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REVIEW

Management of hepatocellular carcinoma with portal vein thrombosis

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Abstract

Management of hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) is complex and requires an understanding of multiple therapeutic options. PVT is present in 10%-40% of HCC at the time of diagnosis, and is an adverse prognostic factor. Management options are limited, as transplantation is generally contraindicated, and surgical resection is only rarely performed in select centers. Systemic medical therapy with sorafenib has been shown to modestly prolong survival. Transarterial chemoembolization has been performed in select cases but has shown a high incidence of complications. Emerging data on treatment of PVT with Y-90 radioembolization suggest that this modality is well-tolerated and associated with favorable overall survival. Current society guidelines do not yet specifically recommend radioembolization for patients with PVT, but this may change with the development of newer staging systems and treatment algorithms. In this comprehensive literature review, we present current and available management options with the relative advantages, disadvantages and contraindications of these treatment options with summarized data on overall survival.

Key words: Hepatocellular carcinoma; Portal vein thrombosis; Yttrium 90; Selective internal radiation therapy; Management

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Core tip: Management for hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT) is more challenging and limited than for HCC without PVT. Currently, liver transplantation is generally contraindicated and surgical resection with curative intent is controversial. Systemic chemotherapy with sorafenib has been shown to modestly prolong survival. Transarterial chemoembolization has traditionally been considered to be contraindicated due to its high embolic effect causing hepatic necrosis and worsening liver dysfunction. External radiation therapy is limited by the sensitivity of the liver to radiation toxicity. In this review, these

treatment options are comprehensively presented, along with a relatively new modality in the treatment of HCC, selective internal radiation therapy with yttrium-90.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, the sixth most common cancer overall, and the third most common cause of cancer-related death worldwide[1]. It is responsible for over 700000 deaths annually[2,3]. In Western countries, the incidence of HCC is expected to increase in the coming years because of an aging cohort of patients infected with hepatitis C several decades ago and the rising epidemic of nonalcoholic fatty liver disease[4-7].

Portal vein thrombosis (PVT) is a common complication of HCC, which is associated with a poor prognosis. Approximately 10%-40% patients with HCC have PVT at the time of diagnosis[8-10], and approximately 35%-44% will be found to have PVT at the time of death or liver transplant[11]. Patients with PVT are more likely to have metastatic disease at diagnosis, have fewer therapeutic options, and have shortened overall survival compared to patients without PVT. In patients with PVT treated with supportive care, studies have reported overall survival ranging from two to four months, compared to 10-24 mo in HCC patients without PVT[9,10,12]. Thrombus involving the main portal vein is a worse prognostic factor than thrombus involving a branch portal vein[13].

Management options for HCC with PVT are more limited than for HCC without PVT. Liver transplantation is generally contraindicated in these patients, and surgical resection with curative intent is controversial and not performed in most centers. Percutaneous ablation, another potentially curative therapy for small tumors, is less effective and potentially unsafe for tumors with PVT due to their proximity to the hepatic vascular structures. Transarterial chemoembolization (TACE) has traditionally been considered to be contraindicated in cases of PVT due to its high embolic effect and the potential for inducing hepatic necrosis and worsening liver dysfunction. External radiation therapy is limited by the sensitivity of the liver to radiation toxicity and the poor hepatic reserve of most HCC patients. These treatment options are reviewed below, along with a relatively new modality in the treatment of HCC, selective internal radiation therapy with yttrium-90, which is finding application in the treatment of HCC with PVT (Table 1).

SURGICAL MANAGEMENT

For eligible patients, liver transplantation remains the definitive curative treatment for cirrhosis as well as for hepatocellular carcinoma. However, due to high rates of tumor recurrence after transplantation in cases of HCC with PVT, transplantation is generally regarded as contraindicated in these patients[14-16]. Surgical resection is often technically infeasible in patients with PVT, and is associated with poorer outcomes. In a series of 406 patients who underwent partial hepatectomy for HCC with PVT, the one- and three-year overall survival were 34% and 13%, respectively, and the corresponding disease-free survival rates were 13% and 5%[17]. Another large series of 438 PVT patients who underwent resection for PVT found main portal vein tumor thrombus to be a significant risk factor for recurrence at 1 year, compared to branch portal vein (79% *vs* 45%)[18]. Overall survival in this series was 18.8 mo with branch portal involvement and 10.1 mo with main portal involvement. Smaller series have reported overall survivals of 9 to 15 mo in selected patients, mostly with good underlying liver function, many of whom received additional treatments[19-22]. These series generally report operative mortality rates of 0%-6%.

The most common staging system for HCC employed in American and European centers, the Barcelona Clinic Liver Cancer (BCLC) system, recommends against surgical resection in cases of PVT[23]. Surgical resection for HCC with PVT is more frequently employed across Asia[24], where hepatitis B is more common as a predisposing risk factor and patients tend to have better underlying liver function. Some centers have reported survival outcomes for patients with various degrees of portal vein invasion ranging from 9 to 33 mo[13]. Outcomes of surgical resection for tumors involving the main portal vein remain relatively poor in these series, with reported median survival of nine to ten months, and 3-year survival rates of zero to six percent.

SYSTEMIC THERAPY

Sorafenib is an oral multikinase inhibitor that targets tumor cell proliferation and angiogenesis. It was the first systemic agent shown to improve overall survival in patients with unresectable HCC, including those with PVT, and it is currently the only therapy specifically recommended for HCC with PVT in American Association for the Study of Liver Disease (AASLD) and European Association for Study of the Liver (EASL) guidelines[25,26]. The Sorafenib HCC Assessment Randomized Protocol (SHARP) trial[27] compared sorafenib to placebo in patients with good baseline liver function (mostly Child-Pugh A) with advanced, unresectable HCC. Median survival in the treatment group was 10.7 mo compared to 7.9 mo in the

Table 1 Up-to-date summary of management options for hepatocellular carcinoma with portal vein thrombosis

	Survival data (mo)					Adverse effects	Key references	Additional comments
	Overall survival	Main PVTT	Branch PVTT	CP-A	CP-B			
Supportive care	2-4						Schoniger *et al*[12], Minagawa *et al*[9], Llovet *et al*[10]	
Surgical resection	9-33	9-10				0%-6% operative mortality	Lau *et al*[13], Shi *et al*[17], Chen *et al*[18], Lin *et al*[21]	Employed in select centers
Sorafenib	6-8			8.1		skin reaction, diarrhea, fatigue	Llovet *et al*[27], Cheng *et al*[29]	Recommended by AASLD and EASL guidelines; Dose reduction in 25%, interruption in 44%
XRT	9.6					radiation induced liver disease	Toya *et al*[53]	Investigational
TACE	7-10	5.3	10.2	7.4	2.8	liver failure, postembolization syndrome	Pinter *et al*[40], Chung *et al*[41], Luo *et al*[43], Xue *et al*[48]	Lowest risk with nonocclusive thrombus, cavernous transformation, superselective TACE
Y-90 SIRT	5-17	9	17	10.4	5.6	fatigue, hyperbilirubinemia, GI ulceration	Salem *et al*[70], Hilgard *et al*[69], Sangro *et al*[71]	Currently, PVT is one of the indications for Y90

control group. In a subgroup analysis[28], patients with macroscopic vascular invasion, presumably largely consisting of PVT, had an overall survival of 8.1 mo in the sorafenib group, compared to 4.9 in the control group. The respective times to progression were 4.1 and 2.7 mo. Both of these differences were significant. The Sorafenib Asia-Pacific Trial, the other landmark trial of oral sorafenib for patients with advanced stage HCC, obtained largely concordant results[29]. Sorafenib was found to prolong overall survival in all patients with unresectable HCC (6.5 mo *vs* 4.2 mo). In subgroup analyses[30], sorafenib was found to have modestly prolonged survival in patients with macroscopic vascular invasion and/or extrahepatic spread of tumor (5.6 *vs* 4.1). Time to progression was likewise somewhat prolonged (2.7 mo *vs* 1.2 mo).

Subsequent studies have confirmed that sorafenib confers a relatively similar survival benefit to patients with PVT compared to those without, with a similar safety profile[31]. The most frequent adverse reactions to sorafenib are hand-foot skin reaction, diarrhea, and fatigue, which necessitate dose reduction or discontinuation in a minority of patients.

Sorafenib is considered appropriate for patients with unresectable HCC whose liver disease remains well-compensated (Child-Pugh A). A portion of Child-Pugh B patients may benefit from sorafenib[32], however Child-Pugh C patients are unlikely to benefit from sorafenib due to their limited life expectancy and inability to tolerate the medication[33]. Treatment is generally continued until there is evidence of disease progression or death. Combination of sorafenib with locoregional therapies remains an area of active investigation. Besides sorafenib, multiple additional agents are under investigation, but so far none have demonstrated efficacy in phase Ⅲ trials, either in the setting of progression on sorafenib or as primary therapy[34]. Although a select group of patients responds remarkably to sorafenib, even to the point of downstaging[35,36], the majority of patients with PVT have relatively short overall survival expectancy despite treatment, which has inspired continued efforts at developing locoregional therapeutic options.

TRANSARTERIAL CHEMOEMBOLIZATION

TACE is a percutaneous technique for delivering chemotherapeutic agent (generally either cisplatin or doxorubicin) directly to a liver tumor *via* its arterial blood supply. The drug is suspended in iodized ethyl esters of poppyseed oil (lipiodol), or impregnated into drug-eluting beads, and is then delivered directly into the feeding tumoral artery. TACE takes advantage of the fact that HCC is preferentially fed by the hepatic arterial circulation, while the majority of blood flow to the normal liver comes from the portal vein, which allows relatively selective targeting of tumor and sparing of uninvolved liver. TACE has an established role as a locoregional therapy for inoperable tumors, which has been shown to prolong survival[37-39], and as a means of maintaining local control of tumor while a patient awaits definitive surgical management, the so-called "bridge to transplant"[26].

Historically, PVT has been considered a contraindication to TACE due to the risk of precipitating liver necrosis and worsened liver dysfunction, related to the embolic effect of TACE on an already compromised hepatic vascular supply. In more recent years, several groups have reported that subselective and superselective TACE can be performed safely in some patients with PVT, and is associated with improved overall survival[40-47]. Overall survival among PVT patients treated with TACE in these studies ranged from 7.0 to 10.2 mo. In a large nonrandomized study, Luo

and colleagues prospectively treated 164 patients with PVT with either lipiodol TACE or conservative treatment[43]. Twelve and 24 mo survival rates in the TACE group were significantly prolonged (30.9% and 9.2%, *vs* 3.8% and 0%), and the benefit was consistent across patients with segmental and main PVT. A 2013 meta-analysis examined eight controlled trials involving 1601 patients with PVT[48]. TACE was favored over conservative treatment in all studies, and pooled analysis estimated TACE to have a significantly beneficial effect on 6 mo and 1 year mortality (HR = 0.41 and 0.44, respectively). In this analysis, TACE was favored for main as well as branch portal vein tumor thrombus, and in both Child-Pugh A and B cirrhotics, although there were fewer patients and more heterogeneity in these comparisons. A 2014 meta-analysis of 5 studies involving 600 patients likewise found TACE to be associated with improved 1-year survival compared with placebo in patients with PVT[47].

Overall, TACE is now regarded as a viable therapeutic option for select patients with PVT, especially for those with nonocclusive thrombus or cavernous transformation of the portal vein, provided their underlying liver function is relatively preserved and their tumor burden is such that the procedure is technically achievable. However, reported overall survival of 7.4 to 10.2 mo is only marginally better than systemic sorafenib, and inferior to survival that has been reported with other modalities, in particular selective internal radiation therapy.

EXTERNAL RADIATION THERAPY

Use of external radiation therapy for liver lesions has traditionally been limited in patients with compromised underlying liver function. These patients are especially prone to develop radiation-induced liver disease, in the form of hepatic veno-occlusive disease[49,50]. However, newer techniques, in the form of stereotactic body radiation therapy, allow high doses of radiation to be delivered very selectively, with relative sparing of uninvolved liver[51,52].

There have been few studies specifically examining the effect of external radiation therapy in HCC with PVT. Toya and colleagues[53] achieved a median survival of 9.6 mo in 34 HCC patients with PVT using conformal radiation therapy. Lee and colleagues treated 46 patients with PVT with conformal radiation therapy and reported complete or partial response in 33%[54]. In this series, patients who initially responded to treatment showed a 1-year survival of 66.8%, compared to 27.4% among nonresponders. Other groups have reported overall survival of 10 mo or more in these patients when external radiation therapy is combined with other modalities[55-57], and some studies have specifically combined radiation with sorafenib[58,59] and TACE[60-63]. A recent retrospective series of 97 patients compared radiotherapy to systemic sorafenib in patients with PVT, and found that, after performing propensity score matching, radiotherapy was associated with longer overall survival[64]. Use of external radiation therapy for HCC is not yet regarded as standard treatment, but remains an area of active investigation.

SELECTIVE INTERNAL RADIATION THERAPY

Selective internal radiation therapy (SIRT) or transarterial radioembolization with yttrium-90 is a relatively new therapeutic modality for HCC and other liver tumors, in which therapeutic doses of radiation are delivered to the tumor transarterially. There are two commercial products currently available, SIR Spheres, which are 20-60 μm particles made of a biocompatible resin, and Therapheres, which are 20-30 μm glass particles. Both are considered permanent embolic agents, although due to their small size have much less embolic effect than a TACE procedure, with less effect on hepatic vascular dynamics[65]. Indeed, continued blood flow to treated tissue is necessary and desirable for radiation to have its intended effect through the production of free radicals. Yttrium-90 is a pure beta-emitting isotope that decays to zirconium-90 with a half-life of 64.1 h. Ninety-four percent of the total radiation dose is delivered within 11 d of the procedure. The emitted radiation penetrates surrounding liver tissue to an average depth of 2.5 mm and a maximum depth of 11 mm, such that there is essentially no expected radiation exposure to non-treated individuals in contact with the patient, and post-procedure isolation precautions are not necessary. Radiation doses delivered to the tumor, however, can be very high due to preferential flow of embolic particles toward hypervascular tumor tissue, in a ratio of between 3:1 and 20:1 compared to unaffected liver[66]. Particles preferentially accumulate in the periphery of tumor masses, where most viable tumor cells are located. On the basis of explant studies, it has been estimated that local radiation doses on a microscopic scale may vary from 100 Gy to more than 3000 Gy[66]. The radiation dose may be delivered to the whole liver, to both lobes sequentially, to a single lobe, or to a segment.

SIRT has found application as a locoregional therapy for unresectable HCC that is not amenable to TACE because of diffuse or multifocal disease, or as an alternative to TACE[13,67]. Although no randomized controlled trials have been performed directly comparing SIRT with TACE or other local therapies, numerous retrospective series have reported favorable outcomes and acceptable safety profiles in HCC patients[68-71]. Subgroup analyses from the three largest series of HCC patients treated with SIRT, together totaling over 700 patients, 234 of whom had PVT, demonstrated remarkably similar overall survival

times ranging from 10.0 to 10.4 mo among all patients with PVT[68-71]. The largest group of PVT patients, reported by Salem and colleagues, showed overall survival of 16.6 mo among Child-Pugh A cirrhotics with branch PVT, decreasing to 4.5 mo among Child-B cirrhotics with main PVT[70]. This and other series have reported better overall survival in patients who demonstrate complete or partial response by WHO or EASL criteria following SIRT. Smaller series of patients with PVT treated with SIRT have demonstrated largely concordant results, with overall survival ranging from 7.2 to 13 mo[72-75]. A recent prospective phase Ⅱ trial including 35 patients with branch or main PVT treated with SIRT has reported an overall survival of 13 mo[76]. In this study, Child-Pugh A patients showed an overall survival of 16 mo, compared to 6 mo for Child-Pugh B patients. A small nonrandomized study compared outcomes in 32 patients with unresectable HCC, one half of whom had major vascular invasion, following either TACE or SIRT[77]. Among patients with major vascular invasion, the SIRT group showed an overall survival of 12.0 mo, compared to 8.0 mo in the TACE group.

Toxicity of SIRT is generally mild compared to TACE. A robust post-embolization syndrome with fever, abdominal pain and elevated liver enzymes, such as is common after TACE, is infrequently seen. The most common side effects are fatigue (occurring in approximately 40% of treated patients) and elevated bilirubin (in approximately 20%)[78]. Most serious complications, including radiation pneumonitis, radiation cholecystitis, hepatic abscess, and radiation induced liver disease are reported in < 1% of patients. Gastrointestinal ulceration has been reported to occur in approximately 5% of patients[78], but several recent large series have reported a 0% rate of GI ulceration[70,76], and this complication may be largely avoidable with careful pre-procedure preparation and appropriate quantitative radiation dosing[79]. SIRT is commonly performed as an outpatient procedure, unlike TACE which usually requires at least an overnight hospital admission. However, SIRT does require a separate prior mapping procedure, consisting of mesenteric angiography to ensure that there are no branching vessels near the intended catheter position, such as the gastroduodenal artery or left gastric artery, which could result in off-target embolization to bowel. If these vessels are identified they may be preemptively coil-embolized. Generally as part of the same pre-SIRT mapping procedure, technetium-labelled macroaggregated albumin is injected from the intended catheter position, and subsequent scintigraphic or SPECT imaging is performed to quantify the fraction of embolic particles that are shunted to the lungs. The accepted safe radiation dose to the lungs is < 30 Gy in a single procedure, and < 50 Gy total over multiple procedures. Inability to prevent excessive lung dose or off-target embolization are contra-indications to SIRT. Additionally, ideal candidates for the procedure will have good ECOG performance status (≤ 2), relatively preserved liver function (bilirubin < 2, albumin > 3, platelets > 50), and adequate renal function (creatinine < 2)[78,80].

GUIDELINES FOR MANAGEMENT OF PORTAL VEIN TUMOR THROMBUS

The BCLC staging system regards portal vein invasion as advanced (stage C) disease, for which systemic therapy in the form of sorafenib is the recommended treatment[23]. Current guidelines from the AASLD[26] and the EASL[81] largely embrace BCLC staging and treatment recommendations. AASLD guidelines recognize radioembolization as an effective treatment, but stop short of recommending it for any specific HCC-related indication due to lack of data directly comparing it to alternatives such as TACE or sorafenib. Current EASL guidelines discourage TACE for patients with macroscopic vascular invasion, and state that radioembolization can be safely performed on patients with PVT with promising results, but more study is needed before it can be recommended as standard therapy. 2015 guidelines from the National Comprehensive Cancer Network state that sorafenib and locoregional therapy are both options for patients with unresectable disease who are not transplant candidates, but that arterially directed therapies are relatively contraindicated in patients who have main portal vein thrombosis[82]. Resection for patients with major vascular invasion is described as controversial, but may be considered.

FUTURE DIRECTIONS

There are a number of staging systems to characterize HCC[25,83-87]. The BCLC system has been widely adopted due to its robust prognostic and therapeutic validation. However, as therapeutic options for HCC, particularly for those patients with PVT, continue to evolve, limitations of the BCLC system have become evident. All patients with macroscopic vascular invasion are considered to have advanced, stage C disease, and are recommended for systemic treatment. Given the data on other surgical and locoregional treatments reviewed above, it is likely that this recommendation will come to be regarded as too limiting. The recently published Hong Kong Liver Cancer (HKLC) staging system[88] is based on a cohort of 3856 patients, and was developed using rigorous statistical modeling. This system separates extrahepatic from intrahepatic vascular invasion, and generally recommends more aggressive management of early and intermediate disease, which is likely more in line with current and evolving practice in specialized centers. The HKLC staging system may represent an important step in classifying HCC and guiding treatment, but requires

further validation, including in Western cohorts, before it is likely to be adopted in major guidelines.

An active area of investigation concerns the combination of sorafenib with locoregional therapies such as TACE and SIRT[89]. This combination may maximize tumor cell killing by preventing compensatory revascularization in response to proangiogenic factors elaborated by ischemic tumor cells. Subgroup analyses of the SHARP and Asia-Pacific trials both found sorafenib to be beneficial in patients who had received prior TACE[28,30], however these patients received sorafenib long after their TACE procedure. The two largest randomized controlled trials to combine TACE and sorafenib, involving 458 and 307 patients with unresectable HCC randomized to receive sorafenib or placebo following TACE, reported only modest benefits associated with the addition of sorafenib[90,91]. However, a smaller randomized controlled trial has shown a significant survival benefit[92], and nonrandomized series have likewise shown promising results[93-98]. These studies used varying protocols for combining TACE and sorafenib. Some, including the two largest, excluded patients with PVT. The ongoing START trial is a phase Ⅱ prospective study of the effect of combined TACE and sorafenib in patients with good performance status and mostly BCLC B tumors, although second order branch portal vein involvement was allowed. In an interim analysis of 147 patients[99], adverse events appeared similar to those associated with the treatments independently, and early outcomes data appeared encouraging. Overall, the safety and efficacy of combined TACE and sorafenib in the population of patients with PVT remains to be determined.

Fewer studies have focused on the combination of SIRT with sorafenib. A recently published phase Ⅱ trial of 29 patients with BCLC stage B or C disease treated with yttrium-90 SIRT followed by sorafenib initiated 14 days post procedure, reported similar rates and severity of treatment-related adverse events as would be expected with the treatments separately[100]. Importantly, eligibility for treatment with sorafenib, whether in the context of a trial or in routine clinical use, requires that the patient's liver function be maintained, ideally at the Child-Pugh A level. A recent series of 63 patients with PVT and Child-Pugh score $\leqslant$ 7 treated with yttrium-90 SIRT found that progression of Child-Pugh A to Child-Pugh B disease at the time of tumor progression following SIRT occurred in 55% of patients[101]. It may therefore be prudent to initiate therapy with sorafenib relatively soon after the procedure, rather than waiting until the time of tumor progression, to derive the maximum survival benefit before the patient's underlying liver function deteriorates to the point where sorafenib is contraindicated. The safest and most effective combination of TACE, SIRT and sorafenib in PVT and in HCC generally remains an area of active investigation, with several ongoing clinical trials[89]. Additionally, data from the ongoing GIDEON study, a global observational database of HCC patients treated with sorafenib, may likewise yield insights into the safety and efficacy of various combinations of therapies in the real-world clinical setting[102,103].

CONCLUSION

HCC is a significant source of worldwide morbidity and mortality, and one that is likely to increase in prevalence in Western countries in the coming years. Despite the emergence of numerous effective, life-prolonging treatments for HCC, patients with PVT remain especially challenging to treat and continue to experience shortened survival. Orthotopic liver transplantation is generally contraindicated in these patients due to high rates of recurrence. Hepatic resection with curative intent is controversial and infrequently employed in American and European centers, but may offer favorable overall survival in selected patients, especially those with branch portal vein involvement and good liver function. In patients who are not surgical candidates, various therapies including systemic sorafenib, TACE, and yttrium-90 SIRT may be management options. Of these, SIRT has demonstrated excellent safety and tolerability, and a growing body of data supports its use in patients with PVT.

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