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A Multi-Disciplinary Team Approach Optimizes Therapy Selections and Improves Survival Outcomes in Patients with Hepatocellular Carcinoma and Portal Vein Tumor Thrombus

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1. Abstract

1.1. Background: The treatment of hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT) is complicated and requires a coordinated multidisciplinary approach. The impact of a multidisciplinary team (MDT) approach on selecting therapies and long-time survivals of patients with HCC with PVTT is retrospectively studied.

1.2. Methods: The clinical and survival data of patients with HCC and PVTT who were managed before (April 2007- March 2013) and after (April 2013-September 2020) the establishment of an MDT were retrospectively compared.

1.3. Results: Of 1906 patients included, 1094 were in the MDT-group and 812 in the pre-MDT group. After introducing an MDT procedure, the proportions of patients who underwent surgical resection (34.6% *vs.* 29.3%, $p = 0.014$) and received molecularly targeted drugs (19.4% *vs.* 7.8%, $p = 0.00$), were significantly increased. Patients managed through the MDT approach had a significantly improved survival compared with who didn't (13.5 *vs.* 11.5 months, $p = 0.00$). After stratification with treatment modalities, the MDT procedure significantly improved survival in patients received surgery (16.3 *vs.* 13.9 months, $p = 0.038$), while marginally increased survival in patients had non-curative local treatments (11.8 *vs.* 11.0 months, $p = 0.064$). The implementation of an MDT significantly reduced long-term HCC-related deaths, with a hazard ratio (HR) of 0.78 (95% Confidential Interval, 0.70–0.86, $p = 0.00$).

1.4. Conclusion: The implementation of an MDT approach to patients with HCC and PVTT allowed a better selection of therapies and provided long-term survival benefits.

2. Introduction

Hepatocellular carcinoma (HCC) is the fourth most common cancer and the third leading cause of cancer-related death in China [1]. HCC has a high propensity to invade the portal venous system, leading to a formation of portal vein tumor thrombus (PVTT) in 44 to 62.2% of patients with HCC [2]. The PVTT is one of the most important predictors of a poor survival in HCC [3]. The manage-

ment of HCC with PVTT is complicated with controversy exists among experts from the West and the East [4]. Therapeutic modalities include systemic therapies, surgical treatment, transcatheter arterial chemoembolization (TACE), external or internal radiotherapy (RT) and supportive treatment. Each of the treatments can be used either alone or in combination [3-5]. However, there is still a lack of a worldwide consensus on the treatment strategies to those patients, which can differ significantly among clinicians in different medical specialties. A multi-disciplinary team (MDT) approach has been reported to optimize patient selection and improve the long-term survival in many cancers, including HCC [6-8]. The treatment of patients with HCC and PVTT is more complicated, but there have been very few published studies in this area. This study was conducted to determine the impact of introducing the MDT approach on selecting treatments and long-term survivals of those patients.

3. Methods

3.1. Setting-up of The MDT Approach

Our institution is a major clinical and research center for liver cancer in China, admitted more than 30,000 patients with HCC and carried out 8,000 hepatectomies in 2021. A multi-disciplinary diagnosis and treatment center for HCC with PVTT was set-up in April 2013 to meet the growing demand and challenges of HCC with PVTT, which we have previously reported[9]. Our center consisted of clinicians from the departments of hepatic surgery, diagnostic radiology, pathology, radiotherapy, interventional radiology and hepatology. A weekly MDT meeting was attended by experts and staffs from these departments to determine individualized treatment plans for patients with HCC with PVTT seen in the center. In the MDT meetings, the clinical information of each patient, including the imaging findings, the types of PVTT, the resectability of primary tumor, the classification of liver function and patients' comorbidities are carefully studied. Individualized therapeutic plans of patients are then made, referring to a treatment protocol based on the therapeutic plan recommended by the Chinese Expert Consensus/Guideline on Multidisciplinary Diagnosis and Treatment of HCC with PVTT, which was regularly updated in 2016, 2018 and 2021[3,10,11]. If a consensus cannot be reached on the treatment plan of a patient, the opinion of the majority of the experts presented was taken to be the final decision. The medical information and decision made on every patient at the meeting were recorded on a chart which includes the clinical presentation, underlying liver diseases, laboratory/imaging findings and any prior treatments received. The opinions of the experts are also recorded. After the MDT meeting, efficient communications between the specialists, and unscheduled joint meetings are held, whenever necessary, to further discuss the management of patients.

4. Patient Selection

A prospective database was established with the introduction of the MDT in April 2013. An analysis of the data from the inception to September 2020, with follow-up data collected until September 2021, was performed. For comparison, the medical and follow-up data of patients with HCC and PVTT treated at our institution from April 2007 to March 2013 (before the inauguration of the MDT) were retrospectively studied. The database included the demographics, tumor and liver function parameters, imaging findings, treatment modalities and the follow-up information. The inclusion criterion of this study was HCC patients with a presence of PVTT shown on radiological examinations and treated in our institution. The exclusion criteria were patients refused the recommended therapies; incomplete medial or follow up data. The study protocol was approved by the Institutional Ethics Committee of our institution. All patients who were enrolled in this study signed an informed consent that their clinical data and specimens could be used for scientific researches.

5. Diagnosis of HCC and PVTT

The diagnosis of HCC was made based on biopsy or by the non-invasive criteria of the European Association for the Study of Liver guidelines [12]; The presence of PVTT which was assessed by 4-phase dynamic computed tomography (CT) using the following criteria: the presence of low attenuation intraluminal masses that expanded the portal vein, or there were filling defects in the portal venous system. Because the treatment and prognosis of patients with HCC with PVTT are closely related to the extent of PVTT, we developed a staging system based on the extent of portal vein invasion in 2007 [13]. The EHBH classification(also known as Cheng's classification), which has been shown efficient in stratifying patients with HCC and PVTT [13-15], divides PVTT into four types: type I, tumor thrombus involving segmental or sectoral branches of the portal vein or above; type II, involvement of the right or left portal vein; type III, thrombus extending to the main trunk of portal vein; and type IV, thrombus invaded the superior mesenteric vein . In this study, patients were stratified into 4 types (I-IV), according to the EHBH classification.

6. Follow-up

The follow-up examination was performed at our outpatient clinic every 1 to 3 months. Serum α-fetoprotein (AFP) measurements and abdominal ultrasounds were performed once every month. Contrast computed tomography (CT) or magnetic resonance imaging (MRI) was performed once every three months for surveillance of recurrence, or if HCC recurrence was suspected clinically. Surgical treatment, TACE, RT, local ablative therapy or systemic therapy was used for the treatment of HCC recurrence, depending on the time of tumor progression, locations of the lesions, the size and number of lesions, the liver functional status, and the presence/absence of extrahepatic disease. Palliative treatments were provided to patients with an end-stage disease, poor general status or poor liver function.

7. Statistics

Data on patient characteristics, treatments and survival were compared between the MDT and Pre-MDT cohorts. Continuous and categorized data were compared using the Pearson's chi-squared test, Fisher's exact test, or Student's t test, as appropriate. Patients' overall survival (OS) was calculated using the Kaplan-Meier method, and comparison was performed using the log-rank test. Factors influencing OS were identified using a Cox proportional hazards regression model. All calculations were performed using the Stata 12.0 software (StataCorp, Texas 77845 USA). A $p < 0.05$ was considered statistically significant.

8. Results

8.1. Study Population

From April 2013 to September 2020, 1198 patients with a diagnosis of HCC with PVTT were managed using the MDT approach. From April 2007 to the establishment of MDT in March 2013, a retrospective chart review showed 902 patients with HCC with PVTT were treated in our center. A total of 194 patients were excluded from the further analysis, with 71 didn't comply with recommended therapy and 123 lacked of clinical or follow up information. Finally, 1906 patients were included in the study, with 1094 in the MDT-group and 812 in the pre-MDT group. There was no significant difference in baseline demographic data between the 2 groups, including age, gender, hepatitis B virus (HBV)/ hepatitis C virus (HCV) status, liver function status, degrade of cirrhosis, AFP level, tumor size, tumor number, presence of distant metastasis and extent of PVTT, except the proportion of patients received previous anti-HCC treatments was significantly higher in the Pre-MDT group compared with the MDT group (20.2% *vs.* 16.1%, p =0.020) (Table 1).

Table 1: Baseline characteristics of patients before and after MDT meeting.

Characteristics	MDT group (n=1094) (%)	Pre-MDT group (n=812) (%)	*p*
Male	926 (84.6)	675 (83.3)	0.360
Age >= 50 years	623(56.9)	480(59.1)	0.344
HBsAg positive	1061(97.0)	781(96.2)	0.337
HCV antibody positive	14(1.3)	10(1.2)	0.926
Child B liver function	146(13.3)	123(15.1)	0.264
Degrade of cirrhosis (Severe)	171(15.6)	149(18.3)	0.116
Positive AFP (> 20 ug/l)	627(67.3)	480(59.1)	0.431
Tumor diameter (>5 cm)	860(78.6)	658(81.0)	0.194
Multiple lesions	179(16.4)	159(14.5)	0.069
Distant metastasis	25(2.3)	28(3.4)	0.127
Previous treatment	176(16.1)	164(20.2)	0.020*
PVTT(type III/IV)	718(65.6)	504(62.1)	0.109

MDT: Multi-disciplinary team; HBsAg, Hepatitis B surface antigen; HCV: Hepatis C virus; AFP, α-fetoprotein; PVTT: Portal Vein Tumor Thrombus;

* $p < 0.05$

8.2. Comparison of Treatments Before and after MDT Approach

The treatment methods analyzed in this research were defined as therapeutic strategies initially recommended in the MDT meeting (the MDT group) or in consultation with specific experts (the Pre-MDT group). Patients didn't implement the recommended therapies were excluded from this research. However, we were unable to depict the whole spectrum of therapies these patients received after tumor progression, with the enormous possibilities relating to the timing of tumor progression, locations of lesion, size and number of lesions, liver functional status, and presence/absence of extrahepatic disease. A comparison of initial therapeutic strategies between groups was showed in Table 2. The proportion of patients who underwent surgical treatment was significantly higher after than before the implementation of the MDT approach (34.6% vs 29.3%, p = 0.014). There were only 17 patients (2 in the MDT-group, 15 in the Pre-MDT group) received surgery as mono-therapy, while 157 (128 in the MDT group, 29 in the Pre-MDT group) underwent a neo-adjuvant RT and 461(309 in the MDT group, 152

in the Pre-MDT group) had adjuvant TACE/RT/systemic drugs. A total of 25 patients with initially un-resectable lesions received hepatectomy after "downstaged" with other local or systemic therapies, with 18 in the MDT group and 7 in the Pre-MDT group. Immune Checkpoint Inhibitors (ICIs) and novel Tyrosine Kinase Inhibitors (TKIs), such as Lenvatinib, were only available after 2018 in our institution. Partially for this reason, there were a significantly higher proportion of patients with a multi-disciplinary review, when compared with those without, to receive molecular targeted therapies (19.4% vs 7.8%, $p = 0.00$). Most of those patients had combined therapy with RT and/or TACE (190 in the MDT group, 40 in the Pre-MDT group). For patients in the Pre-MDT group, the majority of targeted drugs administrated was Sorafenib (59/63, 93.7%), while for patients managed through the MDT procedure, 83 (39.2%) had Sorafenib, 66 (31.1%) had Lenvatinib and 71 (33.5%) underwent therapies containing ICIs. There were significantly lesser patients who underwent RT and/or TACE after the implementation of MDT, compared with patients in the Pre-MDT group (42.0% *vs.* 60.0%, $p = 0.00$). 311 patients in the MDT group, while 370 in the control group, received RT combined with TACE. Those patients had a significantly higher chance to receive RT prior to TACE in the MDT group compared with patients in Pre-MDT period (74.0% *vs.* 55.4%, $p = 0.00$).

Table 2: Comparison of the spectrum of treatment strategies for patients with HCC and PVTT before and after MDT meeting.

Therapeutic strategies	MDT group (n=1094) (%)	Pre-MDT group (n=812) (%)	*p*
Surgical resection [a] (Surgery only or combined with other therapies)	379 (34.6)	238 (29.3)	0.014*
Molecularly targeted therapies (TKIs/anti-VEGFs and/or ICIs) with or without RT/TACE [b]	212 (19.4)	63 (7.8)	0.00*
RT and/or TACE	459 (42.0)	486 (60.0)	0.00*
Other anti-HCC treatment (Chemo/HAIC/radioembolization)	26 (2.4)	13 (1.6)	0.237
Palliative treatment	18 (1.6)	12 (1.5)	0.771

a: including 25 patients with initially un-resectable lesion "downstaged" using other therapies, with 18 in the MDT group and 7 in the Pre-MDT group

b: ICIs was only used in the MDT group because of availability; not include 51 patients received previous or following hepatectomy, with 42 in the MDT group and 9 in the Pre-MDT group

RT: Radiotherapy; TACE: transcatheter arterial chemoembolization; TKIs: Tyrosine Kinase inhibitors; VEGFs: Vascular endothelial growth factors; ICIs: Immune checkpoint inhibitors; Chemo: Chemotherapy; HAIC: Hepatic artery infusion chemotherapy

* $p < 0.05$

8.3. Survival

The median follow-up for the MDT group was 41.4 months (interquartile 24.5-51.5 months) and 67.5 months (interquartile 59.0-80.4 months) for the Pre-MDT group. As of data cutoff on September 2021, 1632 patients (85.6%) had died of HCC, and 73 patients had died of diseases other than progression of HCC. The median OS for patients managed through the MDT was 13.5 months (interquartile range, 6.8-25.3 months), which was significantly higher than that of patients managed without a multi-disciplinary review (11.5 months, interquartile range, 6.3-17.5months) ($p = 0.00$, Figure 1). Patients received surgical treatment (15.3 months, 8.3-28.4 months) or molecular targeted therapies (13.4 months, 6.3-25.4 months) had a better OS than those had RT and/or TACE (11.5 months, 6.1-16.9 months) (Figure 2A). After stratification with therapeutic methods, the MDT procedure significantly improved survival in patients received surgery (16.3 vs. 13.9 months, $p = 0.038$) (Figure 2B), while marginally increased survival in patients had non-curative local treatments (11.8 *vs.* 11.0 months, $p = 0.064$) (Figure 2C). However, for patients treated with molecular targeted drugs, the survival benefit of MDT didn't reach statistical significance (13.4 months *vs.* 12.0 months, $p = 0.356$) (Figure 2D). On multivariate Cox model analysis, compared with the pre-MDT group, the implementation of an MDT significantly reduced HCC-related deaths, with a hazard ratio (HR) of 0.78 (95% CI, 0.70–0.86). Other parameters, including positive HBsAg (HR: 1.42; 95%CI: 1.0-2.0), presence of severe cirrhosis (HR: 1.15; 95% CI, 1.01-1.32), multiple lesions (HR: 1.31; 95% CI, 1.16-1.49) and type III/IV PVTT (HR: 1.76; 95% CI, 1.59-1.96), also predicted HCC-related deaths. (Table 3).

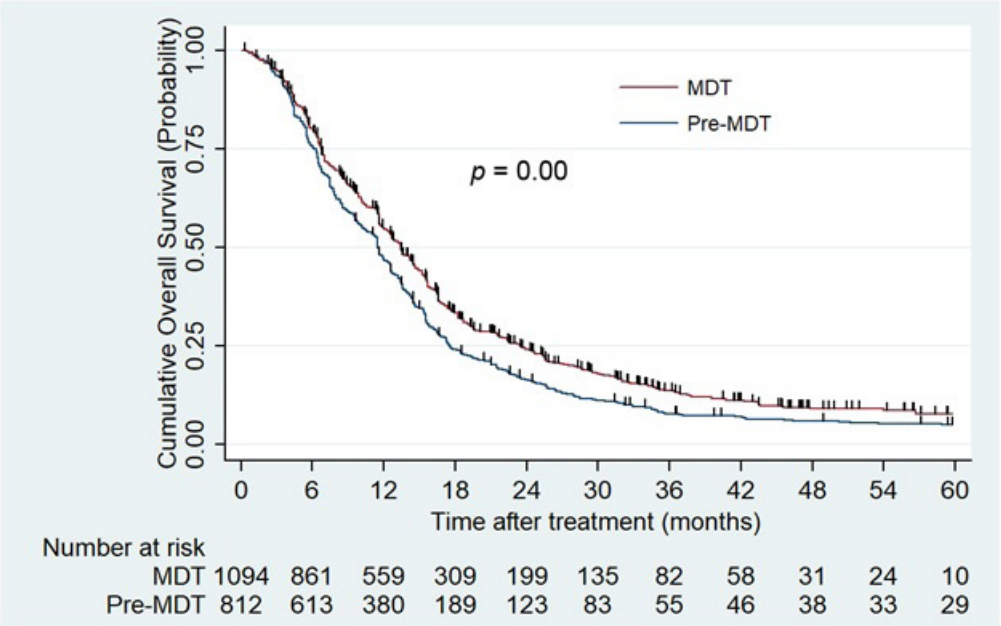

Figure 1: Kaplan-Meier analysis of overall survival in the MDT and the Pre-MDT groups ($p = 0.00$)
MDT: Multi-disciplinary Team.

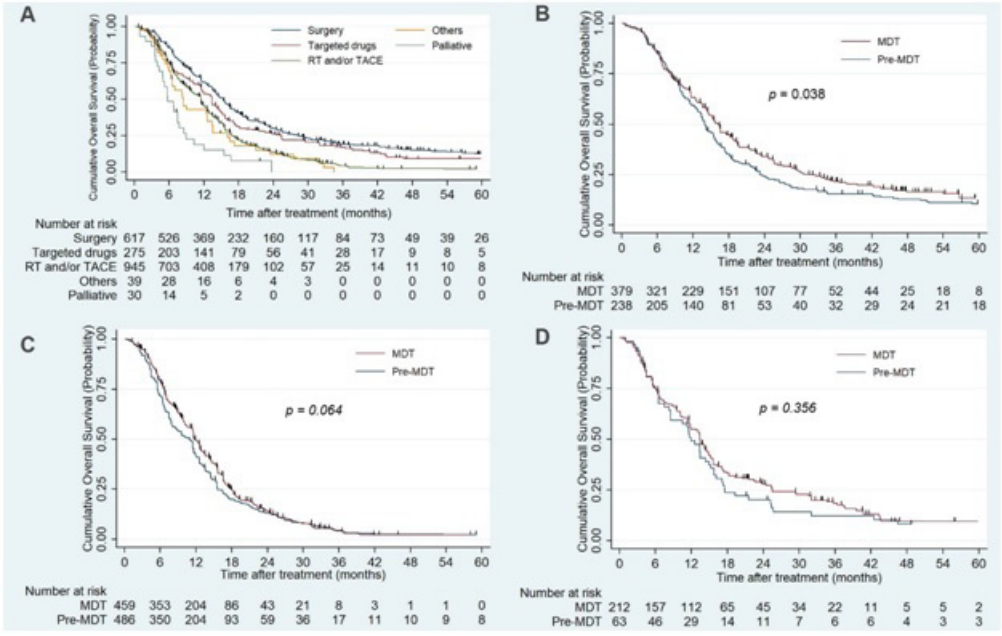

Figure 2A: Kaplan-Meier analysis of overall survival of patients received different types of treatment modalities ; **B.** Kaplan-Meier analysis of overall survival of patients received surgical treatment in the MDT and the Pre-MDT groups ($p = 0.038$) ; **C.** Kaplan-Meier analysis of overall survival of patients received Radiotherapy and/or Trans-arterial Chemoembolization in the MDT and the Pre-MDT groups ($p = 0.064$) ; **D.** Kaplan-Meier analysis of overall survival of patients received molecularly targeted drugs in the MDT and the Pre-MDT groups ($p = 0.356$)

RT: Radiotherapy; TACE: Trans-arterial Chemoembolization; MDT: Multi-disciplinary Team.

Table 3: Factors associated with hepatocellular carcinoma-related death using multivariate Cox regression analysis.

Variables	HR	95% CI	*p*
Age (>=50 vs <50)	0.96	0.87-1.06	0.382
Gender (male vs female)	1.0	0.92-1.09	0.958
HBsAg status (positive vs negative)	1.42	1.0-2.0	0.032*
HCV antibody (positive vs negative)	1.60	0.98-2.61	0.058
Cirrhosis (severe vs mild/none)	1.15	1.01-1.32	0.037*
Liver function (Child-Pugh Grade B vs A)	1.05	0.91-1.22	0.479
AFP level (> 20 ug/l vs <= 20 ug/l)	1.01	0.92-1.12	0.809
Tumor diameter (>= 5cm vs <5cm)	1.13	1.0-1.28	0.054
Tumor number (multiple vs single)	1.31	1.16-1.49	0.000*
Distant metastasis (yes vs no)	1.31	0.98-1.75	0.066
Previous treatment before MDT (yes vs no)	1.08	0.95-1.23	0.221
Type of PVTT (III/IV vs I/II)	1.76	1.59-1.96	0.000*
Implement of MDT (yes vs no)	0.78	0.70-0.86	0.000*

HR : Hazard Ratio; CI: Confidential interval; HBsAg: Hepatis B virus surface Antigen; HCV: Hepatis C virus; AFP, α-fetoprotein; PVTT: Portal vein tumor thrombus; MDT: Multi-disciplinary team.

9. Discussion

The management of HCC with PVTT is extremely complex, and it has to simultaneously address the triple challenges posed by the tumor, severity of PVTT and liver functional status. For the treatment of those patients, Sorafenib has been recommended as the only standard first-line therapy in the Barcelona Clinic Liver Cancer (BCLC) guideline for one decade [16]. With developments in certain therapeutic strategies and drugs, including ICIs, TKIs and anti-VEGF drugs, the landscape of systemic therapy for HCC with PVTT has changed in recent years [17-19]. However, patients with HCC coming from China/Southeastern parts of Asia have different etiologies and biological behaviors from patients in Europe and North America [4,20-22]. For instance, in China/Southeast Asia, the common etiology for HCC is HBV, and these patients usually have better liver functional reserves and long-term survival outcomes after hepatectomy when compared to patients with HCV-related HCC [20,22], which is predominant in the west. Therefore, in eastern countries, more aggressive therapies are recommended for selected patients diagnosed with HCC and PVTT, with promising survival benefits being reported using surgical resection, RT, TACE and other therapies [4,10], whereas HCC with portal vein invasion is still a contraindication for liver resection according to western guidelines [12,23,24]. As a consequence, with tremendous differences currently exist in different regions, there is a lack of widely recognized guidelines for the treatment of HCC with PVTT [4]. The best treatment strategy for HCC with PVTT should be based on a coordinated multidisciplinary approach with a full coordination and communication among experts in the relevant medical disciplines. However, patients are often treated by a single specialist, or successively by single specialists at various stages of the treatment, which can lead to delayed or even inappropriate treatments. The establishment of an MDT approach has increasingly been recognized to provide effective therapies with an improvement in survival of HCC patients [6,8,25,26]. Chang TT et al. retrospectively evaluated a cohort of 121 HCC patients managed through a multidisciplinary collaboration and compared with 62 patients in the Pre-MDT era, indicating an advantage of an MDT in treatment and improving survival of HCC [8]. Agarwal PD and his associates showed the implementation of an MDT resulted in a higher rate of HCC-related treatment and improved patients' survival [6]. Although we firstly reported the setting-up of an MDT procedure in our institution for HCC with PVTT in 2020 [9], up to now, there is still no specific research analyzing the impact of an MDT approach on optimizing treatment selection and improving survival of those patients. In this study, the significance of MDT was evaluated by comparing the data on patients who were managed before and after the inauguration of an MDT approach. It is notable that the therapeutic landscapes were dramatically changed since the implement of MDT, with similar baseline characteristics between the 2 groups. More patients managed through the MDT received curative treatments and molecularly targeted therapies, with lesser had traditional non-curative therapies (Table 2). Survival analysis showed that patients managed through the MDT approach had a significantly better OS than those didn't. Undoubtedly, this result is open to biases. The change of treatment strategies in the MDT cohort may be due in part to improvements in the availability and efficacy of treatment modalities over time, which in turn, may have contributed to the improved survival of patients. To minimize those bias, we analyzed the effect of MDT on patients' survival after stratification with treatment methods. We found the impact of an MDT procedure on the survival gain is also significant in patients received surgical resections, and marginally significant in patients received RT with/or TACE. Although techniques and drugs for treating HCC have been developing in recent years, we believe a better patient management using the multi-disciplinary approach had made substantial contributions to the improved survival of patients with HCC and PVTT. First, in our research, the establishment of MDT approach led to a more appropriate selection and management of patients to receive surgical treatments. In the Pre-MDT era, patients treated in departments other than surgery tended to have more conservative therapies, even though a part of them had resectable lesions and a limited PVTT extension. For patients managed by surgeons without an MDT setting, the lack of appropriate peri-operation treat-

ments also hampered the postoperative prognosis. In the MDT era, patients were classified into several subtypes by comprehensively evaluating the resectability of tumor, PVTT types and liver function status, leading to an increased access to curative therapies and sensible neoadjuvant/adjuvant therapies. For patients with resectable tumors and type II/III PVTT, a neoadjuvant RT was usually recommended to further confine the lesion extension and improve postoperative prognosis [27,28]. What's more, a considerable number of patients with initially un-resectable lesions received surgical treatment after "down-staged" by local or systemic therapies, which was difficult to achieve without well communications between surgeons and hepatologists. Second, patients received RT with/or TACE, who accounted for a substantial portion of the total patients included, had unsatisfying response rates and survival outcomes. In the MDT period, we have optimized the treatment strategy by placing RT prior to TACE, and achieved improved response rates and survival rates, especially for patients with HCC and PVTT in the main trunk of portal vein (type III/IV) [29]. Other improvements through the MDT approach may be hard to quantify statistically, including the more accurate evaluation of tumor and PVTT, developing more appropriate and individualized treatment protocols, preventing unnecessary or repetitive investigations and interventions. The current study clearly indicated the advantage of applying an early multi-disciplinary review for patients with HCC and major vascular invasion. This study has limitations. Except from advances in management might have affected the survival outcomes, the reliability of results is also limited by the retrospective nature of the study, as well as inevitable biases in the survival analysis with inconsistency existed in selecting therapies beyond tumor progression. In conclusion, the management of patients with HCC and PVTT continues to be a challenging clinical problem. For those patients, the implement of an MDT meeting enables an optimized selection of therapies and provides survival benefits.

10. Fundings

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