF) receptor α) have proven noninferiority in terms of OS in treated vs. untreated advanced HCC patients [23]. Finally, during the last few years, a novel, more efficient breakthrough in systemic therapy emerged and is showing exciting results in terms of OS (19.2 months) [24] and PFS (6.8 months). Indeed, the combination of atezolizumab (anti-PDL1) and bevacizumab (anti-VEGF) is currently the first-line treatment for hepatocellular carcinoma [11][25], and new trials involving immune checkpoint inhibitors (anti-PD1/PD-L1 or anti-CTLA4) combined with molecularly targeted drugs are currently ongoing, producing promising preliminary results [26][27][28][29][30]. However, the administration of these promising treatments requires a Child–Pugh A status and a minimum risk of bleeding in order to avoid acute hepatic failure. Therefore, systemic therapy is highly discouraged in patients with CSPH and decompensated liver cirrhosis. In fact, the prognosis of patients with untreated advanced HCC (BCLC C or D) is poor [31].

In this scenario, TIPS use has a pivotal role in the management of decompensated cirrhotic patients with advanced HCC. Although up-to-date guidelines are unclear about symptomatic portal hypertension and portal vein thrombosis treatment in advanced HCC patients, recent evidence from the literature supports the use of TIPS and sequential systemic therapy in these patients [32].

Indeed, portal hypertension and its assessment also have a role in guiding physicians regarding HCC aggressiveness and its recurrence rate after liver resection. For example, Marasco et al. [33] demonstrated that spleen stiffness (the major noninvasive parameter of HVPG in patients with CSPH [34]) is the only independent variable that correlated with tardive HCC recurrence (namely, after 3 years from liver resection). Moreover, at a molecular level, the relationship between portal hypertension and HCC development can be explained considering the onset of shear and oxidative stress due to chronic inflammation and the fibrotic distortion of sinusoids with increased levels of proinflammatory and neo-angiogenetic molecules [35]. This is followed by reduced a homeostatic autophagic phenomenon, promoting the development of more aggressive phenotypes of HCC [36].

In this field of investigation, Takemura et al. [37] further highlighted the role of perioperative portal vein pressure management (e.g., endoscopic varices ligation or Hassab decongestion operation) to improve prognosis in patients undergoing hepatectomy for hepatocarcinoma. An interesting case report was described by Polacco et al. [13], realizing a surgical porto-systemic shunt in order to achieve a “salvage” hepatectomy to control HCC progression in a patient affected by decompensated cirrhosis, perhaps a candidate for a liver transplant.

Two case reports described hepatic surgery after a TIPS procedure in cirrhotic patients affected by HCC. The first patient [38] was diagnosed with one nodule of hepatocarcinoma (50 mm, segment VII) in compensated cirrhosis (Child–Pugh A5) complicated with low platelet count (<100,000/mmc): anatomic segmentectomy was realized after TIPS positioning between middle hepatic vein and left portal vein branch. The second patient with a TIPS [39], which was previously received for decompensation, underwent liver resection of intermediate HCC (11 cm) without severe complications.

5. Conclusions

TIPS placement is technically feasible and safe in HCC patients with CSPH when performed in selected cases. TIPS use may improve liver function, enabling subsequent anticancer therapies in HCC patients, potentially leading to better outcomes. The combination of TIPS use with locoregional treatments and systemic therapy shows promising results and may improve survival rates. Moreover, TIPS can be safely considered, upon multidisciplinary evaluation, in patients with CSPH and resectable HCC or candidates for OLT. Patient selection for TIPS use in HCC with CSPH should be based on a multidisciplinary approach involving hepatologists, interventional radiologists, and oncologists. Careful consideration should be given to the overall liver function, tumor characteristics, and the of other comorbidities. Experienced surgeons should perform TIPS procedures in HCC patients to minimize the risk of complications. Close monitoring and surveillance for potential tumor-related complications, such as rupture and dissemination, should be carried out following TIPS placement. Long-term studies evaluating the impact of TIPS use on OS and quality of life in HCC patients are necessary. Multicenter prospective studies are needed to provide stronger evidence of the selection criteria, safety, and efficacy of TIPS use in HCC patients in different therapeutic scenarios. These studies should include larger sample sizes, control groups, and standardized protocols to address the current knowledge gaps and provide more definitive recommendations.

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