Pathol. Oncol. Res. (2015) 21:131–138
DOI 10.1007/s12253-014-9798-2

RESEARCH

Clinicopathological Predictors of Poor Survival and Recurrence After Curative Resection in Hepatocellular Carcinoma Without Portal Vein Tumor Thrombosis

Li Zhou · Jing-An Rui · Shao-Bin Wang · Shu-Guang Chen · Qiang Qu

Received: 10 December 2013 / Accepted: 12 May 2014 / Published online: 8 June 2014

Abstract Many factors associated with long-term outcome in hepatocellular carcinoma (HCC) with portal vein tumor thrombosis (PVTT) were previously identified. However, those in HCC without PVTT have not been elucidated. This study was designed to define the risk factors of poor post-surgical survival and recurrence in this subgroup of HCC. Medical records and follow-up data of consecutive 152 patients with PVTT-absent HCC underwent curative resection were reviewed. The impacts of clinical and pathological variables on patient survival and recurrence were evaluated by univariate and multivariate analyses. It was shown that Edmondson-Steiner grade, TNM stage, microvascular invasion (MVI), satellite nodule, serum AFP level, tumor size and number were significant for tumor-specific and/or tumor-free survival in univariate analysis. Among them, Edmondson-Steiner grade and TNM stage were of independent significances for both, whereas satellite nodule independently predicted tumor-free survival. In Chi-square test, Edmondson-Steiner grade, TNM stage and MVI were significantly related to overall as well as early recurrence. Stepwise logistic regression identified Edmondson-Steiner grade as the single independent predictor of both. To be summarized, variables that are associated with poor prognosis and recurrence in HCC without PVTT are all tumor-related ones. Of these, differentiation degree might be of particular importance.

Keywords Hepatocellular carcinoma · Portal vein tumor thrombosis · Survival · Recurrence

L. Zhou (✉) · J.-A. Rui · S.-B. Wang · S.-G. Chen · Q. Qu
Department of General Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences/Peking Union Medical College, Beijing 100730, China
e-mail: lizhou02@hotmail.com

Introduction

Hepatocellular carcinoma (HCC) was one of leading prevalent and lethal cancers worldwide [1–3]. Up to now, long-term prognosis of HCC is still poor, although progress in therapeutic modalities resulted in exciting results in some highly selected patients [4–6]. Thus, identification of prognostic markers of HCC has long been of interest. Some clinicopathological variables, such as tumor size, a-fetoprotein and Child–Pugh class, were shown to be significant prognosticators of HCC, according to a recent systemic review involving many studies [7]. Among them, portal vein tumor thrombosis (PVTT) was suggested to be one of the most robust predictors of death. There have been many published articles referring to prognostic factors of HCC with PVTT, after different treatments including resection, transarterial chemoembolization (TACE), radiotherapy and conservative management [8–22]. However, the variables associated with clinical outcome of HCC without PVTT, a subgroup escaping the impact of the strong prognostic indicator, remain unknown.

In the present study, the influences of clinicopathological variables on post-surgical survival and recurrence of HCC without PVTT were investigated by uni- and multi-variate analyses, based on a Chinese patient series.

Materials and Methods

Patient Characteristics

Consecutive 152 patients with HCC without PVTT, who underwent curative hepatic resection, were included, after exclusion of patients with PVTT, that was first suggested by imaging examinations and proven pathologically. One hundred and thirty-two (86.8 %) were men and 20 (13.2 %) were

Table 1 Edmondson-Steiner grade of HCC

Grades	Main features
I	Minimal cytologic atypia and architectural distortion (near normal nucleus-to-cytoplasm ratio)
II	Well differentiated (typically with trabecular pattern), larger nuclei
III	Moderately differentiated (greater cytologic atypia and architectural variability)
IV	Poorly differentiated, or anaplastic (including spindle cell and small cell HCC)

HCC hepatocellular carcinoma

women. Patient ages ranged from 15 to 78 years (mean±SD, 53.5±12.3 years). Hepatitis B surface antigen (HBsAg) was positive in 123 patients (80.9 %), while hepatitis C virus detection was positive in 14 (9.2 %). Liver cirrhosis was found in 121 cases (79.6 %). Pre-surgical classification showed that 138 patients (90.8 %) were in grade A and 14 (9.2 %) were in grade B. Serum α-fetoprotein (AFP) levels higher and lower than 20 ng/ml were found in 101 (66.4 %) and 51 (33.6 %) patients, respectively. Tumor sizes ranged from 0.7 to 26 cm (mean±SD, 7.2±4.3 cm). Microvascular invasion (MVI), defined as tumor within a vascular space lined by endothelium that was visible only on microscopy [23], was detected in 43 patients (28.3 %), by postoperative histological examination. Macroscopic satellite nodules, a special type of intrahepatic metastasis close to the main lesion, according to the criterion that was proposed by the Liver Cancer Study Group of Japan and previously used [24], i.e., tumors surrounding the main tumor with multiple other satellite nodules or small solitary tumors located near the main tumor that are histologically similar or less differentiated than the main tumor, were found in 16 patients (10.5 %). Histological grading [25], according to Edmondson-Steiner criteria (Table 1), revealed that 18 (11.8), 69 (45.4), 55 (36.2) and 10 (6.6 %) patients carried grade I, II, III and IV HCCs, respectively. According to 7th edition tumor-node-metastasis (TNM) staging system [26], 65 (42.8), 59 (38.8), 25 (16.4) and 3 (2.0 %) patients were classified as stage I, II, III and IVa, respectively.

Procedures, Endpoints and Evaluated Variables

Procedures were right trisectionectomy (17 patients), left trisectionectomy (2), extended right hepatectomy (11), extended left hepatectomy (2), central hepatectomy (4), right hepatectomy (23), left hepatectomy (10), combined segmentectomy (47), segmentectomy (14), left lateral segmentectomy (12) and un-anatomic resection (10). Major hepatic resection, defined as removing at least 3 Couinaud segments [27], was performed for 83 out of 152 patients (54.6 %). Tumor-specific/tumor-free survival and overall/early recurrence (early recurrence: recurrence within 1 year after curative resection) served as endpoints. Thirteen variables that might have impacts on prognosis of HCC were selected to be evaluated in statistical analyses, including those reflecting general situation (age and sex), liver disease background (HBsAg, HCV, liver cirrhosis and Child-Pugh grading) and tumor-related factors (serum AFP value, tumor size, tumor number, TNM stage, MVI, satellite nodule and Edmondson-Steiner grade).

Follow-up

All the patients accepted our strict follow-up, with intervals ranging from 1 to 3 months. Imaging examinations, including as B-type ultrasonography (BUS), computed tomography (CT), magnetic resonance imaging (MRI) and angiography, and serum AFP level were used to monitor tumor progression. Follow-up terms ranged from 3 to 108 months (median, 20 months).

Statistical Analyses

Survival curves were calculated by Kaplan-Meier method and compared by log rank test. Cox regression (Proportional hazard model) was used for multivariate prognosis analysis. A

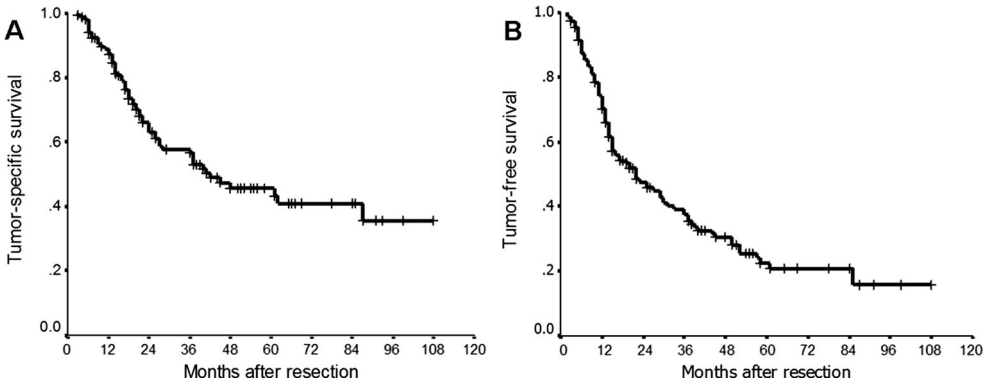

Fig. 1 Survival curves of HCC without PVTT after curative resection. **a** tumor-specific survival; **b** tumor-free survival. *PVTT* portal vein tumor thrombosis

patient who died of non-malignant disease (cardiac infarction) was excluded from tumor-related survival analyses. Uni- and multi-variate risk factors of both overall and early recurrence were determined by Chi-square and stepwise logistic regression tests. Statistical software package SPSS11.5 (SPSS Inc, Chicago, Ill) was adopted for all the analyses. A P value of <0.05 was defined as statistically significant.

Results

Patient Survival of HCC Without PVTT After Curative Resection

One, 3- and 5-year tumor-specific survival rates of patients with PVTT-absent HCC after curative resection were 87.4,

Table 2 Univariate analysis for tumor-specific and tumor-free survival of HCC without PVTT

Variables	Number	Tumor-specific survival			Tumor-free survival		
		median±SE	95%CI	*P*	median±SE	95%CI	*P*
Age				0.166			0.271
≥65 years	44	68±8	52–84		23±5	14–32	
<65 years	107	40±9	22–58		22±5	13–31	
Sex				0.772			0.978
Male	131	42±13	17–67		22±4	14–30	
Female	20	41±4	32–50		29±12	5–53	
HBsAg				0.910			0.517
Present	123	41±16	9–73		22±4	15–29	
Absent	28	45±6	33–57		29±14	2–56	
HCV				0.810			0.957
Present	13	66±14	38–94		38±20	0–77	
Absent	138	41±10	21–61		22±4	15–29	
Cirrhosis				0.567			0.838
Present	121	42±11	20–64		22±4	15–29	
Absent	30	41±11	19–63		29±8	13–45	
Child-Pugh grade				0.363			0.124
Grade A	137	45±9	27–63		23±4	15–31	
Grade B	14	24±5	14–34		15±2	11–19	
Tumor size				0.005			0.188
≥5 cm	104	36±6	25–47		16±4	9–23	
<5 cm	47	76±7	62–90		30±11	9–51	
MVI				<0.001			<0.001
Present	43	21±3	15–27		13±1	11–15	
Absent	108	68±5	58–78		31±6	19–43	
Satellite nodule				<0.001			0.016
Present	16	18±3	12–24		14±2	10–18	
Absent	135	62±21	20–104		22±5	12–32	
Tumor number				0.046			0.351
Solitary	138	61±19	23–99		22±5	13–31	
Multiple	13	26±10	6–46		20±8	4–36	
TNM satge				<0.001			<0.001
I–II	123	66±5	56–76		27±6	16–38	
III-IVa	28	18±3	11–25		13±3	7–19	
AFP>20 ng/ml				0.011			0.003
Present	100	27±6	16–38		15±2	11–19	
Absent	51	71±6	58–84		39±12	16–62	
Edmondson-Steiner grade				<0.001			<0.001
I–II	86	81±5	71–91		50±7	35–65	
III–IV	65	18±2	14–22		12±1	10–14	

HCC hepatocellular carcinoma, *PVTT* portal vein tumor thrombosis, *SE* standard error, *CI* confidence interval, *HBsAg* hepatitis B virus surface antigen, *HCV* hepatitis C virus, *MVI* microvascular invasion, *TNM* tumor-node-metastasis, *AFP* α-fetoprotein

56.6 and 45.8 %, respectively (Fig. 1a). Correspondingly, tumor-free survival rates of the patients at 1-, 3- and 5-years were 70.1, 37.3 and 22.5 %, respectively (Fig. 1b).

Prognostic Factors in Patients With PVTT-Absent HCC After Curative Hepatic Resection

Univariate analysis revealed that MVI, satellite nodule, TNM stage, serum AFP level and Edmondson-Steiner grade were significant indicators of tumor-specific and tumor-free survival in patients with PVTT-absent HCC after curative resection, while tumor size and number were associated with tumor-specific survival (P <0.05, Table 2). After these variables were included in Cox regression tests, Edmondson-Steiner grade and TNM stage were independent prognosticators for both tumor-specific and tumor-free survival (P <0.05, Table 3). Besides, satellite nodule was independently predictive for tumor-free survival (P=0.009, Table 3).

Risk Factors of Overall Recurrence in HCC Without PVTT After Curative Resection

By Chi-square test, MVI, satellite nodule, TNM stage and Edmondson-Steiner grade were significantly associated overall recurrence (P <0.05, Table 4). Multivariate stepwise logistic regression analysis found that Edmondson-Steiner grade was the single independent risk factor for overall recurrence (P <0.001, Table 4).

Risk Factors of Early Recurrence in HCC Without PVTT After Curative Resection

Univariate Chi-square test showed that MVI, TNM stage and Edmondson-Steiner grade were statistically significant risk factors of early recurrence (P <0.05, Table 5). Of them, Edmondson-Steiner grade was of independent significance (P <0.001, Table 5).

Discussion

PVTT, formation of tumor embolus in portal vein, was thought as a special type of metastasis in HCC [28]. It was concluded that PVTT functioned as one of the most robust predictors of death in HCC [7]. Therefore, prognostic factors of HCC with PVTT were long of particular interest and identified in many previous investigations [8–22]. However, post-surgical survival and prognostic factors in HCC without PVTT, a subset without the influence of the powerful prognostic determinant, remain to be elucidated. In the present study, the authors first found a 5-year tumor-specific survival of near 50 %, suggesting a relatively good prognosis of HCC without PVTT. Then, univariate analysis showed that Edmondson-Steiner grade, TNM stage, MVI, satellite nodule, serum AFP level, tumor size and number were of prognostic implication for tumor-specific and/or tumor-free survival. Apparently, these variables were all tumor specific. It might be interesting that these factors are different, to some extent, with those in PVTT-present HCC. A large number of previous reports indicated that liver function status could influence long-term prognosis in HCC with PVTT [9, 10, 12–14, 17, 18, 20, 22]. The fact that PVTT formation can cause ascites, jaundice, hepatic encephalopathy and liver failure through several mechanisms might account, at least in part, the difference in prognostic factors between HCC with and without PVTT [29]. The finding that many liver function parameters differ between the two types of HCC also provided supporting evidence [19]. On the other hand, we established that TNM stage, a powerful prognostic indicator previously reported in other groups of HCC [26], were one of main independent determinants for both tumor-specific and tumor-free survival. These results are quite different with those negating the predictive role of the variables for post-surgical prognosis of HCC with PVTT [9, 13, 19]. However, it is a pity that this important parameter was not included in many outcome analyses for patients with PVTT [8, 10–12, 14–19, 21, 22], especially those comparing PVTT-present and -absent HCC [19]. No doubt the current investigation reminds us to pay much attention to this factor. Besides, it is divergent for the impact of Edmondson-Steiner grade on prognosis of HCC with PVTT

Table 3 Multivariate analysis for tumor-specific and tumor-free survival of HCC without PVTT

Variables	Tumor-specific survival			Tumor-free survival		
	HR	95%CI	P	HR	95%CI	P
Edmondson-Steiner grade	4.980	2.667–9.300	<0.001	5.440	3.337–8.867	<0.001
TNM stage	1.594	1.036–2.454	0.034	3.052	1.317–7.073	<0.001
Satellite nodule				2.017	1.414–2.876	0.009

HCC hepatocellular carcinoma, *PVTT* portal vein tumor thrombosis, *HR* hazard ratio, *CI* confidence interval

Table 4 Univariate and multivariate factors associated with recurrence in HCC without PVTT

Variables	Number	Univariate			Multivariate		
		With	Without	*P*	HR	95%CI	*P*
Age				0.474			
≥65 years	45	28	17				
<65 years	107	73	34				
Sex				0.883			
Male	132	88	44				
Female	20	13	7				
HBsAg				0.579			
Present	123	83	40				
Absent	29	18	11				
HCV				0.907			
Present	14	10	4				
Absent	138	91	47				
Cirrhosis				0.799			
Present	121	81	40				
Absent	31	20	11				
Child-Pugh grade				0.192			
Grade A	138	89	49				
Grade B	14	12	2				
Tumor size				0.932			
≥5 cm	105	70	35				
<5 cm	47	31	16				
MVI				0.014			
Present	43	35	8				
Absent	109	66	43				
Satellite nodule				0.030			
Present	16	15	1				
Absent	136	86	50				
Tumor number				0.079			
Solitary	139	89	50				
Multiple	13	12	1				
TNM satge				0.009			
I–II	124	76	48				
III–IVa	28	25	3				
AFP>20 ng/ml				0.492			
Present	101	69	32				
Absent	51	32	19				
Edmondson-Steiner grade				<0.001			<0.001
I–II	87	43	44		1		
III–IV	65	58	7		6.750	2.649–17.201	

HCC hepatocellular carcinoma, *PVTT* portal vein tumor thrombosis, *HR* hazard ratio, *CI* confidence interval, *HBsAg* hepatitis B virus surface antigen, *HCV* hepatitis C virus, *MVI* microvascular invasion, *TNM* tumor-node-metastasis, *AFP* α-fetoprotein

[16, 19]. The authors first found its role in PVTT-absent HCC, expanding the spectrum of subgroups in that Edmondson-Steiner grade is prognostic. In the future, further validations are needed.

Just as well acknowledged, recurrence of HCC was frequent, although resection was performed [30]. In addition, a large ratio of HCC relapsed in the early period after surgery [31–33]. Therefore, identification of risk factors of recurrence (including early recurrence) in HCC might be of necessity. The current study established that MVI, TNM stage, Edmondson-Steiner grade and satellite nodule were risk factors of overall/early recurrence in HCC without PVTT. Of the factors, the associations of MVI, TNM stage as well as satellite nodule and recurrence of HCC after resection were

Table 5 Univariate and multivariate factors associated with early recurrence in HCC without PVTT

Variables	Number	Univariate			Multivariate		
		With	Without	*P*	HR	95%CI	*P*
Age				0.115			
≥65 years	45	9	36				
<65 years	107	35	72				
Sex				0.676			
Male	132	39	93				
Female	20	5	15				
HBsAg				0.526			
Present	123	37	86				
Absent	29	7	22				
HCV				0.558			
Present	14	5	9				
Absent	138	39	99				
Cirrhosis				0.649			
Present	121	34	87				
Absent	31	10	21				
Child-Pugh grade				0.974			
Grade A	138	40	98				
Grade B	14	4	10				
Tumor size				0.163			
≥5 cm	105	34	71				
<5 cm	47	10	37				
MVI				0.001			
Present	43	21	22				
Absent	109	23	86				
Satellite nodule				0.830			
Present	16	5	11				
Absent	136	39	97				
Tumor number				0.419			
Solitary	139	42	97				
Multiple	13	2	11				
TNM satge				0.024			
I–II	124	31	93				
III–IVa	28	13	15				
AFP>20 ng/ml				0.504			
Present	101	31	70				
Absent	51	13	38				
Edmondson-Steiner grade				<0.001			<0.001
I–II	87	10	77		1		
III–IV	65	34	31		6.527	2.769–15.383	

HCC hepatocellular carcinoma, *PVTT* portal vein tumor thrombosis, *HR* hazard ratio, *CI* confidence interval, *HBsAg* hepatitis B virus surface antigen, *HCV* hepatitis C virus, *MVI* microvascular invasion, *TNM* tumor-node-metastasis, *AFP* α-fetoprotein

previously shown [34–36]. We here provide new evidence for those in HCC without PVTT. However, Edmondson-Steiner grade (Table 1), a long applied grading system for differentiation of HCC in that size and morphology of HCC cells were mainly considered [25], was not revealed to be significant for recurrence after hepatectomy in HCC [37]. In our series, Edmondson-Steiner grade was a significant predictor for overall and early recurrence after curative resection, and the sole one proven by multivariate analysis, in HCC without PVTT. In viewing of the previous reports that high Edmondson-Steiner grade was an independent predictor of microvascular invasion [38] and was associated with various differentially regulated metastasis- and invasion-related genes [39], such as matrix metalloproteinase 2 [40], its significant

influence on relapse of HCC might be easily understood. In the future, the exact role of the histological variable in prediction of post-resectional recurrence in HCC remains to be evaluated in further large-scale prospective studies.

To be summarized, our data suggested that variables that are associated with poor prognosis and recurrence in HCC without PVTT are all tumor-related ones. Of these, differentiation degree might be of particular importance.

Acknowledgment This work was supported by the grant for the municipal key discipline of Beijing, China (HK100230446).

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Parkin DM, Pisani P, Ferlay J (1993) Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer 54:594–606
2. Pisani P, Parkin DM, Bray F, Ferlay J (1999) Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 83:18–29
3. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
4. Poon RT, Fan ST, Lo CM, Ng IO, Liu CL, Lam CM, Wong J (2001) Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. Ann Surg 234: 63–70
5. Shimozawa N, Hanazaki K (2004) Longterm prognosis after hepatic resection for small hepatocellular carcinoma. J Am Coll Surg 198: 356–365
6. Verhoef C, de Man RA, Zondervan PE, Eijkemans MJ, Tilanus HW, Ijzermans JN (2004) Good outcomes after resection of large hepatocellular carcinoma in the non-cirrhotic liver. Dig Surg 21:380–386
7. Tandon P, Garcia-Tsao G (2009) Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. Liver Int 29:502–510
8. Sugimoto C, Saito A, Kikuzato M, Hayashi N (2002) Angioechographic evaluation of tumor thrombi and the effect of transcatheter arterial embolization in patients with hepatocellular carcinoma. J Gastroenterol 37:363–368
9. Ando E, Tanaka M, Yamashita F, Kuromatsu R, Yutani S, Fukumori K, Sumie S, Yano Y, Okuda K, Sata M (2002) Hepatic arterial infusion chemotherapy for advanced hepatocellular carcinoma with portal vein tumor thrombosis: analysis of 48 cases. Cancer 95:588–595
10. Lai YC, Shih CY, Jeng CM, Yang SS, Hu JT, Sung YC, Liu HT, Hou SM, Wu CH, Chen TK (2003) Hepatic arterial infusion chemotherapy for hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol 9:2666–2670
11. Fan J, Zhou J, Wu ZQ, Qiu SJ, Wang XY, Shi YH, Tang ZY (2005) Efficacy of different treatment strategies for hepatocellular carcinoma with portal vein tumor thrombosis. World J Gastroenterol 11:1215–1219
12. Li Q, Wang J, Sun Y, Cui YL, Juzi JT, Li HX, Qian BY, Hao XS (2006) Efficacy of postoperative transarterial chemoembolization and portal vein chemotherapy for patients with hepatocellular carcinoma complicated by portal vein tumor thrombosis–a randomized study. World J Surg 30:2004–2011
13. Takizawa D, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, Katakai K, Kojima A, Matsuzaki Y, Mori M (2007) Hepatocellular carcinoma with portal vein tumor thrombosis: clinical characteristics, prognosis, and patient survival analysis. Dig Dis Sci 52: 3290–3295
14. Toya R, Murakami R, Baba Y, Nishimura R, Morishita S, Ikeda O, Kawanaka K, Beppu T, Sugiyama S, Sakamoto T, Yamashita Y, Oya N (2007) Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma. Radiother Oncol 84:266–271
15. Kamiyama T, Nakanishi K, Yokoo H, Tahara M, Nakagawa T, Kamachi H, Taguchi H, Shirato H, Matsushita M, Todo S (2007) 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 12:363–368
16. Liang LJ, Hu WJ, Yin XY, Zhou Q, Peng BG, Li DM, Lu MD (2008) Adjuvant intraportal venous chemotherapy for patients with hepatocellular carcinoma and portal vein tumor thrombi following hepatectomy plus portal thrombectomy. World J Surg 32:627–631
17. Lin DX, Zhang QY, Li X, Ye QW, Lin F, Li LL (2011) An aggressive approach leads to improved survival in hepatocellular carcinoma patients with portal vein tumor thrombus. J Cancer Res Clin Oncol 137:139–149
18. Luo J, Guo RP, Lai EC, Zhang YJ, Lau WY, Chen MS, Shi M (2011) Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. Ann Surg Oncol 18:413–420
19. Chen JS, Wang Q, Chen XL, Huang XH, Liang LJ, Lei J, Huang JQ, Li DM, Cheng ZX (2012) Clinicopathologic characteristics and surgical outcomes of hepatocellular carcinoma with portal vein tumor thrombosis. J Surg Res 175:243–250
20. Yoon SM, Lim YS, Won HJ, Kim JH, Kim KM, Lee HC, Chung YH, Lee YS, Lee SG, Park JH, Suh DJ (2012) Radiotherapy plus transarterial chemoembolization for hepatocellular carcinoma invading the portal vein: long-term patient outcomes. Int J Radiat Oncol Biol Phys 82:2004–2011
21. Peng ZW, Guo RP, Zhang YJ, Lin XJ, Chen MS, Lau WY (2012) Hepatic resection versus transcatheter arterial chemoembolization for the treatment of hepatocellular carcinoma with portal vein tumor thrombus. Cancer 118:4725–4736
22. Jia L, Kiryu S, Watadani T, Akai H, Yamashita H, Akahane M, Ohtomo K (2012) Prognosis of hepatocellular carcinoma with portal vein tumor thrombus:assessment based on clinical and computer tomography characteristics. Acta Med Okayama 66:131–141
23. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, Labow DM, Llovet JM, Schwartz ME (2009) A system of classifying microvascular invasion to predict outcome after resection in patients with hepatocellular carcinoma. Gastroenterology 137:850–855
24. Okusaka T, Okada S, Ueno H, Ikeda M, Shimada K, Yamamoto J, Kosuge T, Yamasaki S, Fukushima N, Sakamoto M (2002) Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. Cancer 95:1931–1937
25. Edmondson HA, Steiner PE (1954) Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 7:462–503
26. Cheng CH, Lee CF, Wu TH, Chan KM, Chou HS, Wu TJ, Yu MC, Chen TC, Lee WC, Chen MF (2011) Evaluation of the new AJCC staging system for resectable hepatocellular carcinoma. World J Surg Oncol 9:114
27. Terminology Committee of the International Hepato-Pancreato-Biliary Association (2000) The Brisbane 2000 terminology of liver anatomy and resections. HPB 2:333–339
28. Wang T, Hu HS, Feng YX, Shi J, Li N, Guo WX, Xue J, Xie D, Liu SR, Wu MC, Cheng SQ (2010) Characterisation of a novel cell line (CSQT-2) with high metastatic activity derived from portal vein tumour thrombus of hepatocellular carcinoma. Br J Cancer 102: 1618–1626
29. Minagawa M, Makuuchi M (2006) Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol 12:7561–7567

30. El-Serag HB (2011) Hepatocellular carcinoma. N Engl J Med 365: 1118–1127
31. Poon RT, Fan ST, Ng IO, Lo CM, Liu CL, Wong J (2000) Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. Cancer 89: 500–507
32. Shah SA, Greig PD, Gallinger S, Cattral MS, Dixon E, Kim RD, Taylor BR, Grant DR, Vollmer CM (2006) Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. J Am Coll Surg 202:275–283
33. Chun JM, Kwon HJ, Sohn J, Kim SG, Park JY, Bae HI, Yun YK, Hwang YJ (2011) Prognostic factors after early recurrence in patients who underwent curative resection for hepatocellular carcinoma. J Surg Oncol 103:148–151
34. Lim KC, Chow PK, Allen JC, Chia GS, Lim M, Cheow PC, Chung AY, Ooi LL, Tan SB (2011) Microvascular invasion is a better predictor of tumor recurrence and overall survival following surgical resection for hepatocellular carcinoma compared to the Milan criteria. Ann Surg 254:108–113
35. Kaido T, Arii S, Oe H, Mori A, Imamura M (2005) Predictive factors affecting early recurrence after hepatectomy for hepatocellular carcinoma in 5-year survivors. Hepatogastroenterology 52:1484–1487
36. Muscari F, Foppa B, Carrere N, Kamar N, Peron JM, Suc B (2011) Resection of a transplantable single-nodule hepatocellular carcinoma in Child-Pugh class A cirrhosis: factors affecting survival and recurrence. World J Surg 35:1055–1062
37. Arii S, Tanaka J, Yamazoe Y, Minematsu S, Morino T, Fujita K, Maetani S, Tobe T (1992) Predictive factors for intrahepatic recurrence of hepatocellular carcinoma after partial hepatectomy. Cancer 69:913–919
38. Kim BK, Han KH, Park YN, Park MS, Kim KS, Choi JS, Moon BS, Chon CY, Moon YM, Ahn SH (2008) Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. J Surg Oncol 97:246–252
39. Yu GR, Kim SH, Park SH, Cui XD, Xu DY, Yu HC, Cho BH, Yeom YI, Kim SS, Kim SB, Chu IS, Kim DG (2007) Identification of molecular markers for the oncogenic differentiation of hepatocellular carcinoma. Exp Mol Med 39:641–652
40. Xiang ZL, Zeng ZC, Tang ZY, Fan J, Sun HC, Tan YS (2011) Expression of cytokeratin 19 and matrix metalloproteinase 2 predicts lymph node metastasis in hepatocellular carcinoma. Mol Biol Rep 38:3531–3539