Review Article

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Hepatocellular Carcinoma with Hepatic Vein and Inferior Vena Cava Invasion

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Hepatocellular carcinoma (HCC) invades intrahepatic vessels causing tumor thrombosis. Infrequently, there is involvement of the hepatic vein (HV) and inferior vena cava (IVC). In this review, we summarize the epidemiology, classification, clinical features, and management of HCC with HV and IVC invasion. While the involvement of HV and IVC usually portends an overall poor survival, selected patients may be candidates for aggressive treatment and thus improving outcomes. (J Clin Exp Hepatol xxxx;xxx:xxx)

Lay summary/ key points

- Hepatocellular cancer infrequently involves hepatic vein and/or inferior vena cava and results into tumor thrombosis.
- Such involvement is traditionally considered to indicate poor outcomes and only systemic therapy is recommended.
- Selective patients with such tumor thrombosis benefit from aggressive treatment including surgery and radiotherapy or a combination of varied treatments.

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth highest cancer causing mortality globally.[1,2] HCC has a tendency to involve vessels within the liver and tumor thrombosis into a vein is a major adverse prognostic factor, with limited treatment options.[2] Tumor involvement of the hepatic veins (HVs) and inferior vena cava (IVC) is less frequent than portal vein invasion. HCC may involve the contiguous HV and the tumor thrombus may extend via the HV into the IVC and right atrium (RA). There is a paucity of literature on HCC with HV and IVC tumor thrombosis (HVTT and IVCTT) and there is no unequivocal agreement on the optimal management of such patients. As per the widely accepted Barcelona Clinic Liver Cancer (BCLC) staging, these tumors are considered as advanced and qualify for only systemic therapy with very short survival. However, aggressive management of these tumors may lead to better outcome. Here we review the epidemiology, classification, clinical features, and management of HCC with HV and IVC invasion.

PREVALENCE

In an autopsy series, HVTT was seen in 54 (23%) patients with HCC. Of these, 12 were protruding into the IVC and 11 reached the RA. The series also made record of one patient with tumor thrombi in both the pulmonary arteries.[3] Ninety percent of patients with tumor thrombi in the HVs also had tumor thrombosis of the portal veins.

In the Japanese national HCC registry, 5% of patients with HCC had HV invasion on imaging (862/17263).[4] In surgically resected specimens, macroscopic and microscopic HV invasion were seen in 6.9% and 11.4%, respectively.[4] Table 1 shows the distribution of HV invasion as per the Japanese classification.

Pathogenesis

Vascular invasion is an important event in neoplastic lesions, which indicates a stage of tumor progression where they have developed an evolved phenotype that facilitates invasion of the blood vessels.[5] The process of vascular invasion involves invasion of the stroma and vascular structures by tumorous cells, followed by rupture of the endothelium, and finally penetration into the vessel.[6]

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E-mail: drakashshukla@yahoo.com
Abbreviations: AFP: Alfa feto protein; BCLC: Barcelona Clinic Liver Cancer; CR: Complete response; EBRT: External Beam Radiation Therapy; EMT: Epithelial–Mesenchymal Transition; FOLFOX: folinic acid, fluorouracil, and oxaliplatin; HAIC: Hepatic arterial infusion chemotherapy; HCC: Hepatocellular carcinoma; HV: hepatic vein; HVTT: Hepatic Vein tumor thrombosis; IVC: Inferior vena cava; IVCTT: Inferior vena cava tumor thrombosis; OS: Overall survival (OS); PD: Progressive disease; PD-1: Programmed cell death protein-1; PR: Partial response; PV: Portal vein; PVTT: Portal venous tumor thrombosis; RA: Right atrium; RFS: Recurrence free survival; SD: Stable disease; TACE: Transarterial chemoembolisation; 3D CRT: Three dimensional conformal radiotherapy
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Table 1 Distribution of Hepatic Vein Invasion in HCC.

	By imaging (% of total)	Macroscopic invasion on surgically resected specimen (% of total)	Microscopic invasion on surgically resected specimen (% of total)
Vv1	1.8%	4.5%	9.3%
Vv2	1.7%	1.5%	1.3%
Vv3	1.5%	0.9%	0.8%
Total	5%	6.9%	11.4%

HCC is a richly vascular tumor with a predominantly arterial supply and a complex network of capillarized sinusoids. Initially, there is invasion of tumor cells through the peri-tumoral capsule and forms frond-like protrusions within the vascular channels and are covered by the endothelium of the sinusoids. Microscopically, these are appreciated as free floating clusters within the vascular lumen. Next, few of the tumor fronds may detach from the tumor owing to its fragility. This happens due to a combination of numerous reasons like biomechanical blood flow-related shear stress, mismatch between tumor growth and neoangiogenesis, tumoral secretions that lead to disorganization of the basal lamina and endothelium and trigger coagulation. If conditions like continued intravascular neoangiogenesis and an endothelial coating that prevents thrombosis are provided, the tumor would be capable to grow along and survive within blood vessels, while remaining in continuity with the main tumor mass.

Tanaka *et al.*,[7] found a positive tumor–portal vein pressure gradient (mean pressure gradient 6 ± 2 mm H_2O) contributing to invasion of portal vein. They hypothesized that there is a pressure-driven dispersal of the tumorous cells into the vascular lumen aided by tumoral capsular infiltration. Although a direct tumor-HV pressure gradient has not been measured, the normal hepatic venous pressure gradient is 1–4 mmHg[8] and thus a high tumor-HV pressure gradient maybe assumed.

Recently, epithelial–mesenchymal transition (EMT), the mechanism for invasion in a variety of cancers, has been shown to be involved in the vascular invasion in HCC as well.[9] EMT is defined as the process wherein epithelial cells lose their epithelial signatures while acquiring the characteristics of mesenchymal cells including changes in morphology, cellular structure, and biological function.[10] Down-regulation of E-cadherin is regarded as the key step of EMT. Increased expression of cyclin G1 could promote EMT and facilitate HCC metastasis. Cyclin G1 could interact with PI3K and activate the PI3K/Akt/GSK-3b/Snail pathway, by which E-cadherin expression is down-regulated.[9] Increased expression of other promoters of EMT like enhanced myeloid differentiation factor 88,[11] FoxM1,[12] brachyury,[13] JARID2[14] CXCR2/CXCL5,[15] PRMT9,[16] SERPINB3,[17] TFAP4,[18] FAM134B,[19] STK17B,[20] UBE2Q1[21] have also been implicated in HCC.

CLASSIFICATIONS

The Japanese classification of hepatic venous tumoral thrombosis (HVTT) in HCC is as shown in Figure 1. There are 4 stages: vv0 represents the absence of invasion of (or tumor thrombus in) the HV. vv1 is the invasion of (or tumor thrombus in) peripheral branches of the HV. vv2 is the invasion of (or tumor thrombus in) the right, middle, or left HV, the inferior right HV, or the short HV and vv3 is the invasion of (or tumor thrombus in) the IVC.[4]

The Third Affiliated Hospital of Sun Yat-sen University, China classified macrovascular invasion of HCC as follows: V1—invasion of a distant branch of the HV or portal vein (PV); V2—invasion of the first branch of the HV or the second branch of the portal vein; V3—invasion of the HV or the first branch of the portal vein; V4—Invasion of the main portal vein or IVC.[22]

Recently, a newer classification has been proposed by Chen *et al.*[23] for HVTT and this predicted prognosis (OS at 1–3 years) for different treatment modalities.

CLINICAL FEATURES

The patients with invasion of major HVs may develop secondary Budd-Chiari syndrome. They frequently develop

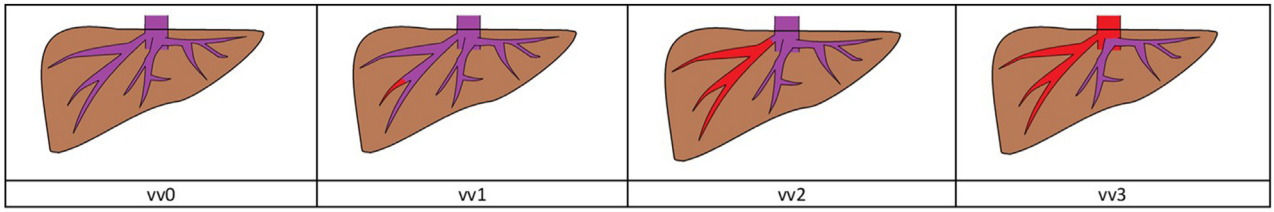

Figure 1 Japanese classification of hepatic venous tumoral thrombosis (HVTT). vvo: absence of invasion of the hepatic vein; vv1: invasion of peripheral branches of the hepatic vein; vv2: invasion of the main hepatic vein; vv3: invasion of the inferior vena cava.

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bilateral pedal edema from venous congestion and worsening of liver function. Invasion into RA may lead to pulmonary metastasis sometimes leading to dyspnea on exertion and respiratory distress.[24] Pulmonary infarction may lead to pleuritic pain. Sudden death may occur from tumor embolization.[25] Signs of right-sided heart failure are seen when the tumor invades the RA.[24] There are no data on how many are asymptomatic or the differences in symptoms as per stage of vascular invasion.

Metastasis

Tanaka *et al.*[26] reported that HV invasion was an independent risk factor for extra hepatic spread with a relative risk of 9.25 (95% confidence interval [CI] 1.58–55.5, p = 0.004).

In study by Zhang *et al.*,[27] the group with HV/IVC involvement reported more extrahepatic metastasis on follow-up, compared to a higher incidence of intrahepatic recurrence for patients with PV invasion.

On the other hand Kokudo *et al.*,[28] reported that the commonest site for tumor recurrence was intrahepatic, irrespective of tumor extent of invasion into HV (peripheral HV, main HV, or IVC). Lung metastasis was most frequent in the main HV group, and multiple metastasis was commonest in the IVC tumor thrombosis group.[28]

ASSOCIATION WITH PVTT

HVTT and IVCTT were associated with additional portal venous tumor thrombosis (PVTT) ranging from 48 to 88%[28–34] and 27–77%,[15,28,35,36] respectively. In a study, the median overall survival (OS) for combination of PVTT with HVTT was similar to that of HVTT alone.[37]

Diagnosis

The diagnosis of HVTT or IVCTT in HCC is primarily done on cross sectional imaging, like contrast-enhanced computed tomography or magnetic resonance imaging (MRI). The imaging findings that suggest tumoral invasion of the hepatic vein are arterial phase hyperenhancement within the venous lumen—with the findings similar to the liver parenchymal mass, an expansile thrombus, occluded vein with ill-defined walls, or direct contiguity with the tumor and high intensity on diffusion-weighted MRI sequence.[2,38]

In a study,[39] HV or IVC invasion was predicted by preoperative imaging in only 59%. But, they also reported improved detection as technology in imaging advanced. With advances in imaging, more HVTT will be detected especially in the vv1 stage.

HV invasion leads to a higher alpha-feto protein and a higher positivity rate for des-gamma-carboxy prothrombin than portal venous invasion.[28]

TREATMENT

As per the most widely used BCLC staging, invasion into major veins is considered as advanced HCC (BCLC stage C), which is not amenable to curative treatments.[2] The proposed treatment for advanced HCC is systemic therapy, most commonly Sorafenib.[2] The median survival of such patients is expected to be 10.7 months.[40]

In contrast to the more popular recommendations, the Japanese practice guidelines allow for active treatment such as resection, transarterial chemo embolization (TACE) and hepatic arterial infusion chemotherapy in addition to systemic therapy for tumors with vascular invasion, provided conditions like good liver function and the absence of extrahepatic metastasis are met.[41]

Macrovascular invasion at the level of HVs is an absolute contraindication for liver transplantation. It is an independent risk factor for recurrence of HCC in the post-transplant setting.[2,41,42]

- Surgical resection

Hepatic resection is a viable treatment option in appropriately selected patients.

Intraoperative ultrasonography to estimate the location and extent of the TT as well as to detect occult lesions is advocated.[27,43] Transsection of the liver is carried out using continuous or intermittent clamping of the hepatic pedicle (Pringle maneuver).[43] Mobilization of the liver and dissection of the IVC and HVs was performed first by Le Treur *et al.*, except large right-sided tumors which were approached anteriorly.[27] For HVTT, hepatic vascular exclusion (HVE) is used only if necessary and as briefly as possible,[27] with anatomic hepatic resection wherever possible.[29] The tumor thrombus can either be resected en bloc with the tumor or extracted out of the vascular lumen according to its location and extent.[27] For IVCTT, the TT was removed under total HVE with or without veno-venous bypass.[27,29,35] In patients with TT extending to the RA, the TT was removed under cardiopulmonary bypass.[29,43]

In a retrospective study, surgically treated patients of HCC with HVTT between 1985 and 2001 were analyzed.[29] The 5 year survival of patients with vv0, vv1, vv2, and vv3 thrombi were 43%, 19%, 11%, and 0%, respectively. Patients with hepatic trunk invasion survived significantly longer than those with invasion of the IVC (P = 0.008). No significant survival differences were found among patients with tumor invasion in only HV compared to both portal and HVs. There were no differences in the 5-year survival rate for patients with HV invasion who underwent curative or palliative resection (6% vs 8%). No patients with tumoral invasion of the IVC survived more than 2 years; this was primarily due to early lung metastasis.

Jiang *et al.*[22] showed that the extent of vascular invasion was an important determinant of OS and recurrence free

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survival (RFS). The study did not report results for patients with portal vein and HV invasion separately. 3-year OS and RFS rate of the V3 plus V4 group were 56.9% and 25.0%, respectively; the 3-year OS and RFS rate of the V1 plus V2 group were 90.2% and 51.0%, respectively.[22]

Pawlik *et al.*[44] reported 1-, 3-, and 5-year survival rates of 45%, 17%, and 10%, respectively, for patients with HCC with invasion of main PV or HV undergoing resection. On multivariate analysis, moderate to severe fibrosis in the liver parenchyma was an independent predictor of short-term and long-term mortality.[44]

Roayaie *et al.*[39] reported a median survival of 4.7 months (±2.1 m) in patients with HVTT or ICVTT. The survival was the lowest in this group when compared to segmental or main PV invasion. On multivariate analysis, alfa feto protein (AFP) > 30 ng/ml, tumor size >7 cm, and extent of invasion were independent markers of prognosis.[39]

Zhang *et al.*[27] compared surgical outcomes for HCC with HV ± IVC versus PVTT. The group with PVTT had a longer OS of 52 weeks than HV/IVC group with an OS of 38 weeks ($p < 0.01$). However, there was no difference in RFS (69.5% vs 71.3%, $p = 0.1$). Survival for better when the tumor thrombosis was within the hepatic veins compared to IVC ($p = 0.03$). In multivariate analysis, major vascular invasion, type of resection (anatomic vs non anatomic) and the presence of liver cirrhosis were predictors of OS.[27]

Le Treurt *et al.* reported median survival of 4 months for patients with HVTT undergoing surgery, whereas it was 9 months for PVTT.[43] This study only had 6 patients, all who had HVTT with IVCTT, which may account for a poor outcome.

In the largest series, 187 patients (153 with microscopic HVTT, 21 with major HVTT and 13 with IVCTT) were studied who underwent surgical treatment at a tertiary Japanese hospital between 1994 to 2011.[28] The median survival of each of the three groups were 5.27, 3.95, and 1.39 years, respectively. There was no different in survival between groups with microscopic or major invasion of the HV, $p = 0.7$. IVC tumor thrombosis was an adverse prognostic factor on multivariate analysis.

In a retrospective study of HCC involving IVC and/or RA, the results of surgical treatment were superior to non surgical treatments like TACE.[45] They reported 1-, 3-, and 5-year survival rates of 68.0, 22.5, and 13.5%, respectively, with a median survival of 19 months with hepatectomy.

o Post surgical recurrence

The median time to recurrence after surgery in patients with microscopic HV invasion, major HV invasion, and IVC invasion was 1.06, 0.41, and 0.25 years.[28]

- Radiotherapy

Historically, application of radiotherapy for liver tumor was limited despite the HCC being radiosensitive because liver is radiosensitive. But with recent advances in radiotherapy techniques, it is possible to deliver tumoricidal doses to target organ and minimize adverse effects.[30]

In a retrospective study, the median survival of 47 patients of HCC with PV or HV invasion who underwent radiotherapy was 8 months.[30] The study included 5 patients with HV invasion and 5 patients with a combination of PV and HV invasion. The results for HV invasion alone were not elucidated.

In another retrospective study, the outcome of external beam radiation therapy (EBRT) in patients with macrovascular invasion varied as per the location of tumor thrombus. The median survival was 10.2, 7.4, 17.4, and 8.5 months for patients with PV branch, PV trunk, IVC, and PV plus IVC tumor thrombosis, respectively. The focus of EBRT was on the tumor thrombi with or without primary intrahepatic tumors. EBRT delivered a median total dose of 50 Gy (range, 30–60 Gy).[36]

In another study, 42 patients with IVC or combination of IVC with PV thrombosis were evaluated for response to EBRT given at a median dose of 50 Gy (range 30–60 Gy).[46] The percentage of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were 61.9%, 19%, 19.1%, and 0%, respectively. These patients were also compared to those with PVTT. The objective response was higher in IVC than PVTT, $p < 0.001$. The survival rates at 1, 2, and 3 years were 31.8%, 17.5%, and 8.8% for patients with PVTT; 66.3%, 21.1%, and 15.8% for IVCTT; 25%, 8.3%, and 0% for PVTT plus IVCTT, respectively.

In a recent meta-analysis of use of EBRT for IVCTT and RA involvement, consisting of 8 studies and 9 cohorts the pooled 1- and 2- year OS rates were 53.6% (95% CI: 45.7–61.3%) and 36.9% (95% CI: 27.2–42.4%), respectively.[47] The pooled response rate (CR + PR) was 59.2% (95% CI: 39.0–76.7%). The pooled local control rate (CR + PR + SD) was 83.8% (95% CI: 78.8–97.1%), respectively. The overall rate of possible grade ≥3 complications was 1.2% (2 of 164).

- Systemic therapy

In a case report, tumor thrombus involving HV, IVC, and RA were treated with sorafenib alone. The treatment was deemed ineffective.[48]

In a small study, the use of check point (PD-1) inhibitors was found effective in patients with IVCTT with 70% showing PR and 30% having PD.[49] The OS was higher among those patients exhibiting radiological response to the tumor thrombosis.

- TACE

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Sixty-two patients with HV/IVC invasion underwent an average of 2.48 (±2.14) sessions of TACE at a single center.[33] The commonest etiology for HCC was hepatitis B. A majority of patients had a good performance status and Child-Pugh class A or B. Patients with extrahepatic tumors and who had received prior treatment were excluded. The response rates for primary tumor and tumor thrombi were 55.6 and 13%, respectively. A majority (85%) of patients developed post-TACE syndrome. Major complications included pulmonary edema in one and liver abscess in another; neither were fatal. A post treatment reduction in AFP by ≥ 50% and tumor thrombi treatment response were independent prognostic factors. The median OS was 10.9 months (range 0.1–23.0 months). The cumulative survival rates at 3, 6, 9, and 12 months were 73.8, 58.1, 53.9, and 45.8%, respectively.

In a study of 18 patients with HCC invading the IVC and RA,[15] TACE was carried out and the 1- and 3-year OS rates were 50% and 16.7%, respectively, with a median survival of 15.2 months. One patient died of pneumonia, with no other major adverse events.

In a small study, 3 unresectable patients with HCC with tumor thrombus through the HV underwent hepatic artery chemoembolisation with aclarubicin, mitomycin C, lipiodol, and/or Gelfoam. Two of these patients subsequently underwent surgical resection with good survival.[50]

The arterial supply for tumors invading the IVC and RA were hepatic artery (5/11) and inferior phrenic artery (6/11).[51] In another study, hepatic artery was the only feeding vessel in 7/18 cases, while 11 had extrahepatic feeding arteries including right inferior phrenic artery, left inferior phrenic artery, and the left gastric artery.[15] A summary of various modalities for treatment of PVTT and IVCTT is mentioned in Table 2.

COMPARISON OF VARIOUS MODALITIES AND THEIR COMBINATIONS

Active treatment vs best supportive care

Chun *et al.*[52] compared outcomes of the active treatment group, including chemotherapy (31%), TACE (25%), radiotherapy (6%), surgery (3%), or combination (15%) to the best supportive care group in patients with HCC and IVC and/or cardiac invasion. The survival of the treated group was better than the supportive care group with hazard ratio of 0.509 (95% CI of 0.262–0.992; p = 0.047). Similar results favoring active treatment were found in another study on patients with invasion of the RA.[24]

TACE+chemotherapy vs TACE alone

Kim *et al.*[34] studied outcomes of conventional TACE compared with modified TACE (TACE followed by infusion of 50–100 mg of cisplatin). The median survival was significantly longer in the modified TACE group (9.7 mo, 95% CI [4.3–15.1]) compared with the conventional group (6.7 mo, 95% CI [4.8–8.5]).[34] In contrast, results from sub group analysis for modified TACE showed better, but statistically insignificant results in another study (11mo vs 4.2 mo, p = 0.23).[33]

o TACE vs surgery

Yoshidome *et al.*[35] reported higher survival with hepatectomy when compared to transarterial chemoembolisation (TACE) alone in patients with major portal vein and/or IVC invasion. Of 34 patients analyzed in the study, about 1/3rd (n = 11), had IVC invasion. Patients with tumor size <10 cm and tumor size reduction or necrosis of 50% or higher by TACE had a favorable outcome.[35]

o TACE + EBRT

In a small study of patients with IVC and RA tumor thrombus,[53] TACE sessions were conducted followed 2 weeks later by EBRT. Patients with metastasis were given folinic acid, fluorouracil, and oxaliplatin regimen or sorafenib. The reported median survival of 21 months.

o Chemotherapy + RT

Murakami *et al.* evaluated hepatic arterial infusion chemotherapy using 5-fluorouracil and systemic interferon-α for HCC with vv2 and vv3.[32] This was combined with three dimensional conformal radiotherapy in 14

Table 2 Modalities for Treatment of PVTT and IVCTT.

Treatment Modality	Survival	Special comments
Systemic therapy	Median survival 10.7 months[47]	Data available with Sorafenib only and found ineffective
Surgical resection	3 year survival of patients 10–59% (depends on extent of thrombosis)	Possible for patients with compensated cirrhosis and adequate future liver remnant.
Radiotherapy	Median survival 17.4 months for IVCTT[36]	Data available with IVCTT only. Data for isolated HVTT not available.
Immunotherapy	Objective response rate 70% in IVT [T[49]	Only one study currently. Data for isolated HVTT not available. Promising therapy for future.
Transarterial chemoembolisation (TACE)	Median survival 10.7 months[33]	High prevalence of post embolization syndrome
Combination therapies	Variable results	No clear preferred combination with currently available literature

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(42%). The median survival was 7.9 months. CR was seen in 3 (9%) and PR was seen in 7 (21%). Radiotherapy-related reduction in VTT significantly improved survival.

o TACE + Sorafenib vs TACE alone

Zhang *et al.*[53] compared the combination of TACE and sorafenib to TACE alone for patients with HV tumor thrombosis. OS of the combined group was found to be significantly higher than the monotherapy group (14.9 vs 6.1 months, $P = 0.010$). The time to progression was found to be significantly longer in the combined group (4.9 vs 2.4 months, $P = 0.016$).

o TACE + thermal ablation vs TACE alone

In a retrospective study, TACE followed by percutaneous thermal ablation compared to TACE alone showed median OS of 18 months vs 6.5 months.[54] Patients who achieved CR with treatment had the best survival (42 months). Only minor complications were observed for TACE in this group.

- Other treatments

There are few case reports. Li[55] reported microwave ablation of tumor thrombus with invasion of HV, IVC, and reaching upto RA along with the intrahepatic tumors. The patient had a follow-up of 16 months in a good condition.[55]

Current guidelines of HCC or Budd-Chiari syndrome have not addressed HCC with secondary HV thrombosis in detail or addressed it very superficially since there is paucity of data.[2,56,57]

HCC invading HV and IVC is a distinct entity with poor survival and high incidence of metastasis. With advancement in imaging, there will be an increase in the incidence of these tumors. The prognosis depends on the extent of vascular involvement, presence of liver cirrhosis, and extrahepatic metastasis. There is emerging evidence of improved survival with treatment over no treatment, but small sample size in all the studies is an inherent limitation. The outcome is improved over time with better surgical technique. These patients have better survival with aggressive treatment which should be offered to appropriately selected individuals.

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CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Dr AS: Conceptualisation, Data collection, Analysis and editing. Dr AJ: Conceptualisation, Data collection, Manuscript writing.

CONFLICTS OF INTEREST

All authors have none to declare.

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