World Journal of

Gastroenterology

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ABOUT COVER

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RESPONSIBLE EDITORS FOR THIS ISSUE

MINIREVIEWS

Will the collaboration of surgery and external radiotherapy open new avenues for hepatocellular carcinoma with portal vein thrombosis?

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Abstract

Portal invasion of hepatocellular carcinoma (HCC) occurs in 12.5%-40% of patients diagnosed with cancer and yields poor clinical outcomes. Since it is a common cause of inoperability, sorafenib was regarded as the standard treatment for HCC in the Barcelona Clinic of Liver Cancer guidelines. However, the median survival of the Asian population was only approximately 6 mo, and the tumor response rate was less than moderate (< 5%). Various locoregional modalities were performed, including external beam radiotherapy (EBRT), transarterial chemoembolization, hepatic arterial infusion chemotherapy, and surgery, alone or in combination. Among them, EBRT is a noninvasive method and can safely treat tumors involving the major vessels. Palliative EBRT has been commonly performed, especially in East Asian countries, where locally invasive HCC is highly prevalent. Although surgery is not commonly indicated, pioneering studies have demonstrated encouraging results in recent decades. Furthermore, the combination of neo- or adjuvant EBRT and surgery has been recently used and has significantly improved the outcomes of HCC patients, as reported in a few randomized studies. Regarding systemic modality, a combination of novel immunotherapy and vascular endothelial growth factor inhibitor showed results superior to that of sorafenib as a first-line agent. Future clinical trials investigating the combined use of these novel agents, surgery, and EBRT are expected to improve the prognosis of HCC with portal invasion.

Key Words: Surgery; Hepatocellular carcinoma; Radiotherapy; Systemic treatment

Core Tip: The prognosis of hepatocellular carcinoma with portal vein involvement is poor, and there had been few available local modalities. However, with the develop-ment of radiotherapy techniques, the 1-year survival rate has been reported to be close to 45%-50% after palliation. Recently, a surgical approach has also been attempted showing encouraging results. Furthermore, the combination of surgery and radiation therapy showed effective results in studies including randomized studies. The combination of these two modalities are expected to increase efficacy of treating hepatocellular carcinoma with portal invasion.

INTRODUCTION

Portal invasion of hepatocellular carcinoma (HCC) is a known clinical factor associated with poor prognosis. Portal vein invasion might cause portal hypertension, which can lead to decreased liver function and enlarge the gastrointestinal varices[1]. In addition, portal tumor thrombosis acts as a tumor deposit that can induce intra- and extrahepatic metastases[2,3]. Without active treatment, the survival period of HCC patients with portal invasion is usually less than 4 mo[4-6]. Portal invasion occurs in 12.5%-40% of all HCC patients in the clinical setting[7-11]. According to the 16th National Survey for Primary Liver Cancer conducted in Japan, portal involvement was found in 16% (808/5130) of patients who underwent hepatic resection[12]. In our previous study using data from the Nationwide Liver Cancer Registry, 2553 of 10743 patients (approximately 10% randomly extracted patient records from all administrative districts of South Korea), or about a quarter, had portal vein involvement at the time of diagnosis[13].

To date, there is no standard treatment for HCC with portal invasion; hence, various systemic and locoregional modalities have been used. Since portal invasion is a component of the Barcelona Clinic of Liver Cancer (BCLC) stage C, the European Association for the Study of the Liver (EASL)[14] and American Association for the Study of Liver Diseases (AASLD) guidelines[15], which were published in 2018, support the use of sorafenib for the treatment of HCC with this stage. Although sorafenib was the only modality that achieved an overall survival (OS) benefit, as reported in a phase 3 randomized study conducted within a period of 15 years, the tumor response rate was not satisfactory (less than 5%), and the median OS was only 6 mo after treatment as shown in an Asian population study[16]. In addition, it should not be overlooked that approximately 95% of the enrolled patients were in Child-Pugh class A in this study, even though a significant portion of the HCC patients with PVT have a liver function of Child-Pugh class B or C[17]; data on the use of sorafenib in these patients is limited. A randomized phase 3 trial was done comparing sorafenib *vs* best supportive care alone in Child-Pugh class B patients, and the results are expected to provide further guidance[18]. A recent study investigated the use of regorafenib for the HCC patients who have failed to improve on sorafenib; the median OS of 10.6 mo was achieved in patients who received regorafenib, which was better than the OS of 7.8 mo for those receiving the placebo[19]. Although several studies on the expansion of indications for systemic and rescue therapies are in progress, satisfactory results have not yet been obtained.

Therefore, various locoregional modalities have been used to improve the patient outcomes. Despite that the AASLD guidelines endorsed treatment recommendations of BCLC system previously[20], in its updated version in 2018, it is mentioned that systemic therapy for HCC with macrovascular invasion is recommended but not over locoregional treatments[15]. The preferred option of locoregional modality was not suggested, although recent studies regarding transarterial chemoembolization (TACE), external beam radiotherapy (EBRT), and hepatic arterial infusion chemotherapy (HAIC) were referenced, because evidence is limited to suggest relative superiority among those modalities.

The application of locoregional treatment for HCC with portal invasion varies regionally, and treatment strategies also differ between Eastern and Western countries[21]. In Asian countries, hepatitis B virus-related HCCs comprise the majority of diagnosed diseases. These diseases are mainly caused by insertional mutagenesis of viral oncoproteins and tend to progress rapidly and invasively, whereas liver function can be relatively preserved. In Western countries, the common causes of HCC include alcohol consumption or fatty liver of other causes. These diseases are associated with somatic alterations and chromosomal instability accumulated due to cirrhosis progression; they tend to be less progressive and have higher differentiation, but the liver function is commonly damaged due to persistent cirrhosis[22]. Therefore, the active locoregional treatments including TACE, surgery, EBRT, and HAIC are more rigorously attempted in Asia than in Western countries[21]. For instance, the surgical approach is

preferentially recommended for portal invasion cases that do not invade the main branch, as indicated in the recent Chinese expert consensus guidelines[23], although the vast majority of international guidelines did not suggest surgery as the preferred option for those cases[24,25]. Based on the Korean Liver Cancer Study Group guidelines, the combination of TACE and EBRT was suggested as the best option for HCC patients without extrahepatic metastases but with major vessel invasion[26].

Various locoregional modalities have been used independently or in combination to treat HCC with portal invasion. In particular, despite the fact that surgery is not generally recommended for portal invasive cases, recent studies have achieved favorable oncologic results by reducing the extent of tumors through EBRT and surgery. In this review, we aimed to discuss the role of locoregional modalities in the treatment of HCC with portal invasion, focusing on the recent results of surgery and EBRT as individual treatments and as a combination therapy.

PALLIATING PORTAL INVASION WITH EXTERNAL RADIOTHERAPY

In the early 1990s, before the generalization of a planning system using computed tomography, EBRT was known to have a limited role in HCC. EBRT had been "technically radioresistant" during the era of two-dimensional radiotherapy, of which the treatment was planned and performed under plain radiographic guidance. Since EBRT relies on bony and organ shadows available on plain films, radiation therapy inevitably encompasses a significant portion of the normal liver. Due to the possibility of hepatic radiotoxicity, only doses lower than 30 Gy could be administered, which is not sufficient to control the tumor[24,27].

Although the risk of radiation-induced liver disease steeply increased after delivering 30 Gy of irradiation to the entire liver, CT-based planning has enabled the safe delivery of high doses of over 50 Gy. The application of a more updated technology, such as intensity-modulated radiotherapy (a special type of EBRT that increases the conformality of the radiation target by actively modulating the dose intensity, portal shape, and beam movements), enabled the irradiation of advanced intrahepatic tumors while saving the necessary portion of the normal liver (Figure 1). Furthermore, despite the fact that tumor vascular invasion makes the application of local modalities difficult, EBRT is feasible because the major blood vessels can withstand more than approximately 100 Gy (in conventional fraction) and the target dose can be delivered regardless of the location of tumor[28]. Indeed, the HCC cells are radiosensitive and highly proliferative tumor cells with an alpha/beta ratio of approximately 15, which is similar to that of head and neck cancer (a radiosensitive cancer commonly treated with chemotherapy or radiotherapy)[29,30]. Previous studies using radiation therapy for locally advanced HCCs, which recruited patients from the 90s to the 2000s, have shown that HCC responds well to high doses of radiation. In a previous study including 158 unresectable HCC patients (about 50% of patients had portal invasion), Park *et al*[31] reported that the tumor response rates in patients who received irradiation doses of < 40 Gy, 40-50 Gy, or > 50 Gy increased to 29.2%, 68.6%, and 77.1%, respectively. Similarly, our previous study reported that as a result of prescribing a median total EBRT dose of 61.2 Gy, a high tumor response rate of 62.2% was reported in 45 HCC patients with portal vein thrombosis (PVT)[32].

Various studies have reported the use of EBRT in HCC patients with portal invasion in recent decades. In order to integrate the data from several studies, we performed a meta-analysis of 26 studies and 2,111 HCC patients treated with EBRT[33]. The pooled 1- and 2-year OS rates were 43.8% [95% confidence interval (CI): 37.6%–50.2%] and 22.3% (17.7%-27.6%) in patients who underwent three-dimensional conformal radiotherapy (3DCRT), and 48.5% (39.4%-57.8%) and 26.8% (19.0%-36.3%) in patients who underwent stereotactic body radiotherapy (SBRT). The pooled tumor response rates were 51.5% (95%CI: 45.7%-57.0%) and 70.7% (95%CI: 63.7%-76.8%) in patients who underwent 3DCRT and SBRT, respectively. Severe gastrointestinal or hepatic complications rarely occurred and were either not reported in most studies or were documented in less than 5%-10% of treated patients. Various locoregional modalities have been applied for the treatment of unresectable HCCs, and TACE is the most common modality performed in combination with EBRT. Huo *et al*[34] reported that the combination of TACE and RT had higher survival benefit [odds ratio (OR): 1.36, 95%CI: 1.19-1.54 for 1-year OS] and complete response rate (OR: 2.73, 95%CI: 1.95-3.81) than TACE alone for unresectable HCCs. They also pointed out that the benefits of OS progressively increased (ORs: 1.55, 1.91, 3.01, and 3.98 for 2-, 3-, 4-, and 5-year OS, respectively). In a recent randomized trial, Yoon *et al*[35] reported that the combination of TACE and EBRT improved the OS (median: 55 wk *vs* 43 wk, $P = 0.04$) and progression-free survival (median: 31 wk *vs* 11.7 wk, $P < 0.001$) of HCC patients with major vascular invasion compared with sorafenib. Recently, our team performed a study using nationwide data from all administrative districts of South Korea[13]. Strict propensity matching was performed, and data of 444 HCC patients with portal invasion (222 who underwent local treatment including EBRT and 222 who did not undergo active oncologic treatment) were analyzed. Local treatment, including radiotherapy, had significant benefits on the OS (median: 8 mo *vs* 2 mo, $P < 0.001$) and cancer-specific survival. Table 1 summarizes the key results of the cited studies.

Table 1 Summary of key studies according to the treatment method

Ref.	Study type	Number of patients	Main outcomes
Radiotherapy studies			
Rim *et al*[33], 2018	Meta-analysis of observational studies	2111 with PVT	Pooled 1- and 2-yr OS: 43.8% and 22.3%, respectively (3DCRT)
			Pooled 1- and 2-year OS: 48.5% and 26.8%, respectively (SBRT)
			Grade 3 complications less than 5% to 10%
Huo *et al*[34], 2015	Comparative meta-analysis	2577 underwent TACE or RTx	TACE and RT had OS benefit compared with TACE alone
			ORs: 1.55, 1.91, 3.01, and 3.98 for 2-, 3-, 4-, and 5-yr OS rates, respectively
Yoon *et al*[35], 2018	Randomized trial	90 with major vascular invasion	TACE and RT had survival benefit compared with sorafenib
			Median OS 55 wk *vs* 43 wk, $P = 0.004$
			Median PFS 31 wk *vs* 11.7 wk, $P < 0.001$
Lee *et al*[13], 2021	Observational study using national database	444 propensity-matched patients with PVT	Local treatment including RTx had survival benefit compared with no oncologic treatment
			Median OS: 8 mo *vs* 2 mo, $P < 0.001$
			Median CSS: 8 mo *vs* 2 mo, $P < 0.001$
			OS and CSS benefit persist in the CPC A and CPC B subgroups
Surgery studies			
Kokudo *et al* [41], 2016	Observational study using national database	2116 propensity-matched patients with PVT	Surgery had benefit compared with non-surgery
			Median OS: 2.45 yr *vs* 1.57 yr, $P < 0.001$
			Surgery benefit was not observed in the Vp4 subgroup ($P = 0.242$)
Wang *et al*[42], 2016	Retrospective study	1580 with PVT underwent (1) surgery, (2) TACE, (3) TACE with sorafenib, or (4) TACE with RTx	Median OS:
			Cheng's type I: 15.9 *vs* 9.28 *vs* 12.0 *vs* 12.2 ($P < 0.001$)
			Cheng's type II: 12.5 *vs* 4.9 *vs* 8.9 *vs* 10.6 ($P < 0.001$)
			Cheng's type III: 6.0 *vs* 4.0 *vs* 7.0 *vs* 8.9 ($P = 0.001$)
Shi *et al*[43], 2010	Retrospective study	406 with PVT underwent surgery	Surgery showed better outcomes in Cheng's type I and type II (1-yr OS: 52% and 38%, respectively) PVT than type III and IV (1-yr OS: 25% and 18%, respectively)
Chen *et al*[44], 2006	Retrospective study	438 with PVT underwent surgery	Surgery yielded satisfactory results in Cheng's type I and II PVT (1- and 2-yr OS: 58.7% and 39.9%, respectively), not in types III and IV (1- and 2-yr OS: 39.5% and 20.4%, respectively)
Combined surgery and radiotherapy			
Chong *et al* [46], 2018	Retrospective study	26 underwent surgery following CCRT *vs* 18 underwent surgery alone	Surgery following CCRT had benefit on surgery alone
			Median DSS: 62 wk *vs* 15 wk, $P = 0.006$
			Median DFS: 32 wk *vs* 3 wk, $P = 0.002$
Sun *et al*[47], 2019	Randomized trial	26 underwent surgery with adjuvant IMRT *vs* 26 surgery alone	Adjuvant IMRT significantly improved clinical outcomes
			Median OS: 18.9 mo *vs* 10.8 mo, $P = 0.005$
			Median DFS: 9.1 mo *vs* 4.1 mo, $P = 0.001$
Wei *et al*[49], 2019	Randomized trial	82 neoadjuvant RT *vs* 82 surgery alone	1- and 2-yr OS: 75.2% and 27.4%, respectively (neoadjuvant RT)
			1- and 2-yr OS: 43.2% and 9.4%, respectively (control)
			RT benefited Cheng's type I and II PVT as well as type III PVT
Li *et al*[50], 2016	Comparative study	45 neoadjuvant RT *vs* 50 surgery alone	Neoadjuvant RT decreased the rates of HCC recurrence [49% *vs* 88.7%, respectively ($P < 0.001$)] and increased overall survival [1-yr OS: 69% *vs* 35.6%, respectively ($P < 0.01$)]

PVT: Portal vein thrombosis; OS: Overall survival; 3DCRT: 3-dimensional conformal radiotherapy; SBRT: Stereotactic body radiotherapy; TACE: Transarterial chemoembolization; RTx: Radiotherapy; PFS: Progression-free survival; CSS: Cause-specific survival; CPC: Child-Pugh class; CCRT:

Concurrent chemoradiotherapy; DSS: Disease-specific survival; IMRT: Intensity-modulated radiotherapy.
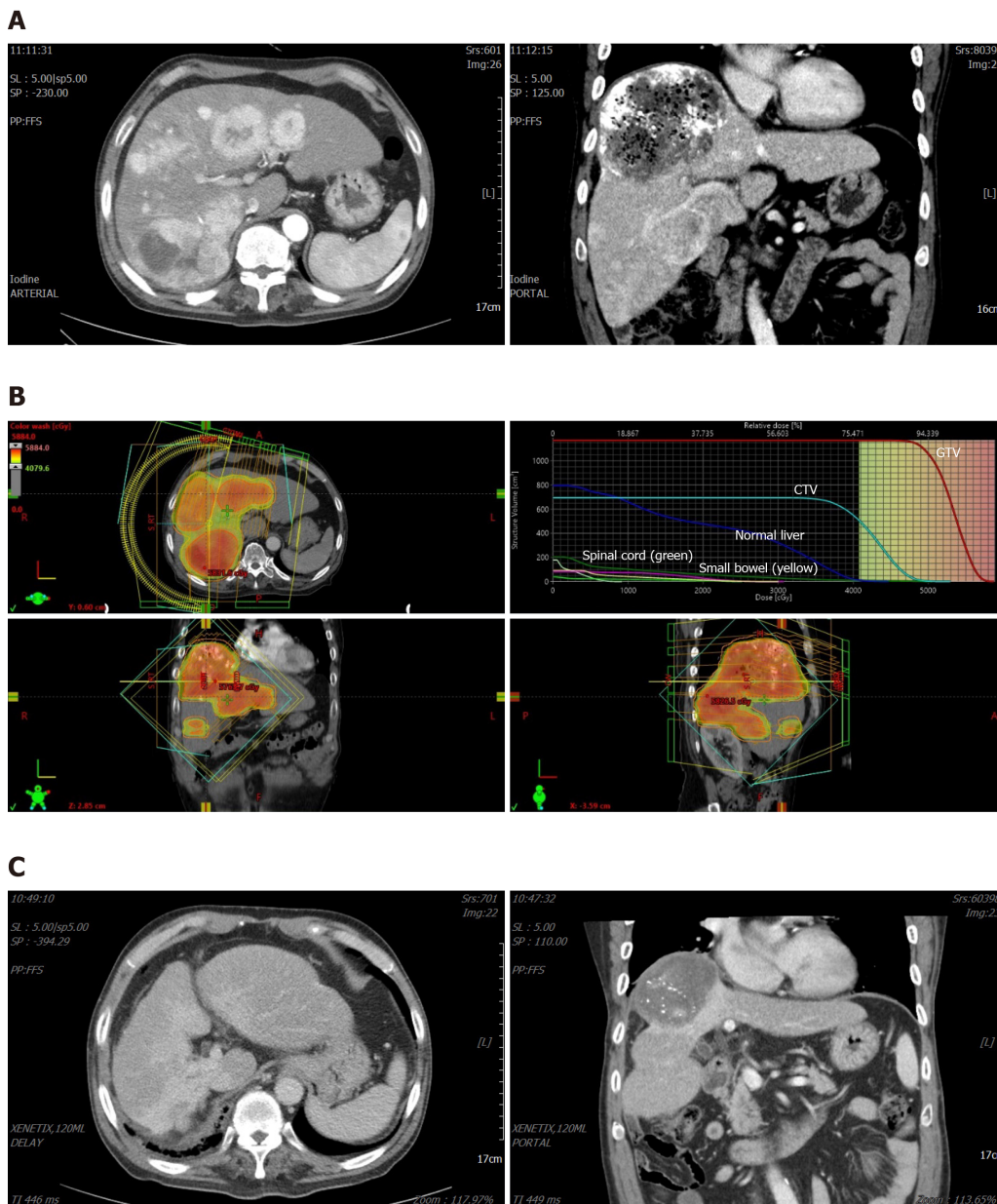

Figure 1 A case of a locally advanced hepatocellular carcinoma with portal thrombosis treated with radiotherapy. A: Multiple tumors noted in right lobe and segment 4, with a large tumor in segment 8, and involving right portal vein thrombosis; B: A dose-distribution of external radiotherapy plan. We prescribed 53 Gy/20F to gross tumor volume (red color wash in upper-left figure) with at least 42 Gy/20F were delivered to clinical target volume (green color wash in upper-left figure). Quantitative dose-histogram for specific organs is generated (upper-right figure). We planned to save at least 70% of normal liver to be irradiated less than 30 Gy; C: One year after radiotherapy and three times of transarterial chemoembolization, tumors were remised without active enhancing lesions. Liver function was maintained at Child-Pugh score A. GTV: Gross tumor volume; CTV: Clinical target volume.

In addition, particle therapy (*e.g.*, proton or heavy ion therapy) can provide additional benefits compared to conventional EBRT, which uses X-rays in treating locally advanced HCC. Particle therapy is most similar to conventional EBRT in terms of the overall principle of causing cancer cell death. However, dose escalation and complication reduction could be achieved based on the physical characteristic called Bragg peak (*e.g.*, the phenomenon that energy deposits almost disappear after radiation passes through the body and progresses to a certain depth)[36]. Sanford *et al*[37] reported the benefit of proton therapy as compared to conventional EBRT for 133 unresectable HCC patients based on survival (median OS; 31 mo *vs* 14 mo, HR = 0.47, P = 0.008) and liver toxicities (odds ratio: 0.26, P = 0.03). Cheng *et al*[38] also reported the benefit of proton therapy as compared to conventional EBRT based on survival (HR 0.56, P = 0.032) and radiation-induced liver disease (11.8% *vs* 36.4%, P = 0.004), using a propensity-matched cohort. The current hurdle for using particle therapy is its accessibility; currently,

there are about 110 particle therapy centers in operation worldwide, but most of them are in major developed countries such as the US, Japan, and Germany[39]. The financial burden of treatment due to the high cost of equipment is also a problem to be resolved. However, the efficiency of EBRT could be greatly improved once these difficulties are gradually resolved.

In summary, EBRT can be used for the treatment of HCC by delivering a high dose of radiation and has technical advances. It is an effective palliative modality for HCC with portal invasion and is commonly performed along with TACE.

SURGICAL RESECTION OF HCC WITH PORTAL INVASION

Previously, surgery was not commonly performed in HCC patients with portal invasion because of the short life expectancy and therapeutic risks. Neither the EASL nor the AASLD guidelines suggest the performance of surgical resection as treatment for HCC with portal invasion[14,15]. However, East Asian countries, including China and Japan, have recently been actively performing surgery for portal invasion[40].

Kokudo *et al*[41] performed a key study to evaluate the efficacy of surgical resection in HCC patients with portal invasion using the nationwide data from Japan. Among 6474 HCC patients with PVT, approximately 2100 patients with Child-Pugh A liver function were matched using propensity scores (liver resection group vs. non-liver resection group). The liver resection group showed significantly longer survival (median: 2.45 years *vs* 1.57 years, $P < 0.001$). However, the OS benefit was not significant in the subgroup with Vp4 PVT ($P = 0.242$). Figure 2 shows an illustration of the two common classifications of PVT. Furthermore, R2 resection was performed in 60.5% of patients, and the 90-day mortality was 8.2% in the Vp4 PVT group. The authors recommended liver resection as the first-line of treatment for HCC with PVT in the first-order branch. Another large series conducted by four Chinese centers[42] which included 1572 HCC patients with PVT, reported similar results. The median survival times of the surgical group were 15.9 and 12.5 mo for PVT of type I and II in Cheng's classification, which were much better than those of their nonsurgical counterparts. However, for patients with Cheng's type III PVT, the TACE and RT group showed higher survival rate than the surgery group (8.9 mo *vs* 6.0 mo). Therefore, authors suggested that surgery should be considered for type I and II PVT, but TACE and RT should be recommended for type III PVT (PVT in the main trunk or contralateral branches). Other series from East Asian countries reported the feasibility of surgical resection in HCC patients with branch thrombosis, but this modality may lead to poor outcomes and increase the surgical risks in those with main PVT[43,44].

Based on the above studies, consensus guidelines in East Asia recommend the use of surgery for the treatment of HCC with portal invasion. The recent treatment guidelines of the Japan Society of Hepatology[45] suggested four possible options for HCC with major vessel invasion: three locoregional modalities including TACE, surgical resection, hepatic arterial infusion chemotherapy, and molecular-targeted therapy. They stated that it is difficult to provide a universal ranking for the four modalities; therefore, the four modalities are recommended in parallel. On the contrary, the Chinese Expert guidelines for HCC with PVT recommend surgical resection as a preferred option for patients with Child-Pugh A, PVT type I and II based on Cheng's classification (branch PVT), and good performance. Type III PVT cases are recommended to undergo surgery after downstaging *via* EBRT or TACE[23].

In summary, surgical treatment is being actively performed for HCC with PVT, especially in East Asia. Although surgical resection is a considerable modality for HCC with branch PVT (types I and II based on Cheng's classification; Vp1-3 based on the Japanese classification), this modality can lead to poor outcomes and increase the risk for perioperative complications when used in patients with main PVT. Table 1 summarizes the key studies related to this topic.

PROMISING RESULTS OF SURGERY AND RADIOTHERAPY AS COMBINATION TREATMENT

In cancer treatment, the application of radiotherapy before and after surgical treatment to lower the recurrence and survival rates is a widely used method. Previously, patients with HCC with portal invasion were deemed to have a dismal prognosis; therefore, active treatment combining surgery and EBRT has not been widely accepted. However, several researchers have recently reported promising outcomes of neo- or adjuvant EBRT.

The multidisciplinary team of Yonsei University[46] reported their experience of trimodality treatment for HCC with portal invasion, which is neoadjuvant CCRT (HAIC plus EBRT) yielding downstaging and surgical resection. Patients who underwent trimodality treatment had a median disease-specific survival of 62 mo, while those who underwent resection alone had a median disease-specific survival of only 15 mo ($P = 0.006$). Sun *et al*[47] from the Eastern Hepatobiliary Surgery Hospital performed a randomized study to investigate the benefit of adjuvant IMRT in HCC patients with PVT
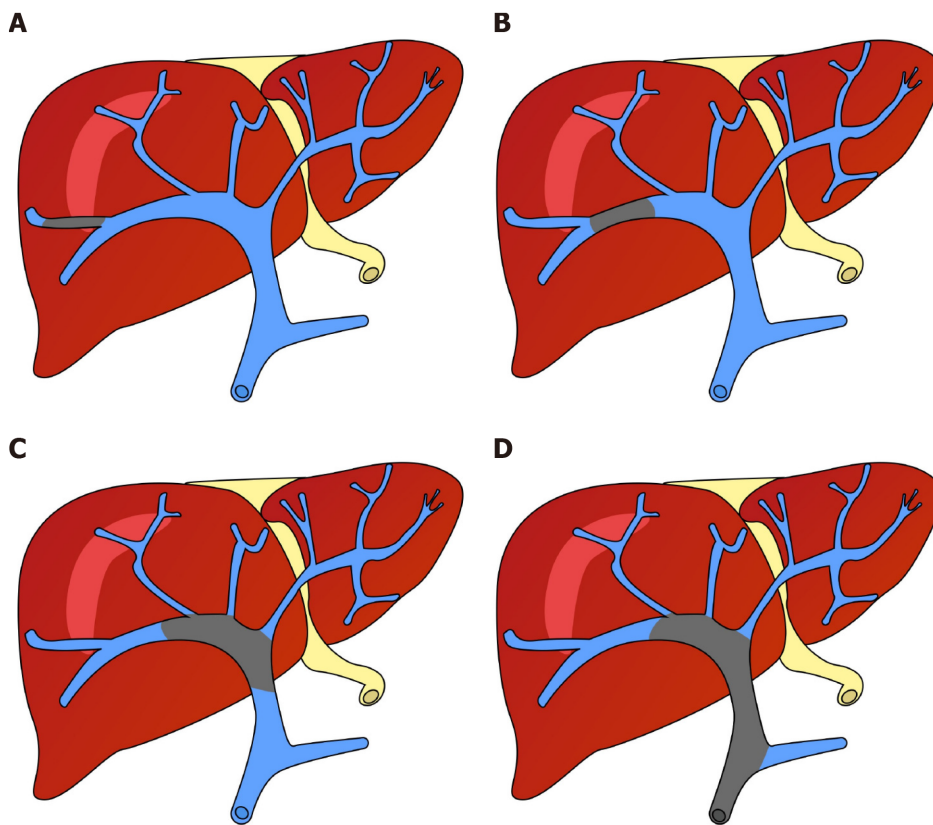
Figure 2 Illustration of two systems categorizing portal vein thrombus. A: Invasion of the second-order branch of the portal vein: VP2 in the liver cancer study group of Japan (*e.g.*, Vp1 denotes the invasion distal to the second-order branch) and Cheng's classification type I; B: Invasion of the first-order branch: VP3 and Cheng's type II; C: Invasion of the main branch and/or bilateral first-order branches: VP4 and Cheng's type III; D: Invasion of the superior mesenteric vein: Cheng's type IV.

(adjuvant RT *vs* surgery alone). The adjuvant radiotherapy group showed significantly higher disease-free survival (DFS) (median: 9.1 mo *vs* 4.1 mo, P = 0.001) and OS (median: 18.9. vs. 10.8 mo, P = 0.001). The most common complications after RT were fatigue or anorexia, and grade 3 gastrointestinal complications occurred in 2 of 26 patients (7.7%). Grade 4 or higher adverse effects have not been reported. Although OS difference was significant in subgroup analyses among patients with Cheng's type I or II PVT (median 20.7 mo *vs* 11.7 mo, P = 0.008), due to the limited number of patients (only 6 and 7 patients had Cheng's type III or IV PVT, respectively, in both arms), the difference was not considered significant in the subgroup with PVT at main branch or trunk. Soin *et al* [48] reported encouraging results that comparable survival was achieved in HCC patients with PVT after down-staging, including SBRT, and liver transplantation, to those without PVT who underwent transplantation (5-year OS 57% *vs* 65%, P = 0.06).

Wei *et al*[49] performed a cornerstone study related to this topic, randomizing 164 patients into the neoadjuvant EBRT and surgery group and surgery groups. The 1- and 2-year OS rates in the neoadjuvant arm were 75.2% and 27.4%, whereas those in the surgery arm were 43.1% and 9.4%, respectively (P < 0.001). EBRT improved the OS and DFS of patients with type II PVT (P = 0.01 and P = 0.016, respectively) and those with type III PVT (P < 0.001 and P = 0.002, respectively), according to Cheng's classification. No significant difference was observed in the perioperative complications between the two groups, although a few more grade 3 or 4 complications were reported after RT (two cases of abdominal hemorrhage in the neoadjuvant EBRT arm and none in the surgery arm). In a previous non-randomized comparative study on HCC with main PVT (type III based on Cheng's classification), Li *et al*[50] investigated the benefit of neoadjuvant radiotherapy. The 1- and 2-year OS rates in the neoadjuvant group were 69% and 20.4%, whereas those in the surgery group were 35.6% and 0%, respectively (P < 0.01). The recurrence rates were 49% and 88.7% at 6 mo in the neoadjuvant and surgery groups, respectively (P < 0.001).

In summary, recent studies demonstrated that combining neo- or adjuvant EBRT and surgery could further improve the oncologic outcomes of HCC patients with portal invasion, possibly those with main PVT. Table 1 presents a list of related studies.

FUTURE PERSPECTIVE AND SUMMARY

Until the 2000s, there were limited practical treatment methods for HCC with portal invasion. Since the mid-2000s, sorafenib, the first effective systemic agent for unresectable HCC, has been established. In recent decades, aside from TACE, which is the most commonly used locoregional modality, other methods including EBRT, TARE, HAIC, and surgery have also been attempted. Furthermore, the use of a novel systemic modality (atezolizumab-bevacizumab)[51] that surpassed sorafenib in terms of survival and tumor responses, which had been established as a standard systemic agent for 15 years, was reported in 2020. Atezolizumab-bevacizumab is a combination of anti PD-L1 (an immune checkpoint inhibitor) and anti-vascular endothelial growth factor (VEGF) (a tumor microenvironment-modulating agent). As the anti-VEGF therapy reverses the VEGF-mediated immune suppression and increases the T-cell infiltration in tumors, the efficacy of anti PD-L1 could be enhanced[51]. Radiation therapy also enhances the performance of tumor antigen presentation and T-cell infiltration in the tumors[52]. In addition, radiation itself induces the sensitization of tumor cells to immune-mediated cell death by upregulating FAS expression. Therefore, the combination of immune checkpoint inhibitors and radiation therapy could be a promising treatment for HCC due to its synergistic effect. In addition, advances in understanding tumor immunity have resulted in new emerging immunotherapies. For example, CD4+ CD25+ regulatory T cells have a well-established immunosuppressive role in the HCC microenvironment and express various chemokine receptors and surface molecules such as PD-1, CTLA4 and others[53]. They can potentially be direct or indirect targets for newly emerging immune checkpoint inhibitor immunotherapy. Future clinical studies investigating the efficacy and feasibility of novel immunotherapy in combination with EBRT are necessary.

CONCLUSION

Although HCC with portal invasion is considered to have a limited benefit from surgery, pioneering researchers have obtained promising outcomes, and recent studies have demonstrated that the addition of EBRT can further increase the treatment efficiency. If effective novel systemic agents, surgery, and EBRT are used in an appropriate combination, the prognosis of HCC with portal invasion can be significantly improved. In other words, we believe that the most potent anticancer modalities known to date, the tripartite collaboration of chemotherapy, surgery, and radiotherapy, commonly used in the treatment of other solid cancers, will be used as a new standard treatment for HCC with portal invasion in the near future. However, clinical trials are warranted to evaluate the efficacy of such collaborations.

FOOTNOTES

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