



Eastern experience: surgical resection may be the first choice of treatment for selected hepatocellular carcinoma patients with portal vein tumor thrombus

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common worldwide cancer and has dismal outcomes because of its high morbidity and mortality, particularly in Eastern countries (1,2); however, the morbidity of HCC is increasing in the Western countries (3). Portal vein tumor thrombosis (PVTT) occurs in 44–62.2% of patients with advanced HCC with a natural median survival time (MST) of 2.7–4 months and is the most commonly recognized risk factor for prognosis (4). PVTT is regarded as an advanced stage of HCC, and sorafenib is only recommended to treat PVTT according to the American Association for the Study of the Liver Disease/Barcelona Clinic Liver Cancer (AASLD/BCLC) staging system and treatment guidelines (5-7). Despite recent advances in the treatment of such patients, the treatment strategies for PVTT remain controversial.

As reported in recent studies in Eastern countries, surgical resection (SR) is no longer contraindicated for HCC with PVTT because of advances in surgical techniques, perioperative management, and patient selection (8,9). Other than SR, transarterial chemoembolization (TACE), radiotherapy (RT), and radiofrequency ablation (RFA) are applied for PVTT, which all may benefit select HCC patients with PVTT (10-12). Giving the multiple therapeutic strategies that are becoming available for PVTT and the practice-changing advances rapidly growing

in last years, the real issue seems to be the combined therapy principle dominated by SR, and SR may be the first treatment of choice for HCC with PVTT as long as the PVTT is limited to a first-order branch. In this perspective, we aim to discuss the recent conceptual changes on treating PVTT, summarize the data on SR for PVTT, and predicting future directions of multidisciplinary diagnosis and treatment.

Classification of PVTT

As for BCLC staging system, PVTT is regarded as HCC metastasis and vascular invasion, BCLC staging C, but this HCC staging system do not further define the extent and location of PVTT. Moreover, PVTT has different classification and each classification has diverse types of PVTT. The classification of PVTT is necessary for the guidance of treatment and a comparison of outcomes between different types of PVTT. The frequently used classification are Cheng's classification [type I₀: microvascular invasion (MVI); type I: tumor thrombus involving segmental branches of the portal vein or above; type II: tumor thrombus involving the right/left portal vein; type III: tumor thrombus involving the main portal vein trunk; type IV: tumor thrombus involving the superior mesenteric vein] (13,14) and Vp classification (Vp1: PVTT involving the third-order branch; Vp2: PVTT involving the second-order branch; Vp3: PVTT involving the first-order branch; Vp4: PVTT involving the main trunk/contralateral branch) (15). Compared with

two classifications, microvascular is prominent as type I₀ in Cheng's classification; Vp4 is subdivided into type III and IV. From the above, Cheng's classification is more detailed and practicable.

Operative indication for HCC with PVTT

PVTT is regarded as a contra-indication of SR for HCC from Western countries. But for Eastern countries, some well-selected HCC patients with PVTT could accept surgery. Based on recent researches, such as expert consensus from China and Hong Kong (16,17), operative indication of SR for HCC patients with PVTT are as follows: (I) patients with good general condition to tolerate anesthesia and surgery, and with Eastern Cooperative Oncology group (ECOG) scores 0–2; (II) moderate liver function with Child-Pugh class A or B and moderate residual liver function reserve; (III) complete HCC resection and PVTT thrombectomy or an embolectomy; (IV) without multiple intrahepatic HCC metastasis and distant extrahepatic metastasis; (V) type I and II PVTT; type III PVTT (relative contra-indication of SR).

Advantages of SR for HCC with PVTT

As a result of recent advances in surgical techniques and perioperative management, SR has become a reasonably safe treatment option with an acceptable mortality and morbidity rate (8). SR of PVTT may provide the following clinical benefits (18): (I) reduced patients' tumor burden after SR; (II) decreased portal venous pressure and reducing the risk of upper gastrointestinal bleeding; (III) portal venous flow recovered to improve of liver function; (IV) prolongation in overall survival (OS); and (V) improvement in quality of patients' life.

Safety and efficacy of SR for HCC with different types of PVTT

Comparison of SR and non-SR for PVTT

The location and extent of a PVTT plays an independent prognostic role in determining surgical outcomes for PVTT patients. In recent advances, a multicenter retrospective study (9) with the largest sample size of 1,580 patients conducted in China showed that surgical treatments (ST) was the best treatment for type I and II PVTT patients with Child-Pugh A and selected B liver function. The MST

for ST (n=745) for type I, II, and III patients (95% CI) were 15.9 (13.3–18.5), 12.5 (10.7–14.3), and 6.0 (4.3–7.7) months, respectively; correspondingly for TACE (n=604), that were 9.3 (5.6–12.9), 4.9 (4.1–5.7), and 4.0 (3.1–4.9) months, respectively; for patients after TACE combined with sorafenib (n=113) 12.0 (6.6–17.4), 8.9 (6.7–11.1), and 7.0 (3.0–10.9) months, respectively; and for patients after TACE combined RT (n=118) 12.2 (0–24.7), 10.6 (6.8–14.5), and 8.9 (5.2–12.6) months, respectively. Comparison among the different treatments for the three subtypes of PVTT patients after propensity score matching showed the effectiveness of ST to be the best for type I and type II PVTT patients, and TACE-RT was most beneficial for type III patients. In addition, another study conducted from Japanese nationwide including 6,474 patients from a number of medical centers showed that SR is associated with a longer survival outcome than non-surgical treatment, such as TACE, RT and sorafenib, as long as the PVTT is limited to the first-order branch, Vp1-3 PVTT (Cheng's type I and II PVTT) and patients had Child-Pugh A and Child-Pugh B liver function. In the Child-Pugh A patients, the MST in the SR group was 1.77 years longer than that in the non-SR group (2.87 vs. 1.10 years; P<0.001). Similarly after propensity score matching of 1,058 patients, the MST in the SR group was 0.88 years longer than that in the non-LR group (2.45 vs. 1.57 years; P<0.001). The survival benefit was not statistically significant only in patients with PVTT invading the main trunk or contralateral branch, Vp4 (Cheng's type III and IV). In this study, the postoperative 90-day mortality rate was 3.7% (68 patients of all 1,058 patients) with high safety in SR group. Some studies (19–23) aimed to comparing SR and TACE and concluded concordant results that SR is superior to TACE for HCC patients with type I and II patients. In a number of reports concerning either type of PVTT, for type I PVTT, 1-, 3-, and 5-year OS rates after SR ranged from 57.2% to 100.0%, 21.0% to 54.4%, and 0% to 37.9%, respectively; for type II PVTT, 1-, 3-, and 5-year OS rates after SR ranged from 35.0% to 66.7%, 0% to 27.4%, and 0% to 17.2%, respectively; for type III PVTT, 1-, 3-, and 5-year OS rates after SR ranged from 25.0% to 36.3%, 0% to 14.3%, and 0% to 11.1%, respectively. From the above, the efficacy and safety of SR for HCC patients with PVTT have greatly improved in the past few decades.

Comparison of diverse methods of SR for PVTT

At present, the commonly performed methods and

techniques of SR included segmental hepatectomy, hemi-hepatectomy, hemi-hepatectomy combined with thrombectomy and hepatectomy and portal vein resection combined with portal vein reconstruction. Segmental hepatectomy and hemi-hepatectomy are suitable for type I and II PVTT, due to the PVTT is confined to segmental branches of the portal vein and located in the left or right half of the liver without extending beyond the hemi-liver. For type III PVTT, hemi-hepatectomy combined with thrombectomy is appropriate. Because type III PVTT invades main portal vein and extends the scopes of SR, hemi-hepatectomy alone is not enough to eradicate lesions of HCC. Thrombectomy is performed to eradicate the lesions of PVTT. If PVTT invades the main portal vein wall and removal is unrealistic, the invaded portal vein is promoted to be resected together with hepatectomy, then portal vein reconstruction is conducted using an end-to-end portal vein anastomosis.

Recently, two surgical techniques are applicable for PVTT widely. For PVTT was located in the hepatic resection area, the tumor en bloc could be removed. Therefore, for PVTT was beyond the resection line, thrombectomy or suction could be performed. Some studies compared survival outcomes, recurrence and complications between the approaches of thrombectomy and en bloc resection. Shaohua *et al.* (24) reported that the median OS for patients (n=38) under en bloc was significantly longer than these patients (n=39) under thrombectomy (14.3 *vs.* 10.4 months, $P=0.047$). However, patients under thrombectomy had significantly higher median blood loss ($P=0.002$) and higher blood transfusion rate ($P=0.002$) during the operation. Wu *et al.* demonstrated that both 5-year OS and disease-free survival (DFS) were not significant reduced in patients with PVTT extended to the bifurcation of portal vein if en bloc resection was performed. And they also revealed that these two approaches are not significant different in morbidity and in-hospital mortality. As reported for type III PVTT, preoperative small-dose RT could downstage from type III PVTT to type I and II PVTT, reduce recurrence rate without increasing surgical risks, and reduce postoperative hepatic failure rates (25). In summary, type I and II PVTT were recommended to en bloc, and SR with thrombectomy could be performed if PVTT was beyond the resection line; type III PVTT may be under SR after preoperative small-dose RT.

Necessity of postoperative adjuvant therapy

PVTT was regarded as intrahepatic and extrahepatic

metastasis, and SR alone hardly achieve the desired effect. SR combined with postoperative adjuvant therapy, such as TACE and RT, could improve patients' outcomes. TACE can be safely performed even in HCC patients with PVTT if they have good liver function and sufficient collateral circulation after portal vein occlusion (26). TACE could embolize the hepatic artery, then reduce the blood supply of HCC, and achieve curative effects. Ye *et al.* (21) reported that the OS of patients with PVTT under TACE was prolonged, and the MST was 7 months. Postoperative adjuvant is necessary to prevent HCC recurrence and prolong survival of patients. Bai *et al.* (27) indicated that MST in patients with postoperative adjuvant TACE (21.91 ± 3.60 months) or RT (14.53 ± 1.61 months) was significantly longer than patients with SR alone (8.99 ± 1.03 months). But the difference between adjuvant TACE and RT was of no significance ($P=0.716$). The median DFS was 6.51 ± 1.44 months in conservative group, 13.98 ± 3.38 months in TACE group, and 14.03 ± 2.40 months in RT group. Thus, they concluded that postoperative adjuvant TACE and RT may be a choice for HCC patients with PVTT. However, these results should be prospective, large samples, multi-center randomized controlled study to further confirm the efficacy.

Controversy on SR for PVTT between Eastern and Western countries

Western guidelines regarded PVTT as advanced HCC combined portal vein invasion. Sorafenib was only recommended treatment for PVTT patients with prolonged OS for 0.23 years (5), and had poor efficacy for prevention of HCC recurrence. However, Eastern guidelines had different views on SR for HCC patients with PVTT. SR could be performed for some selected HCC patients with good liver function and type I and II PVTT. A new published "Chinese expert consensus on multidisciplinary diagnosis and treatment of HCC with portal vein tumor thrombus: 2016 edition" (16) approves SR as eligible for resectable HCC with type I and II PVTT and recommends that adjuvant therapies, preoperative RT or postoperative TACE, should be performed. In addition, an expert consensus from Japanese, "2014 update JSH Consensus-based Clinical Practice Guidelines for the Management of HCC" (28) supports SR as feasible for selected patients with HCC, with VP1-3 type PVTT and Child-Pugh A liver function.

Perspectives in future

From the above perspectives, the surgeons identify PVTT

as not an absolute contra-indication for SR. In the future, the following principles in clinical practice need continued exploration: (I) surgical methods for PVTT need innovations; (II) additional rigorous, multicenter randomized controlled trials with large samples should be conducted assess the long-term curative effects and improve the stability of SR for different types of PVTT; (III) multidisciplinary diagnosis and treatments, with SR as a center, is a development trend for helping HCC patients with PVTT.

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