Diagnosis, treatment and prognosis of hepatocellular carcinoma with inferior vena cava/right atrium tumor thrombus (Review)

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Abstract. Although tumor thrombus (TT) infringement of the inferior vena cava (IVC) and right atrium (RA) is rarely observed in hepatocellular carcinoma (HCC), the prognosis for this condition is extremely poor, with a median survival time of several months, given that the condition is often diagnosed at an advanced tumor stage or combined with multiple systemic metastases. Furthermore, there is no established effective treatment for the condition. However, some investigators insist that active treatment, including surgery, chemotherapy (systemic or intra-arterial), radiation therapy, best supportive care or a combination of these, may help prolong overall survival time in these patients. The management of patients with advanced HCC and a TT extending into the RA and IVC is extremely difficult and risky. To this end, the present review assessed the literature on the clinical features and treatments of this condition in recent years, with the aim of providing assistance for clinical work.

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Abbreviations: TT, tumor thrombus; IVC, inferior vena cava; RA, right atrium; HCC, hepatocellular carcinoma; HV, hepatic vein; DSA, digital subtraction angiography; TACE, transcatheter arterial chemoembolization; 3DCRT, three-dimensional conformal radiotherapy; SBRT, stereotactic radiotherapy; PVTT, portal venous tumor thrombus; OS, overall survival

Key words: hepatocellular carcinoma, tumor thrombus, inferior vena cava, right atrium, treatment

1. Introduction

Hepatocellular carcinoma (HCC) is a type of tumor with a high degree of malignancy and vascular invasion characteristics, such as the formation of a tumor thrombus (TT) in the portal vein system obstructing the hepatic inflow tract (1-3). Data from 2015 indicates that worldwide, the incidence of TTs in HCC is high (44~62.2%) (4). In contrast, the obstruction of the outflow vasculature by the formation of a tumor thrombus (TT) in the hepatic vein (HV), inferior vena cava (IVC), or right atrium (RA) is rare; according to statistics, the worldwide incidence of TT in the IVC and RA in cases of advanced HCC in 2010 was range from 1.4 to 4.9% (2,3,5). The prognosis of these patients is extremely poor, and the median survival duration of untreated patients is 2-5 months (6,7). To the best of our knowledge, there is currently no worldwide consensus regarding the management of HCC with IVC/RA TTs. Such patients are classified under C-stage in The Barcelona Clinic Liver Cancer (BCLC) staging (8) due to vascular invasion; the standard treatment recommended by this staging system is the use of sorafenib (9). However, its clinical benefit remains to be highly controversial. The reported treatment measures for TT in IVC or RA include surgery, radiotherapy, chemotherapy, radiotherapy combined with chemotherapy, intervention, targeted therapy or antiangiogenic drugs and various comprehensive treatments (including combination treatments, such as surgery combined with radiotherapy, and transarterial chemoembolization combined with three-dimensional conformal radiotherapy) (6,9). It is difficult to obtain satisfactory results with a single treatment. For now, it is necessary to make the best treatment decisions for the patient based on the general condition of the patient; the location, size and number of intrahepatic tumors; extrahepatic metastasis; classification of tumor thrombosis; patient will; and the equipment of the treatment facility, among others (2,6,7). To this end, the present review assessed the literature for the treatment of TT in the IVC and RA to provide assistance in clinical practice.

2. Clinical manifestations of TT in IVC/RA

The clinical manifestations associated with the TT are associated with the location of the TT, the stability of the TT and the level of blockage of the vein. Generally, a stable TT that incompletely blocks the HV and IVC has no special clinical manifestation. Such TTs are usually found in imaging

studies. Complete obstruction of the HV and IVC may cause Budd-Chiari syndrome (10). The patient can present with manifestations such as varicose veins of the esophagus, fundus, upper extremity in relation to varicose veins of bilateral upper limbs, thoracic cavity and abdomen, pleural effusion, lower extremity edema, tachycardia and difficulty breathing, syncope, repeated pneumonia and sudden death (6,11). Electrocardiograms can show a complete right bundle branch block. The clinical manifestations are primarily associated with post-hepatic portal hypertension caused by the obstruction of hepatic venous return, low cardiac output caused by obstruction of IVC blood flow, and tricuspid obstruction or pulmonary embolism caused by embolization (6,7). The detachment of the embolus can cause sudden death (6,7,9).

3. Pathophysiology

Of the patients with end-stage HCC, 0.7-22.0% (12) have thrombosis of the IVC, whereas higher rates and different types of vascular invasions have been demonstrated in autopsy reports. The worldwide incidence rates of portal vein invasion, HV invasion, IVC invasion and RA invasion have been reported to be 26.0-80.0, 11.0-23.0, 9.0-26.0 and 2.4-6.3%, respectively (13-17). TT in the RA may be an isolated TT, but the IVC TT is more often observed to be extending into the RA. Anthony (15) found that ~78% cases of TT in the RA originate from the IVC, and ~25% cases of TT in the RA are large enough to prolapse to the right ventricle and cause tricuspid stenosis or insufficiency. Furthermore, 2 cases of TT were reported to have extended through the patent foramen ovale to the left atrium; and 1 case of TT was reported to have developed through lung metastasis to the left atrium. Isolated cardiac TT, involving RA (8%) and RV (9%) is also not uncommon (15). TT can also occasionally occur in the left atrium (potentially secondary to seeding through the patent foramen ovale) and multiple chambers. There have also been cases reported where isolated TTs in the RA occurred as complications following hepatectomy (18). As the tumor cells penetrate the vascular endothelial cells, the invading cells stimulate the formation of the thrombus; furthermore, TT provides favorable conditions for the rapid proliferation of tumor cells (19). After HCC invades the HV and IVC, TT develops centripetally due to the flow of blood, and generally does not exceed the level of the renal vein. Both continuous and discontinuous growth patterns of TT with regard to the primary tumor have been reported (14). A previous study revealed that the fastest growth rate of TT was 4.0 cm over 1 month, and the slowest growth rate was 3.0 cm over 6 months. The average reported growth rate is 3.7 cm over 3.2 months (20). Tumors in the right hepatic lobe usually invade the right HV and directly affect the IVC. The left hepatic lobe tumor first invades the left HV and the middle HV, then enters the IVC, and finally invades the RA (14,17).

The IVC/RA TT is a specific type of blood-rich TT, which is also supplied by the arterial branch. Literature that focuses on this type of TT has stated that its blood supply comes from the left and right hepatic artery branches, as well as the left and right phrenic arteries, left gastric artery and intercostal artery (2,21).

4. Diagnosis

The diagnosis of TT in HV, IVC and RA depends on various imaging examinations, such as ultrasound, digital subtraction angiography (DSA), CT scans and MRI.

Ultrasound. For TT in HV and IVC, gray-scale ultrasound showed a substantial echo mass in the HV and IVC, sometimes extending to the RA; color Doppler ultrasound showed HV or IVC blood flow to be narrow or interrupted; HV and IVC masses showed the same changes as intrahepatic lesions (i.e., hyperechoic enhancement in the arterial phase and hypoechoic enhancement in the portal and delayed phases) on ultrasound angiography; transesophageal ultrasound is important for making surgical decisions, as it can more accurately determine the location and classification of TT (22).

DSA. A typical angiography of the abdominal cavity and hepatic artery exhibits 'thread and streaks sign' and 'asymmetric dumbbell sign' for TT in the IVC or RA (20). TT in the IVC or RA is associated with intrahepatic lesions through the HV. In such cases, the patients often present with different degrees of hepatic artery-HV shunts, which is also one of the main causes of poor transcatheter arterial chemoembolization (TACE) treatment effectiveness and poor lipiodol deposit of tumor and TT (20).

CT. Plain CT scans demonstrate a low-density or iso-density mass, with a CT value of 26-52 HU, which is equal to the density of the cardiac tissue. Although a low-density line is observed at the edge of the TT, distinction is difficult. Enhanced CT shows a filling defect in the invaded vascular lumen, which can extend up to the RA; the vascular lumen is observed to be irregularly narrow and locally compressed or surrounded by the tumor. As enhanced CT for IVC TT can manifest as undeveloped inferior vena cava, it needs to be distinguished from the early stage of the portal vein or when the IVC is compressed. In general, patients with suspected TT in the HV or IVC must also undergo a 5-min delayed CT scan to confirm the diagnosis and eliminate any misinterpretation caused by uneven iodine contrast agent (20). Representative CT findings of HCC with IVC TT and RA TT are presented in Fig. 1A and B.

MRI. TT in the IVC and RA observed via MRI was clearer compared with that observed via the CT scan, and imaging in the coronal plane demonstrated the location and length of the TT, which provided the necessary basis for developing a surgical plan. T1-weighted imaging showed a low signal block of TT in the HV and IVC cavity. T2-weighted imaging manifested as a solid high-signal block of TT in the cavity owing to the flowing void effect of the HV and IVC. The intrahepatic nodule also showed a high signal. Furthermore, scanning with enhanced arterial phase showed mild-to-moderate inhomogeneous abnormal enhancement of the block in the IVC, that with enhanced portal vein phase showed a decreased degree of block shadow enhancement, and the delayed phase showed slight enhancement. The intrahepatic lesions were consistent with those of TT in the IVC (20). Representative MRI findings of HCC with IVC TT and RA TT are presented in Fig. 1C and D.
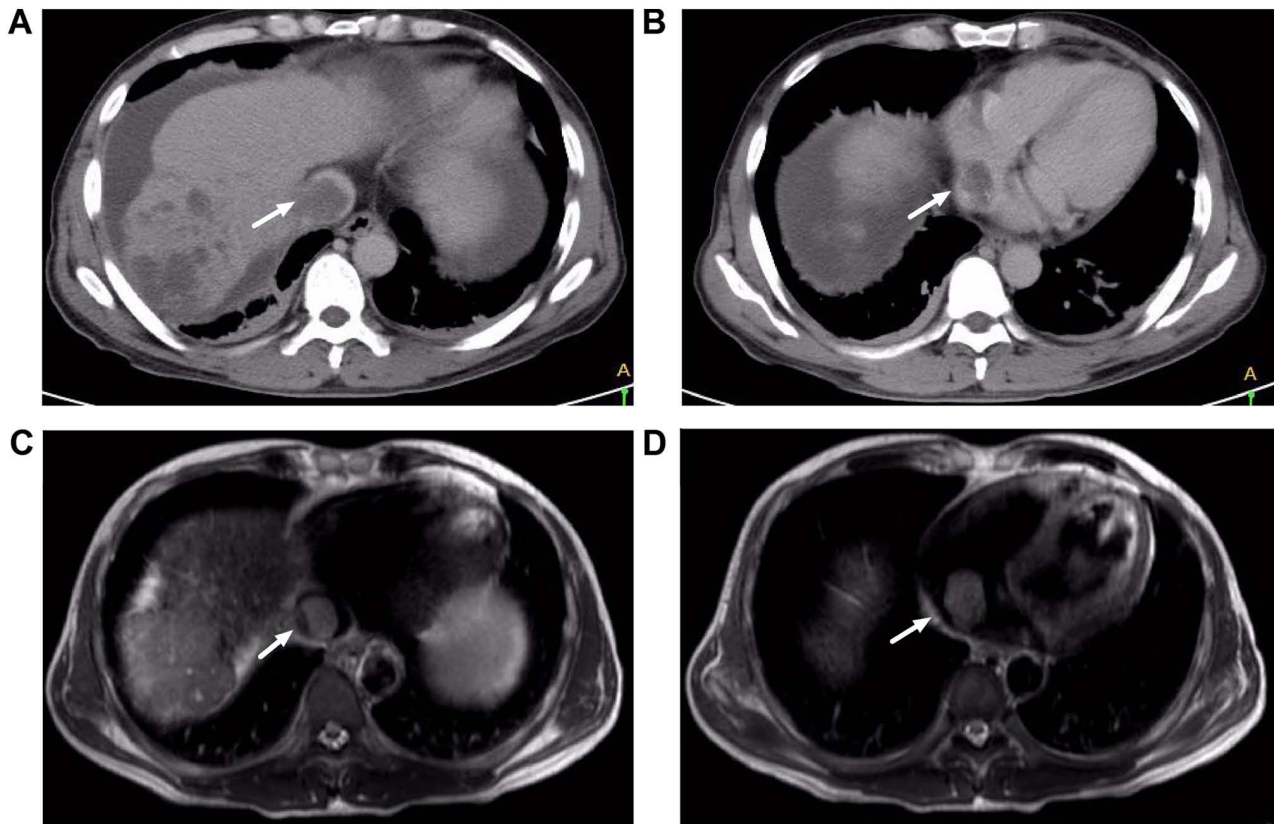
Figure 1. Representative CT and MRI images of hepatocellular carcinoma with IVC TT and RA TT. CT images of TT in the (A) IVC and (B) RA (white arrow). MR images of TT in the (C) IVC and (D) RA (white arrow). The TT margins and irregular internal structures are demonstrated more clearly in the MRI compared with the CT scan. TT, tumor thrombus; IVC, inferior vena cava; RA, right atrium.

5. Treatment

Previous treatments for HCC with TT in the IVC and RA have been conservative, and the majority of clinical treatments include best supportive care. However, with the improvement in the current understanding of the disease and the investigation into associated active treatment measures, an increasing number of clinicians have recognized the necessity of active treatment. The characteristics and clinical results of these studies are summarized in Tables I-IV. Chun et al (6) first studied the differences in survival time between patients treated with the best supportive palliative care (including the control of tumor-related symptoms, psychological counseling and spiritual help) and those undergoing active treatment [mainly including chemotherapy (TACE), surgery and radiotherapy, among others], with a median survival time of 2 and 4 months, respectively. Although the difference is small, it was still statistically significant.

Surgical treatment. HCC with TT in the IVC and RA is generally considered to be an advanced cancer, with patients generally being in poor condition, and may be associated with systemic multiple metastases, making surgical treatment more difficult and limiting patient survival time. However, with continuous advancements in surgical technology and an increase in the current understanding of such TTs, aggressive treatments, particularly including surgical treatment for

selected patients, have been conducted at the most advanced Asian medical centers, which can prolong the survival time of patients and improve their quality of life.

Previous studies have reported a median survival time of 7-8 months after surgery (23,24), but in recent years, with the improvement in surgical techniques, preoperative interventions, and comprehensive postoperative treatment interventions, the median survival time of patients undergoing surgery has markedly improved, with studies reporting a survival time of 10.5-30.8 months (7,25). Wang et al (7) retrospectively analyzed the treatment outcome of 56 patients with advanced HCC. The 1-, 3- and 5-year survival rates in the surgical group were 68.0, 22.5 and 13.5%, respectively, with a median survival time of 19 months. In contrast, the 1- and 3-year survival rates in the TACE group were 15 and 5%, respectively, with a median survival time of 4.5 months. Thus, the survival rate in the surgical group was significantly higher than that in the TACE group.

Li et al (26) reported a classification of HCC with TTs in the IVC/RA to serve as a guide for surgical treatment, wherein based on the anatomical location of the TT relative to the heart, it was divided into three types: Type I, TT is in the IVC below the diaphragm; Type II, the TT extends above the diaphragm but outside the heart; and Type III, the TT extends into the right atrium.

Type I TT can be completely removed with the primary intrahepatic lesion in case of complete hepatic blood flow blockage. First, the hepatic inflow vasculature is blocked and the

Table I. Active surgical treatment outcome for hepatocellular carcinoma with tumor thrombus in the inferior vena cava or right atrium.

Author, year	Patients, n	Extent of resection	Mortality, %	MST, months	1-year OS, %	3-year OS, %	(Refs.)
Wang *et al*, 2013	25	R0:25	0.0	19.0	68.0	22.5	(7)
Li *et al*, 2013	13	NA	0.0	22.0	52.1	25.1	(26)
Wakayama *et al*, 2013	13	R0:5	0.0	30.8	80.0	30.0	(29)
		R1/2:8		10.5	29.2		
Kokudo *et al*, 2014	13	R0:9	7.6	16.7	76.9	15.4	(36)
		R1/2:4					
Kokudo *et al*, 2017	71	NA	9.9	16.4	63.2	33.1	(37)
Liu *et al*, 2012	65	NA	0.0	17.0			(62)

MST, median survival time; OS, overall survival; NA, not available.

Table II. Active RT treatment outcome for hepatocellular carcinoma with tumor thrombus in the inferior vena cava or right atrium.

Author, year	Patients, n	Modality	RT dose, Gy	MST, months	1-year OS, %	3-year OS, %	(Refs.)
Koo *et al*, 2010	42	3DCRT	48.9	11.7	47.7	NA	(47)
Igaki *et al*, 2008	18	3DCRT	50.0	5.6	33.3	NA	(63)
Hou *et al*, 2012	37	2D, 3DCRT	50.0	17.4	67.6	21.0	(43)
	18	2D, 3DCRT	50.0	8.5	41.7	0.0	
Komatsu *et al*, 2011	16	Protein/carbon	91.7	25.4/7.7	61.1	36.7	(42)

RT, radiation treatment; MST, median survival time; OS, overall survival; NA, not available.

Table III. Active TACE treatment outcome for hepatocellular carcinoma with tumor thrombus in the inferior vena cava or right atrium.

Author, year	Patients, n	TACE cycles	Response rate, %	MST, months	1-year OS, %	3-year OS, %	(Refs.)
Chung *et al*, 2014	62	1	NA	10.9	45.8	NA	(46)
Chern *et al*, 2009	26	Repeat for 6-8 weeks	53.8	4.2	41.0	7	(45)
Koo *et al*, 2010	29	Repeat for 6-8 weeks	13.8	4.7	17.2	NA	(47)
Kim *et al*, 2013	60	1	18.0	6.7	37.0	13	(64)
	47	1	53.0	9.7	NA	NA	
Liu *et al*, 2012	50	4-6	NA	8.0	NA	NA	(62)

TACE, transcatheter arterial chemoembolization; MST, median survival time; OS, overall survival; NA, not available.

IVC is clamped under the diaphragm. Subsequently, the invaded HV and IVC are cut longitudinally by the naked eye, and the primary intrahepatic lesion and the TT are both removed by the naked eye. Finally, the IVC is washed and the wall is sutured.

Type II TT is extended into the thoracic cavity, but does require a median sternotomy and thoracotomy (27,28). This TT can be removed by making an incision in the diaphragm anterior to the IVC TT, exposing the TT above the diaphragm. Subsequently, the hepatic blood inflow is blocked and the blood vessels are clamped on top of the TT, following which, the tumor and the TT are removed under direct vision. Finally, the IVC wall, the pericardium and the diaphragm are sutured.

When the TT extends into the RA, a combination of cardiothoracic and hepatobiliary surgery is required for hepatectomy and RA TT resection. To remove the TT extending into the RA, a thoracic surgeon requires surgery under extracorporeal circulation followed by a laparotomy, which requires a sternotomy. Following hepatic transection,

Table IV. Characteristics of included trails.

A, Surgical

Author, year	Country	Mean age ± SD (range), years	Male, %	PVTT, %	Extrahepatic mets, %	AFP, μg/l (%)[a]	Child-Pugh classification, A/B	Previous treatment	Combined modality	HBV infection, %	Tumor size ± SD, cm (%)[b]	(Refs.)
Wang et al, 2013	China	48.5±11.6	96.0	48	NA	>1,000.0 (68.0)	100/0	NA	TACE, RT	100	>10.00 (88.0)	(7)
Li et al, 2013	China	49.7 (35-72)	84.6	NA	NA	NA	100/0	RT	NA	NA	≥10.00 (69.2)	(26)
Wakayama et al, 2013	Japan	63.4±11.8 (37-86)	92.3	NA	61.5	NA	100/0	NA	TACE, RT	53.8	11.8±4.3	(29)
Kokudo et al, 2014	Japan	61.8 (57.4-66.2)	77.0	NA	76.9	22,812.0	85/15	NA	Surgery, TACE	46	8.79	(36)
Kokudo et al, 2017	Japan	NA	NA	NA	NA	NA	100/0	NA	NA	NA	NA	(37)
Liu et al, 2012	China	52.6±4.6	83.1	NA	0.0	391.8	NA	NA	TACE, RFA	NA	≥10.00 (50.8)	(62)

B, RT

Author, year	Country	Mean age ± SD (range), years	Male, %	PVTT, %	Extrahepatic mets, %	AFP, μg/l (%)[a]	Child-Pugh classification, A/B	Previous treatment	Combined modality	HBV infection, %	Tumor size ± SD, cm (%)[b]	(Refs.)
Koo et al, 2010	Korea	54±8	90.5	45.2	NA	>1,000 (47.60)	61.9/38.1	NA	TACE	83.3	10.0±4.0	(47)
Igaki et al, 2008	Japan	70 (45-81)	88.9	NA	NA	>1,000 (16.70)	44.4/55.6	Surgery, TACE, PEI, RFA	NA	NA	NA	(63)
Hou et al, 2012	China	NA	NA	NA / 100	NA	NA	NA	Surgery, TACE / Surgery, TACE	NA	NA	NA	(43)
Komatsu et al, 2011	Japan	68.5 (45-83)	75	58.8	NA	>1,000 (31.25)	75/18.75	NA	RFA in 1 patient	NA	NA	(42)

Table IV. Continued.

C, TACE

Author, year	Country	Mean age ± SD (range), years	Male, %	PVTT, %	Extrahepatic mets, %	AFP, μg/l (%)[a]	Child-Pugh classification, A/B	Previous treatment	Combined modality	HBV infection, %	Tumor size ± SD, cm (%)[b]	(Refs.)
Chung et al, 2014	Korea	56.5±10.6	82.3	79	37	>400 (74.2)	76.2/23.8	NA	NA	NA	≥10.0 (64.5)	(46)
Chern et al, 2009	China	57 (34-74)	76.9	57.7	NA	>400 (46.1)	NA	NA	NA	80.8	10.9	(45)
Koo et al, 2010	Korea	51±12	89.7	51.7	NA	>1,000 (51.7)	58.6/41.4	NA	NA	75.9	12.9±3.8	(47)
Kim et al, 2013	Korea	55.3±9.4	90	52	35	>200 (67.0)	100/0	NA	NA	83.0	≥10.0 (60.0)	(64)
		53.7±9.6	89	66	43	>200 (81.0)	100/0	NA	NA	85.0	≥10.0 (60.0)	
Liu et al, 2012	China	50.9±5.4	82	NA	0	383.3	NA	NA	Chemotherapy Systemic	82.0	>10.0 (54.0)	(62)

PVTT, portal venous tumor thrombus; mets, metastasis; AFP, α fetoprotein; HBV, hepatitis B virus; TACE, transcatheter arterial chemoembolization; RT, radiology treatment; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; NA, not available. [a]In some literatures, the statistical value of AFP is >200, 400 or 1,000, and (%) means that the percentage of patients greater than this value from the total number of people. [b]The statistical value of tumor size in some literatures is a diameter ≥10 cm, (%) indicates the percentage of the number of patients greater than this value from the total number of people.

the superior vena cava and IVC thrombus are clamped and blood flow is bypassed to the ascending aorta after oxygenation *ex vivo*; the RA is incised and the TT is excised *en bloc* under direct vision.

Given the high risk of surgery, strict patient selection measures must be taken. The surgery should be performed only for those with Child-Pugh A HCC (29). Postoperative failure is mainly observed in the form of local recurrence and distant metastasis. Some complications associated with surgery include heart failure, respiratory failure, infection and pulmonary embolism. Prevention of postoperative recurrence is the focus of postoperative management in HCC with TT in the IVC and RA. Measures to prevent postoperative recurrence include postoperative oral sorafenib administration (30-32) and adjuvant TACE (33,34).

Radiation therapy. With the advancement of radiotherapy, it is possible to increase the dose to the target volumes, excluding radiosensitive organs such as the stomach, small intestine, kidneys and spinal cord, which can tolerate lower radiation doses, using three-dimensional conformal radiotherapy (3DCRT), three-dimensional conformal intensity-modulated radiotherapy, stereotactic radiotherapy (SBRT) (35), and particle radiotherapy. Both external and internal irradiation are a treatment option for patients with HCC exhibiting TT, particularly for patients who cannot receive, or are unwilling to receive surgery (29,36,37). Radiation therapy is particularly suitable when the tumor is located on top of the liver, where the lesion cannot be detected by ultrasound, or when the lesion is located near a large blood vessel, making thermal ablation impossible (38).

A meta-analysis and systematic review of external radiotherapy for the treatment of the TT in the IVC or RA in 2018 (39) showed that the median total radiotherapy dose was 48-60 Gy, with a median survival time of 13.2 months (range, 5.6-25.4 months), 1-year overall survival (OS) rate of 53.6% [95% confidence interval (CI), 45.7-61.3%], 2-year OS rate of 36.9% (95% CI, 29.8-44.8%), total effective rate of 59.2% (95% CI, 39.0-76.7%), and disease-free survival rate of 83.8% (95% CI, 64.5-93.7%). Furthermore, a study by Matsuo *et al* (40) included 87 patients, and the total dose in 43 patients in the SBRT group was 45-55 Gy/10-15 f. The efficiency and 1-year OS rates in the SBRT group were 67.0 and 49.3%, respectively. In the 54 patients enrolled in the 3DCRT group, the total dose of planning target volume was 45-50 Gy/15-25 f and the effective rate and 1-year survival rate were 46.0 and 29.3%, respectively.

Komatsu *et al* (25) compared the efficacy between new proton radiotherapy (21 patients) and surgical resection (19 patients) in the treatment of HCC with TT in the IVC. The study found that for stage IIIB patients [All patients were staged according to the Union for International Cancer control/American Joint Committee on Cancer TNM staging system, 7th edition (41)], proton radiotherapy has a significant survival advantage. The median survival time in the two groups was 748 and 272 days, respectively. For stage IV patients, no significant difference in survival rates was observed. Furthermore, Komatsu *et al* (42) investigated the effectiveness of proton radiotherapy for patients with HCC exhibiting TT in the IVC. The 1- and 3-year survival rates

of 16 patients undergoing proton radiotherapy were 61.1 and 36.7%, respectively. The survival time was 24.2 months.

The designation of the irradiation area is still controversial, and it should be determined individually. The majority of studies support the use of radiotherapy when only including the TT, and if the primary tumor is close to the TT and the lesion is small, which may include the primary tumor. The dose of radiotherapy is associated with the choice of radiotherapy technique and the purpose of the radiotherapy. Currently, an optimal radiotherapy dose is under debate, and retrospective studies that have focused on this have shown that the high dose of radiotherapy is positively associated with prognosis.

There is also some correlation between the efficacy of radiotherapy and the location of TT. Hou *et al* (43) retrospectively studied 181 patients with HCC undergoing external radiation therapy (EBRT). The median radiotherapy dose in their study was 50 Gy. It was revealed that the median survival times of patients with portal vein, portal trunk, IVC and IVC TTs were 10.2, 7.4, 17.4 and 8.5 months, respectively. The efficacy of radiotherapy in patients with IVC TT is significantly higher than that in patients with portal vein tumor thrombosis (PVTT) and other types of TT.

Radiotherapy-induced liver damage is a dose-limiting liver radiation injury (40,44). As the majority of patients with HCC have a long history of liver cirrhosis, radiotherapy-induced liver damage requires sufficient attention. It primarily manifests as hepatomegaly after 2-12 months of radiation therapy, with a >5-fold increase in benign ascites and transaminase, an increase in the Child-Pugh score by ≥2 points, and stomach and duodenal ulcers. Vascular TT, poor liver function and a very large proportion of irradiated normal liver tissue are associated with a high risk of radiotherapy-induced liver damage. The key to avoiding radiation-induced liver disease is to design a radiotherapy plan wherein the dose exposure to the normal liver is limited to the tolerance range.

TACE. Transvascular interventional therapy is an important palliative treatment for patients with HCC who cannot undergo surgery. TACE is recognized as the most commonly used treatment. Previously, treatment for HCC with TT in the IVC and RA was contraindicated; however, a small number of literature reports have shown that TACE can improve the patient survival rate compared with optimal supportive care.

The effective rate of TACE has been reported to be 13.8-53.8%, with a median survival period of 4.2-10.9 months. Chern *et al* (45) studied TACE in 26 patients with advanced HCC exhibiting TT in the IVC or RA. The complete response rate of TACE in their study was 53.8%, and the median survival time was 4.2 months (range, 1.5-76.7 months). The 1-, 2- and 3-year survival rates were 41, 25 and 7%, respectively. Furthermore, they verified that a smaller diameter of the polyethylene glycol embolic particle sphere (47-180 μm) was better than a larger diameter (>180 μm), and the response rate was significantly higher in the former than in the latter. Chung *et al* (46) aimed to elucidate the treatment outcomes of TACE in patients with HCC exhibiting HV and/or IVC invasion. TACE response rates for primary tumors and

TTs in HV or IVC were 55.6 and 13.0%, respectively. The median OS time was 10.9 months (range, 0.1-23.0 months). Koo *et al* (47) also evaluated the effects of TACE in patients with HCC exhibiting TT in the IVC, and reported a response rate and progression-free survival rate of 13.8 and 37.9%, respectively, in the TACE group. The 1-year survival rate was 17.2% in the TACE group, and the median survival time was 4.7 months.

TACE enabled selective chemoembolization of angiographically-confirmed or -suspected blood vessels involved in the blood supply to the lesion, with embolization of the collateral artery (right inferior phrenic artery, left gastric artery branch) first, followed by embolization of the hepatic artery. The embolic material includes chemotherapeutic drug-iodinated oil-mixed emulsion, polyvinyl alcohol particles, or a gelatin sponge. The chemotherapeutic drugs used include epirubicin, hydroxycamptothecin, oxaliplatin, lobaplatin and fluorouracil (45,47,48).

Complications of TACE for IVC/RA tumors are pulmonary embolism and high-risk ischemic hepatic necrosis. These primarily manifest as fever, abdominal pain, vomiting and transient deterioration of liver function.

Drugs and other treatments. A small number of studies have reported the use of sorafenib and thalidomide to treat HCC with TT in the HV, IVC and RA (49-51). Simão *et al* (52) reported a rare clinical case that had a complete response to sorafenib with thrombosis in IVC and RA, with no recurrence after 3 years of treatment. Existing evidence from the European, Australasian and Asia-Pacific clinical trials concerning the use of sorafenib suggests that the drug is efficacious in the majority of HCC cases, with a median OS of 6.5 months in the treatment group compared with 4.2 months observed in the placebo group (53,54). There are also vast clinical data for the use of sorafenib in the treatment of advanced HCC; however, data concerning its use in the subgroup of patients with TT in the HV, IVC and RA are scarce. It is unclear whether medical therapy has been studied prospectively in this population, and this requires big data analysis. Chang *et al* (50) reported a case of three patients who received medical treatment with low-dose thalidomide and additional treatment via TACE and documented an OS time of >15 months. To the best of our knowledge, Li *et al* (55) reported the first case of primary intrahepatic lesions and IVC and RA TTs treated via percutaneous microwave ablation, wherein the patient survived for 16 months.

Comprehensive treatment. In a study by Duan *et al* (56), 11 patients with HCC exhibiting TTs in IVC and RA were enrolled. The 1- and 3-year survival rates of patients undergoing TACE combined with external radiotherapy were 54.5 and 27.3%, respectively. The median survival time was 21 months. Koo *et al* (47) performed a retrospective analysis among 42 patients with TTs in the HV, IVC and RA, and subsequently reported the effective and progression-free survival rates of patients undergoing TACE with CRT and TACE alone to be 42.9, 71.4, 13.8 and 37.9%, respectively. The OS rates were 11.7 and 4.7 months, respectively. A survival analysis (57) for TACE combined with bare stent implantation versus I-125 particle stent implantation showed a median

survival duration of 93 and 203 days, respectively, which resolved 97% of lower extremity edema.

6. Conclusion

HCC is the fourth most common malignant tumor in China and the third highest cause of cancer-associated mortality, which seriously threatens the health and life of humans (58). HCC is a highly malignant tumor that is often associated with intrahepatic vascular invasion (PVTT), which is an important prognostic factor, whereas the extrahepatic vascular invasions such as HVTT, IVC TT and RA TT are far less common when compared with PVTT. HVTT, IVC TT and RA TT have a worse prognosis than PVTT. Jun *et al* (59) have demonstrated that the newly revised UICC staging system (60) is later than the IVA period, and that HV invasion, IVC invasion, PVTT and multiple liver cancer nodules are independent risk factors for RA TT. These patients are in the terminal stage of disease, often combined with the formation of TT in the portal vein, multiple intrahepatic metastases, lung metastases, etc. Doppler ultrasound, CT and MRI, and magnetic resonance angiography can be used to detect the size, location, length and degree of TT directly and clearly, which guide the selection of treatment modalities, assessment of the degree of treatment difficulty and risks, and preparation of counter-measures.

The present study assessed the clinical manifestations, pathophysiology, imaging diagnosis techniques and associated positive treatments for HCC with TT in IVC or RA. Previously, these patients only underwent the best supportive treatments, which included the control of tumor-related symptoms, psychological counseling and spiritual help, and their survival time was 2-3 months. At present, with the increasing number of case reports and retrospective analysis of small data, active treatments such as surgery, radiotherapy, intervention, drugs and comprehensive treatment have been demonstrated to improve survival time. Jun *et al* (59) have also demonstrated that with a Cancer of the Liver Italian Program score ≤3 (61), active treatment can prolong the survival time of patients with HCC with RA TT. The current data in small studies (Tables I-III) demonstrate that surgical treatments have the greatest survival benefits, with a median survival time of 10.5-30.8 months, which is higher than the median survival time reported for radiotherapy (5.6-25.4 months). The therapeutic effect of TACE is poor, with a median survival time of 4.7-10.9 months. Liu *et al* (62) retrospectively analyzed 115 cases of HCC with TT in the HV, IVC and RA, and reported the median survival time with surgical treatment and TACE to be 17 and 8 months, respectively, which is consistent with the aforementioned results. Although other treatments such as sorafenib and thalidomide administration may also be effective, they have only been reported in a small number of cases, with little evidence. In addition, such advanced stage patients often undergo comprehensive treatment, such as surgery combined with radiotherapy, radiotherapy combined with TACE, and surgery combined with sorafenib and other treatment models. Koo *et al* (47) retrospectively analyzed 42 cases of HCC with TT in the HV, IVC, and RA, reported the effective and progression-free survival rates for TACE with CRT to be

42.9 and 71.4%, respectively, which were higher than those for TACE alone.

Despite this, there remains to be a lack of consensus on the treatment of HCC with TT in the IVC or RA. The treatment of such patients is recommended for clinical research, and it is expected that the current understanding of treatment of such patients will be improved in the future.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XN designed the study. XN, JZ and YX wrote the paper, performed the literature search and analyzed the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written consent for publication of images without any potential identifying information was provided by the patient.

Competing interests

The authors declare that they have no competing interests.

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