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Research Article

Does Measured Aggression with Stereotactic Hypo Fractionated Radiotherapy and TACE Allow Liver Transplant in Patients with Hepatocellular Carcinoma with Portal Vein Tumour Thrombus - A Retrospective Study

Nangia S[1*], Gupta S[2], Agarwal S[2], Rastogi H[3], Khosa R[4], Singh M[4], Goyal N[5], Vohra S[4], Rawat V[3], Chauhan S[4] and Oomen S[4]

[1]Radiation Oncology, Apollo Proton Cancer Centre, Chennai

[2]Centre for Liver and Biliary Sciences, Max Super Speciality Hospital, Saket New Delhi

[3]Interventional Radiology, Indraprastha Apollo Hospital, New Delhi

[4]Radiation Oncology, Indraprastha Apollo Hospital, New Delhi

[5]Liver, Biliary and Pancreatic Surgery, Indraprastha Apollo Hospital, New Delhi

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[*]Corresponding author:

Sapna Nangia, Radiation Oncology, Apollo Proton Cancer Centre, Chennai, India, E-mail: sapna_nangia@outlook.com

1. Abstract

1.1. Background: Patients with HCC and PVTT have a poor prognosis and are not offered liver transplant.

1.2. Aim: To report survival outcome of living related donor liver transplant for patients with HCC with PVTT (portal vein tumor thrombus) treated with Stereotactic hypo fractionated radiotherapy (SHORT), and TACE.

1.3. Material & Methods: Patients with liver confined HCC with PVTT and minimum 1000 cc volume of uninvolved cirrhotic liver underwent SHORT and TACE, former administered using Rapid Arc, dose 32-50Gy in 5-14 fractions. TACE was performed using gel foam slurry, Inj. Cisplatinum and PVA. Liver transplant was performed on radiological evidence of recanalization or conversion to bland thrombus, liver and venous system confined HCC and good general condition.

1.4. Results: Nineteen patients underwent SHORT, 15 with TACE. Liver transplant could be performed in 7 (37%) patients, and treatment escalated with hepatectomy or reirradiation in 2 (10%) patients, each. Five patients were lost to follow up after progressive disease. The survival of patients undergoing transplant was 100% at 12 months, and 86% at 18 and 24 months. Following transplant, 3 patients died of progressive disease at 13, 26 and 36 months, respectively. One patient is alive with disease, three disease free at 27, 28 and 31 months since registration.

1.5. Conclusion: SHORT and TACE, may allow liver transplant in select patients with HCC & PVTT resulting in excellent 24 month survival, long-term outcome remaining unclear, though.

2. Keywords: Hepatocellular cancer; Portal vein tumour thrombus, Hypo fractionated radiotherapy; TACE

3. Introduction

Hepatocellular carcinoma (HCC), the commonest primary liver tumour, occurs in rising numbers every year, secondary to the rising incidence of hepatitis B & C and alcoholic liver disease [1].

The schema for treatment recommended by the Barcelona Clinic for Liver Cancer restricts resection or liver transplant to patients with single or multiple lesions that are smaller than 3 cm in size [2]. Other guidelines also restrict radical surgery i.e. Liver Transplant (LT), to single lesions smaller than 5 cm [3] or 6.5 cm or 3 or less lesions, largest smaller than 4.5 cm [4]. Vascular invasion has been a contraindication for LT.

Vascular invasion, i.e. infiltration of the portal / hepatic vein has been a mark of advanced and, or, aggressive HCC, the survival of untreated patients documented to be 2.7 - 6 months [5]. The poor outlook for these patients is thought to be due to increased portal venous pressure, a propensity for rupture of oesophageal varices, ascites and hepatic encephalopathy. Treatment options for these patients have been sorafenib, transarterial chemoembolization (TACE), trans-arterial radio-embolisation (TARE) and external beam radiotherapy (EBRT), alone or in combination. The Overall Survival (OS) at 1 year has ranged from 25% to 31.8% [6-9].

Modern EBRT techniques, based in 3 dimensional virtual treatment planning, intensity and volume modulation and image based repositioning for accurate treatments, allowing the uninvolved, usually cirrhotic, liver to be spared, have led to the application of RT using standard daily dose [10,11], and later, hypo fractionated schedules, [12,13] in the treatment of HCC. The indications of EBRT have ranged from palliation to radical treatment as well as bridge therapy for patients waitlisted for LT [14-16]. The latter serves to downstage and prevents progression in addition to identifying aggressive lesions that progress rapidly and hence are unsuitable for transplant. EBRT as sole treatment has also been postulated for HCC with moderate reserves and portal vein tumour thrombus (PVTT) [17].

Notwithstanding developments in EBRT techniques, the functional reserve of the liver remains important. Dose volume parameters i.e. mean liver dose of less than 30 Gy for a normal liver and 28 Gy for a diseased liver, are to be taken into consideration, in addition to the requirement of sparing at least 700 - 800 cc of normal liver [18]. Doses may be individualized for isotoxicity, the alpha /beta ratio postulated to be 2.5 Gy [19]. Though Child Pugh grade C is not an absolute contraindication, most radical EBRT treatments are restricted to patients with Child Pugh status A & B [20, 21].

There is a precedent for using EBRT prior to hepatectomy in patients with PVTT, associated with an OS of 86% at 1 yr, albeit in a small group of 28 patients, as reported by [22]. While vascular invasion has been a contraindication to liver transplant, there are recent reports of transplant following aggressive down staging [23] and without [24, 25].

While these patients do not qualify for deceased donor liver transplants, it is believed that the same contraindication may not be applied in the case of a living related donor, as long as there is a realistic discussion regarding the outcome of transplant [26].

In 2012, we instituted a program comprising TACE and stereotactic hypo fractionated radio therapy (SHORT) followed by living related donor liver transplant (LRDLT) for patients suffering from cirrhosis of liver with HCC with PVTT. We present the technique used and outcome thereof. We believe this is the first series reporting this aggressive approach.

4. Material & Methods

Patients with HCC with PVTT were taken up for TACE and SHORT, after informed consent, if they fulfilled the following criteria:

- HCC confined to liver, as determined by triple phase CT scan of the abdomen and pelvis and high resolution CT chest and Tc99m bone scan.
- Child Turcotte Pugh Grade A or early B
- PVTT, and, or, hepatic vein infiltration / thrombus, defined as tumour thrombus on the basis of contrast enhancement on triple phase CT scan or FDG avidity on whole body PET CT scan.
- Volume of uninvolved cirrhotic liver, i.e. liver excluding the tumour, at least 1000 cc.

Patients underwent transarterial chemoembolization using gel foam slurry, PVA and Inj cisplatinum.

TACE was followed by ultrasound guided insertion of 3 gold fiducials in the liver, in the proximity of, but not into, the lesion, so as to minimize the risk of haemorrhage. This was followed by fabrication of 2 thermoplastic casts, one limited to the upper abdomen and fabricated with a view to act as a compression device to restrict abdominal breathing, followed by a cast encompassing the chest and abdomen, to immobilize the patient. A Triple phase planning CT, including scans in mid-inspiration and mid-expiration was performed on Biograph mCT (Siemens, Erlangen, Germany) followed by a Cone Beam CT (CBCT) on Novalis Tx (Varian, Palo Alto, USA) linear accelerator. The respiratory excursion of the liver was determined by fusing the lesion drawn in different phases of respiration as well as in CBCT images to determine the Internal Target Volume (ITV). The lesion and thrombus, as identified on the triple phase CT were expanded 5 mm to generate a Clinical Target Volume (CTV). This was isotropically expanded to create the Planning Target Volume (PTV).

SHORT was planned on Eclipse (Varian Inc, Palo Alto, USA) using Rapid Arc. The initial 4 patients were treated with dose ranging from 32-50 Gy in 6-14 fractions. Thereafter, the prescribed dose was 50 Gy in 8 fractions, modified if required, to achieve dose constraints to normal structures, viz., uninvolved cirrhotic liver, duodenum, small and large bowel.

The dose constraints prescribed for the 50 Gy in 8 fraction schedule were as follows:

- Uninvolved cirrhotic liver: Atleast 1000 cc to receive < 21Gy; D_{mean}<24Gy
- Duodenum: D_{max} < 21Gy; D_{mean} < 14Gy
- Bowel: D_{max}< 14Gy
- Skin and subcutaneous tissue: D_{max}< 21Gy

- Kidney: D_{mean} < 5Gy

Patients underwent RT daily, 5 days a week, if the daily fraction size was less than 6Gy and on alternate days or with a minimum inter-fraction gap of 24 hours, if the fraction size was more than 6Gy.

Following completion of RT, patients were assessed at regular intervals for response as determined by decreasing sAFP values, and, radiological response, defined as decrease in enhancement on triple phase CT scan or decreased FDG avidity on PET CT. All patients received Sorafenib while awaiting transplant.

Patients were offered LRDLT, after detailed counselling regarding poor prognosis, informed consent and clearance by the institutional transplant committee, if the following criteria were met:

- Lesion confined to the liver and venous system.
- KPS > 80 %
- Radiological evidence of recanalization or conversion to bland thrombus
- Absence of associated co-morbidities.

5. Results

Nineteen patients with HCC and PVTT underwent SHORT with the eventual aim of liver transplant. The thrombus was present in the main or branch portal vein in 8 patients, branch portal vein and segmental vein in 8 patients, segmental vein alone in 3 patients. The hepatic vein was thrombosed in addition to the portal vein in one patient; the thrombus involved the inferior vena cava and the right atrium in 1 patient. The volume of the PTV ranged from 55cc to 1500 cc, median 260 cc and of the liver from 806 cc to 2371 cc, median 1500cc. The detailed demographic and dosimetric parameters were as per (Table 2).

Table 1: Dosimetric and demographic data

Age	Range54-64yrs	Median 51yrs
Gender	Male	19
	Female	0
Child-Pugh	A	14
	B	5
Underlying liver pathology	Hepatitis B	4
	Hepatitis C	14
	Alcoholic liver disease	1
Baseline sAFP value	Upto 400 ng/ml	5
	>400ug/ml	14
Number of liver segments	3-Jan	11
	4 or more	7
Prescribed radiation dose	50Gy in 5-8 fractions	6
	47-50Gy in 10 fractions	7
	Others	6
Biologicaly equivalent dose	<58Gy10	3
	58-99Gy10	15
	100Gy10	1
Volume of non tumour liver receiving dose < BED 45Gy2.5	>700 cc	15
	<700 cc	4

Table 2: Overall survival

	12 month survival (%)	18 month survival (%)
Study population	9/19 (47)	5/19 (26)
Patients with TACE + EBRT + any additional treatment	9/11 (82)	7/11 (64)
Patients treated with TACE + EBRT + OLT	7/7 (100)	6/7 (86)

Additional treatment in the form of TACE was performed in 13 patients prior to, and in 2, following RT. One patient was initially treated with palliative intent but was included in this analysis as he subsequently did undergo liver transplant.

5.1. Outcome

Patients were analysed in Jan 2019. Time since registration ranged from 27 - 77 months; the median was 46 months.

Seven (37%) of 19 patients considered fit for transplant as per criteria defined above underwent LRDOLT. All patients undergoing transplant were alive at 12 months, and 6 of 7 were alive at 2 years (Table 2). Five of the seven transplanted patients developed metastatic disease, three dying of metastatic disease at 36, 24 and 13 months, one alive with disease with lung metastases and one disease free following RF ablation of a doubtful lesion in the transplanted liver. The median survival of this group has not been achieved.

The characteristics of patients who underwent transplant are noted in (Table 4). Complete necrosis was noted in two specimens, both with involvement of the hepatic venous system. Multiple tumour nodules were noted in 4 of 7 explanted livers.

The 12 month survival of the entire group was 47 %; survival was calculated from the date of registration and the date of last communication was used to determine the survival of patients lost to follow up. The 12 month survival of patients undergoing any escalation of treatment, i.e. liver transplant or hepatectomy or reirradiation was 82%.

The median survival of the entire group was 6.5 months and of the group with any escalated treatment was 16 months.

The characteristics of patients who underwent transplant are noted in (Table 3). Complete necrosis was noted in two specimens, both with involvement of the hepatic venous system. Multiple tumour nodules were noted in 4 of 7 explanted livers.

5.2. Adverse effects

The median gap between TACE and EBRT was 11 days. Four patients developed fever and pain and none developed hepatic decompensation following TACE.

In the follow up period after radiation, three patients had documented hepatic decompensation in the form of ascites and or worsening of liver enzymes. In 2 of these 3 patients, the volume of non-tumour liver receiving BED 45 Gy 2.5 was less than 700 cc. The third patient also developed progressive disease in the form of a peritoneal deposit. Adverse effects are unknown in the 5 patients lost to follow up. The remaining 11 patients did not have derangement of liver enzymes / ascites.

Table3: Details of patients who underwent transplant

	Baseline AFP	Size of PTV (cc)	Vascular involvement	BED Gy10	HPE of explant	Outcome	Overall survival
1	4.66	135	SV	47Gy10	Multicentric moderately differentiated HCC in a background of mixed nodular cirrhosis. Vascular emboli seen with tumor thrombus in RPV.	Brain metastases 3 yrs after transpant. Dead.	36 months
2	140.6	260	SV	55Gy10	Necrosis in largest nodule. Multiple nodules in both lobes of the liver.	Oligometastases 1 year after Transplant. Underwent SBRT. Received sorafenib followed by sorafenib alternating with erlotinib. Dead.	26 months
3	498	632	SV	86 Gy10	Largest tumour in four segments, tumour thrombus, additional smaller tumours in one segment. Multiple tumour nodules in both lobes of the liver. LVSI +. No PNI.	Alive, Disease free	31 months
4	40.5	354	MPV, RPV, LPV	75Gy10	Viable tumour tissue in main nodule and PVTT. Satellite tumour nodules noted in 3 adjacent liver segments	Doubtful new liver lesion, treated with RFA	28 months
5	15262	1287	LPV	81 Gy10	The tumour is largely necrotic. More than 60% of larger tumour and whole of the smaller tumour is necrotic. No tumour in portal hepatic vein. No satellite nodules. HCC grade II	Died Lung metastases	12 months
6	2640	230	MPV, RPV, LPV HV	150 Gy10	Totally necrotic HCC; No LVI or tumor in transit noted.	Disease free	27 months
7	3263	1500	RPV, RHV, IVC,	47Gy10	No viable tumor; No LVSI or tumor in transit; Totally necrotic tumor emboli in hepatic vein	Alive with lung metastases	28 months

Table 4: Asian data for transplant outcomes out of Milan criteria

Criteria	Number of nodules	Size of nodules	Additional criteria
Tokyo[25] [37]	Upto 5	<= 5cm	Nil
Asan[26][38]	Upto 5	< = 6 cm	Nil
Kyoto[27] [39]	Upto 10	<= 5 cm	Serum DPT < = 400mAU/ml
Kyushu[28] [40]	Nil	<=5 cm	Serum DPT <=300mAU/ml
Hangzhou[29] [41]		< 8 cm	
Hangzhou[29] [41]		>8 cm	AFP upto 400 ng/ml
Xia et al[30] [42]		>8 cm	AFP upto 1000ng/ml + PLR > 120
Samsung[43]	Upto 7	</=6 cm	AFP < 1000ng/ml

6. Discussion

Current guidelines list ablation, arterially directed therapies, EBRT, sorafenib and clinical trials as possible treatment options for locally advanced HCC [24].

6.1. EBRT in the Management of HCC with PVTT

A number of studies emphasise the impact of EBRT in the management of HCC with PVTT.

In a retrospective study comparing outcome and toxicity of sorafenib versus EBRT in HCC with PVTT [27] noted a median survival 10.9 months in patients undergoing EBRT versus 4.9 months in performance status matched patients treated with sorafenib. Moreover, only 4 % treated with EBRT discontinued treatment due to adverse effects; the corresponding (Figure 1) for sorafenib was 54 % [27].

Huo et al., Carried out a meta-analysis of 25 trials, comprising 2577 patients, comparing TACE + EBRT to TACE alone in patients with unresectable HCC and noted that the odds ratio for OS was significantly better for the combination treatment at 1 year and improved at 2,3,4 and 5 years, respectively. A sub group analysis, relevant to this study, was that the advantage of TACE + EBRT over TACE alone was maintained in patients with PVTT [28].

Zeng et al., [29] in a retrospective analysis of patients with HCC with portal vein and, or IVC thrombi noted that the 1 year survival of 44 patients treated with radiotherapy in addition to other treatments was 34.8 % versus 11.4%. Patients received a median dose of 50 Gy, the tumour thrombus and primary lesion were both treated with RT. In their extensive analysis, the authors noted that patients treated with RT were less likely to die due to the thrombus and more likely, due to their longer survival, to die of intrahepatic and extrahepatic progression of HCC [29].

Kamiyama et al., [30] retrospectively analysed the benefit of a combination of hepatectomy and radiotherapy in 12 patients compared to hepatectomy alone, in 28 patients with HCC with PVTT. The dose administered was 30 -36 Gy in 10 – 12 fractions. The 1, 3 and 5 yr survivals were 86.2%, 43.5% and 34.8% in the group administered radiotherapy versus 39%, 13.1% and 13.1%, respectively, in patients undergoing surgery alone. Five of 6 patients with complete necrosis of the tumour survived 2 yrs [30]. Li et al., have confirmed the benefit of adding neo adjuvant radiotherapy to hepatectomy, in a recent comparative non randomised study [31].

We treated patients with a combination of TACE and SHORT followed by assessment for LRDLT. The dose administered ranged from 43 Gy in 7 fractions to 50 Gy in 5 fractions. The varying doses used were related both to the concept of prescription of doses isotoxic to the liver rather than a standard dose prescription, as postulated by [32]. The biologically equivalent dose (BED) with an alpha/beta value of 10 Gy was > 58 Gy in 16 of 19 patients. This BED has been noted to be significantly correlated with response rate as well as survival at 1 yr [33]. A learning curve is evident; a BED was < 58 Gy10 in 2 of the first five patients treated and in 1 of the subsequent 14 patients treated.

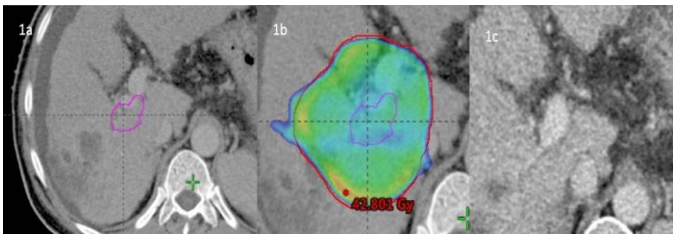

Figure 1a: Contrast CT axial sections reveal hypodense SOL in right lobe of liver with thrombus in regional segment 6 portal vein branch. b: Dose colourwash of RapidArc plan along with GTV, CTV and PTV contours. C: Post RT images refilling in the previously thrombosed segment 6 portal vein branch.

6.2. Liver transplant in HCC with PVTT

Liver transplant is not offered to patients with vascular invasion due to concerns regarding the futility of aggressive surgery, both due to concerns about early recurrence [34] as well as optimal utilisation of donated livers. Deceased donor liver transplant eligibility is based on strict criteria ensuring treatment success, so as to use the scare resource of a donated liver appropriately.

In the case of living related donor liver transplant, there is a more liberal approach to eligibility for liver transplant. The approach to managing these patients has however been more aggressive in Asian countries [35]. A 5 year survival (Figure 1) of 50 -60 % has been deemed acceptable in Asian countries [36] and there is some thought on whether it is justified to deny a patient with a well informed, committed donor, liver transplant as per criteria defined specifically for LRDLT (Table 4).

Reports of transplant for vascular invasion are scarce, though there is evidence to suggest that an aggressive approach may yield satisfactory outcomes. performed 8 liver transplants in patients with HCC with PVTT treated with concurrent chemo radiotherapy and hepatic arterial chemotherapy and have reported an overall survival of 87 % at 1 year [32, 44].The OS of the study population was 47% at 12 months. This compared favourably with 34.8% at 1 yr by [29], who used TACE + RT.

In the first 3 years of the protocol, LT was limited to patients in whom the tumour thrombus has recanalised and 2 of 11 patients underwent transplant; the selection criteria were more liberal in the next 2 years and 6 of the last 8 patients underwent transplant. Escalation of treatment by adding liver transplant was associated with 100% OS at 12 months and 86% at 18 months. The median survival of transplanted patients has not been reached. OS was 80% at 12 months with any escalation of treatment i.e. OLT, re-irradiation or hepatectomy, the latter two options being used to escalate treatment in patients not suitable for OLT due to progressive disease. The median survival of patients with any escalation of treatment was 16 months; this escalation was possible in 11 of 19 patients, notwithstanding a learning curve and the large number of patients with a thrombus in the main or branch portal vein.

Sin et al., [42] Have noted that patients with vascular invasion of segmental braches of the portal vein are likely to have a better prognosis than those with a thrombus in the branch or main portal vein. Similarly, Hou et al., [43] have opined that hepatic vein/ inferior vena cava thrombi may have a better prognosis compared to PVTT. In our series, 3 / 3 patients with segmental vein involvement alone and 2/2 patients with hepatic venous system/ IVC underwent transplant compared to 2/16 patients with main and, or branch portal vein involvement.

6.3. Correlation of Outcome and Toxicity with Radiation Dose

The alpha/beta value of the liver has been proposed to be 2.5 Gy. Extrapolating from the dose constraint prescribed for SBRT, i.e. at least 700 cc of the non tumour liver to receive less than 15 Gy in 3 fractions the BED to prevent RILD may be 45 Gy2.5. The volume of uninvolved liver receiving less than 45Gy2.5 was less than 700 cc in 4 patients all of whom were planned for liver transplant within weeks of radiotherapy. Two of these 4 patients underwent immediate transplant and the remaining two developed hepatic decompensation and died at 3 weeks and 6 months following radiotherapy, while awaiting transplant. Among the 15 patients in whom at least 700 cc received less than BED 45 Gy2.5, 11 remained on follow up and only one developed hepatic decompensation. Since the uninvolved liver is cirrhotic, attention to restricting the BED to a minimum of 700 cc is therefore critical.

The histopathological examination of the explanted liver revealed large number of tumour nodules in 5 of 7 explanted livers. While escalation of dose to a BED > 75 Gy may improve the outcome of patients [44], viable tumour was noted following BED Gy10 ranging from 47 Gy10 to 87 Gy10. Complete tumour necrosis was noted in two patients, with BED of 47 Gy10 and 150 Gy10, respectively; both had involvement of the hepatic venous system. Five of the 7 patients who underwent transplant developed metastatic disease. The long term outlook for patients undergoing the treatment regime detailed above thus remains unclear and may require dose escalation for better results.

7. Conclusion

The 12 month survival was 100% in patients undergoing liver transplant following aggressive down staging of HCC with PVTT with TACE and SHORT. This was achieved without significant morbidity. Assessing long term outcome will of course be essential before widespread application, but we believe that our experience offers a compelling argument against a nihilistic approach towards the management of HCC with PVTT.

References

1. Dhanasekaran R, Limaye A, Cabrera R. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis, and therapeutics. Hepatic Medicine: Evidence and Research. 2012; 4: 19-37.

2. Llovet JM, FusterJ,Bruix J. The Barcelona Approach: Diagnosis, Staging, and Treatment of Hepatocellular Carcinoma. Liver Transpl. 2004; 10: S115–S120.

3. Mazzaferro V, Regalia E, Doci R, Pulvirenti A, Bozzetti F, Montalto F et al. Liver transplantation for the treatment of small hepato cellular carcinomas in patients with cirrhosis.N Engl J Med. 1996; 334: 693-9.

4. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001; 33: 1394-403.

5. Llovet JM, Bustamante J, Castells A, Vilana R, AyusoMdel C, Sala M et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials.Hepatology. 1999 ; 29: 62-7.

6. Jeong SW, Jang JY, Shim KY, Lee SH, Kim SG, Cha SW et al. Practical effect of sorafenib monotherapy on advanced hepatocellular carcinoma and portal vein tumor thrombosis. Gut Liver. 2013; 7: 696-703.

7. Llado L, Virgili J, Figueras J, Valls C, Dominguez J, Rafecas A et al. A prognostic index of the survival of patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. Cancer. 2000; 88: 50-7.

8. Zeng ZC, Fan J, Tang ZY, Zhou J, Wang JH, Wang BL et al. Prognostic factors for patients with hepatocellular carcinoma with macroscopic portal vein or inferior vena cava tumor thrombi receiving external-beam radiation therapy. Cancer Sci. 2008; 99: 2510-7.

9. Lau WY, Sangro B, Chen PJ, Cheng SQ, Chow P, Lee RC et al. Treatment for hepatocellular carcinoma with portal vein tumor thrombosis: the emerging role for radioembolization using yttrium-90. Oncology. 2013; 84: 311-8.

10. Lee JH, Kim DH, Ki YK, Nam JH, Heo J, Woo HY et al. Three-dimensional conformal radiotherapy for portal vein tumor thrombosis alone in advanced hepatocellular carcinoma. Radiat Oncol J. 2014; 32: 170-8.

11. Zou LQ, Zhang BL, Chang Q, Zhu FP, Li YY, Wei YQ et al. 3D conformal radiotherapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. World J Gastroenterol. 2014 7; 20: 17227-34

12. Hou JZ, Zeng ZC, Wang BL, Yang P, Zhang JY, Mo HF et al. High dose radiotherapy with image-guided hypo-IMRT for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombi is more feasible and efficacious than conventional 3D-CRT. 2016; 46: 357-62.

13. Sanuki N, Takeda A, Mizuno T, Oku Y, Eriguchi T, Iwabuchi S et al. Tumor response on CT following hypofractionated stereotactic ablative body radiotherapy for small hypervascular hepatocellular carcinoma with cirrhosis. AJR 2013; 201: W812-20.

14. Hawkins MA, Dawson LA. Radiation Therapy for Hepatocellular Carcinoma From Palliation to Cure. Cancer. 2006; 106: 1653-63.

15. Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, Zook J et al. Stereotactic body radiotherapy for primary hepatocellular carcinoma. Int J Radiat Oncol Biol Phys. 2011; 81: e447-53.

16. Katz AW, Chawla S, Qu Z, Kashyap R, Milano MT, Hezel AF et al. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. Int J Radiat Oncol Biol Phys. 2012; 83: 895-900.

17. Cheng S, Yang J, Shen F, Zhou W, Wang Y, Cong W et al. Multidisciplinary management of hepatocellular carcinoma with portal vein tumor thrombus - Eastern Hepatobiliary Surgical Hospital consensus statement. Oncotarget. 2016; 7: 40816-29.

18. Dawson LA, Normolle D, Balte JM, McGinn CA, Lawrence TS, Ten Haken RK et al.. Analysis of radiation-induced liver disease using the Lyman NTCP model. Int. J. Radiation Oncology Biol. Phys. 2002; 53: 810-21.

19. Guha C, Kavanaugh B. Hepatic radiation toxicity : Avoidance and amelioration. SeminRadiat Oncol. 2011; 21: 256-63.

20. Velec M, Haddad CR, Craig T, Wang L, Lindsay P, Brierley J et al. Predictors of Liver Toxicity Following Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma.Int J Radiat Oncol Biol Phys. 2017; 97 : 939-946.

21. Wang PM, Chung NN, Hsu WC, Chang FL, Jang CJ, Scorsetti M et al. Stereotactic body radiation therapy in hepatocellular carcinoma: Optimal treatment strategies based on liver segmentation and functional hepatic reserve.Rep Pract Oncol Radiother. 2015; 20: 417-24.

22. Kamiyama T, Nakanishi K, Yokoo H, Tahara M, Nakagawa T, Kamachi H et al. Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma. Int J Clin Oncol. 2007; 12: 363-8.

23. Abhishek A, Kataria T, Gupta D et al. Portal Vein Tumor Thrombus Irradiation: Paving the Way for Liver Transplant. Int J Radiat Oncol Biol Phys. 2016; 96: E 164.

24. Miura K, Sugawara Y, Uchida K et al. Adult Living Donor Liver Transplantation for Patients With Portal Vein Thrombosis: A Single-center Experience. Transplant Direct. 2018; 4: e341.

25. Ghazwani S, Panaro F, Navarro F. Is portal vein thrombosis still a contraindication for liver transplantation? A single-institute's 5-year experience and literature review. Transplant research and risk management. 2016; 8: 31-6.

26. National Cancer Comprehensive Cancer Network. Hepatobiliary Cancers, Version 1.2018

27. Nakazawa T, Hidaka H, Shibuya A, Okuwaki Y, Tanaka Y, Takada J et al. Overall survival in response to sorafenib versus radiotherapy in unresectable hepatocellular carcinoma with major portal vein tumor thrombosis: propensity score analysis. BMC Gastroenterology. 2014; 14: 84-90.

28. Huo YR, Eslick GD. Transcatheter Arterial Chemoembolization plus Radiotherapy Compared with Chemoembolization Alone for Hepato-

cellular Carcinoma: A Systematic Review and Meta-analysis. 2015 ; 1: 756-65.

29. Zeng ZC, Fan J, Tang ZY, Zhou J, Qin LX, Wang JH et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. Int J Radiat Oncol Biol Phys. 2005; 61: 432-43

30. Kamiyama T, Nakanishi, Yokoo H, Tahara M, Nakagawa T, Kamachi H et al. Efficacy of preoperative radiotherapy to portal vein tumor thrombus in the main trunk or first branch in patients with hepatocellular carcinoma. Int J Clin Oncol. 2007; 12: 363-8.

31. Li N, Feng S, Xue J, Wei XB, Shi J, Guo WX et al. Hepatocellular carcinoma with main portal vein tumor thrombus: a comparative study comparing hepatectomy with or without neoadjuvant radiotherapy. HPB (Oxford). 2016; 18: 549–556.

32. Dawson LA, Eccles C, Craig T. Individualized image guided iso-NTCP based liver cancer SBRT. Acta Oncol. 2007; 45: 856-64

33. Toya R, Murakami R, Baba Y, Nishimura R, Morishita S, Ikeda O et al. Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma. Radiother Oncol. 2007; 84: 266-71.

34. Sugawara Y, Inomata Y. Indications for living donor liver transplantation in patients with hepatocellular carcinoma. Hepatobiliary SurgNutr. 2016; 5: 429-32.

35. Shimamura T, Akamatsu N, Fujiyoshi M. Japanese Liver Transplantation Society. Expanded living-donor liver transplantation criteria for patients with hepatocellular carcinoma based on the Japanesenation-wide survey: the 5-5-500 rule - a retrospective study. Transpl Int. 2019; 32: 356-68.

36. Lee SG, Hwang S, Moon DB et al. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. Liver Transpl. 2008; 14: 935-45.

37. Kaido T, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama Ketal et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. Surgery. 2013; 154: 1053-60.

38. Uchiyama H, Itoh S, Yoshizumi T et al. Living donor liver transplantation for hepatocellular carcinoma: results of prospective patient selection by Kyushu University Criteria in 7 years. HPB (Oxford). 2017; 19: 1082-90.

39. Zheng SS, Xu X, Wu J. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. Transplantation. 2008; 85: 1726-32.

40. Xia W, Ke Q, Guo H, Wang W, Zhang M, Shen Y et al. Expansion of the Milan criteria without any sacrifice: combination of the Hangzhou criteria with the pre-transplant platelet-to-lymphocyte ratio. BMC Cancer 2017; 17:14.

41. Kim JM, Kwon CH, Joh JW, Park JB, Lee JH, Kim GS et al. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma. Transplant Proc. 2014; 46: 726-9.

42. Sinn DH, Cho JY, Gwak GY, Paik YH, Choi MS, Lee JH et al. Dif- ferent survival of Barcelona clinic liver cancer stage C hepatocellular carcinoma patients by the extent of portal vein invasion and the type of extrahepatic spread.Plos One. 2015; 10: e0124434.

43. Hou J, Zeng Z, Zhang J, Fan J, Zhou J, Zeng M et al, Influence of Tumor Thrombus Location on the Outcome of External-beam Radiation Therapy in Advanced Hepatocellular Carcinoma With Macrovascular Invasion. Int J Radiat Oncol Biol Phys. 2012; 84: 362-8.

44. Holliday EB, Tao R, Brownlee Z, Das P, Krishnan S, Taniguchi C et al Definitive radiation therapy for hepatocellular carcinoma with portal vein tumour thrombus. Clin TranslRadiat Oncol. 2017; 4: 39-45.