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Single-center experience on actual mid-term (≥5 years) and long-term (≥10 years) survival outcome in patients with hepatocellular carcinoma after curative hepatectomy

A bimodal distribution

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Abstract

Analysis for actual mid-term (≥5 years) and long-term (≥10 years) survivors with hepatocellular carcinoma (HCC) following curative hepatectomy are rarely reported in the literature.

This retrospective study aims to study the mid- and long-term survival outcome and associated prognostic factors following curative hepatectomy for HCC in a tertiary referral center.

The clinical data of 325 patients who underwent curative hepatectomy for HCC were reviewed. They were stratified into 3 groups for comparison (Group 1, overall survival <5 years; Group 2, overall survival ≥5, and <10 years; Group 3, overall survival ≥10 years). Favorable independent prognostic factors for mid- and long-term survival were analyzed.

A bimodal distribution of actual survival outcome was observed, with short-term (<5 years) survival of 52.7% (n=171), mid-term survival of 18.1% (n=59), and long-term survival of 29.2% (n=95). Absence of microvascular invasion (OR 3.690, 95% CI: 1.562–8.695) was independent good prognostic factor for mid-term survival. Regarding long-term overall survival, young age (OR 1.050, 95% CI: 0.920–0.986), ASA grade ≤2 (OR 3.746, 95% CI: 1.325–10.587), high albumin level (OR 1.008, 95% CI: 0.920–0.986), solitary tumor (OR 3.289, 95% CI: 1.149–7.625) and absence of microvascular invasion (OR 4.926, 95% CI: 2.192–11.111) were independent good prognostic factors.

Curative hepatectomy results in bimodal actual survival outcome with favorable long-term survival rate of 29.2%. Favorable independent prognostic factors (age, ASA grade, albumin level, tumor number, and microvascular invasion) are identified for overall survival.

Abbreviations: AFP = alpha-fetoprotein, ASA = American Society of Anesthesia, CI = confidence interval, CT = computer tomography, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, ICG = indocyanine green, MRI = magnetic resonance imaging, OR = odds ratio, PET = positron emission tomography, PVE = portal vein embolization, TACE = trans-arterial chemoembolization.

Keywords: actual, survival, hepatectomy, hepatocellular, carcinoma

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1. Introduction

Hepatocellular carcinoma (HCC) is the sixth commonest malignancy globally.[1] Curative hepatectomy for HCC provides the best long-term survival in selected patients with compensated liver function and is commonly practiced worldwide.[2] Nonetheless, the overall long-term survival after surgery remains suboptimal because of the high intrahepatic recurrence rate (up to 60%) from intrahepatic metastases and carcinogenesis from underlying cirrhosis.[3] There were few papers reporting the actual long-term survival following curative hepatectomy for HCC but the actual survival distribution was not mentioned clearly.[4–12] In addition, many retrospective studies only focused on the assessment of actuarial survival, which did not reflect the true picture, especially for mid-term (≥5 years) and long-term (≥10 years) outcomes. Those results only relied on the statistical estimation of patient survival. In fact, the Kaplan–Meier analysis of actuarial survival is hindered by the process of censoring, whereby patients are excluded from the overall statistical analysis. This can result in major distortion of survival outcomes, with big mismatch between the generated actuarial survival and true actual survival rates.[9–11]

The present study aims to analyze the actual survival distribution in a large cohort of HCC patients after curative hepatectomy in a tertiary referral center. Associated independent prognostic factors for mid-term (≥5 years) and long-term (≥10 years) survival outcomes were also determined. Such information is crucial in patient counselling and stratification of high and low risk patients for recurrent tumor surveillance and adjuvant therapy after hepatectomy.

2. Patients and methods

2.1. Study design, patient selection

From 2004 to 2009, 325 patients with HCC treated by curative hepatectomy at the Department of Surgery, The Chinese University of Hong Kong were retrospectively reviewed using a prospectively collected database. The following exclusion criteria were used:

1. patients who received palliative hepatectomy,
2. patients who received combined hepatectomy and local ablative therapy, and
3. patients who received local ablative treatment or trans-arterial chemoembolization or systemic treatment before hepatectomy.

The cohort was divided into group 1 (actual overall survival <5 years), group 2 (5 years ≤actual overall survival <10 years), and group 3 (actual overall survival ≥10 years). The details of patient demographics, operative parameters, perioperative outcome, tumor pathology, tumor recurrence, and overall survival outcome were analyzed. This study was reviewed and approved by the Institutional Review Broad of The Chinese University of Hong Kong/Hospital Authority New Territories East Cluster.

The diagnosis of HCC was based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver.[13] HCC was diagnosed when the radiological imaging techniques (spiral contrast CT scan or contrast MRI) showed typical features of HCC (contrast enhancement in the arterial phase and rapid wash-out of contrast in the venous or delayed phase) and/or the serum alpha fetoprotein (AFP) level was elevated (>400 ηg/mL).

2.2. Management protocol

The selection for curative hepatectomy was determined by the objective assessments of the patients' liver function in terms of Child-Pugh grading and indocyanine green (ICG) clearance test, future liver remnant volume and pre-morbid functional status. Major hepatectomy (resection of ≥three Couinaud segments) would be performed for patients with Child's A liver function with ICG retention at 15 min (R15) of ≤15%, whereas only minor hepatectomy (resection of <three Couinaud segments) would be contemplated for patients with Child's B grade with unsatisfactory ICG (R15) of >15%. In selected cases with insufficient future liver remnant, pre-operative portal vein embolization (PVE) with or without trans-arterial chemoembolization (TACE) will be performed.

The operative details of curative hepatectomy in the authors' center has been reported previously.[14] Hepatectomy was performed by open, laparoscopic or robot-assisted approaches with intra-operative ultrasound guidance. For open hepatectomy, the Cavitron ultrasonic aspirator (CUSA, Valley-Lab, Boulder, CO) with saline coupled dissecting sealer (TissueLink, TissueLink Medical, Dover, DE) was used for liver parenchymal transection. For laparoscopic and robotic-assisted hepatectomy cases, Ligasure (Valley-Lab, Boulder, CO), Harmonic Ace (Ethicon Endo-surgery, Cincinatti, OH) or laparoscopic ultrasonic dissector was used where appropriate. Both anatomical and non-anatomical hepatectomy were performed according to surgeons' preference intraoperatively.

Post-operative follow-up after hepatectomy included ultrasonography at 3-months' interval and contrasted CT scan at 6-months' interval, together with three-monthly monitoring of serum AFP level for initial 2 years after surgery. The imaging studies and serum AFP monitoring would spare out to six-monthly intervals thereafter. Supplementary thoracic CT scan or PET scan was selectively performed to look for extrahepatic metastasis. Recurrent HCC was diagnosed with radiological imaging (CT or PET-CT) to identify the location of intra-hepatic recurrence, tumor disease burden and the presence of extra-hepatic disease recurrence. Treatment options for recurrent HCC included hepatic re-resection, local ablation therapies, transarterial chemo-embolization (TACE), external beam radiotherapy, systemic chemotherapy or targeted immunotherapy, and salvage transplantation. A multi-disciplinary team approach was applied to decide on treatment options, considering the patients' liver functional status, recurrence pattern, comorbidities and patients' wish.

2.3. Prognostic factors

Eighteen clinico-pathologic factors of potential influence on mid- and long-term overall survival were selected in the analyses of associated prognostic factors. Patients' demographic factors were age, sex, hepatitis B and C status, liver function in terms of Child-Pugh classification, ICG – 15, and presence of cirrhosis as indicated by both preoperative imaging studies and histology. Tumor factors were serum alpha fetoprotein level (AFP), tumor size, multiple tumors, satellite nodules, tumor differentiation, and microvascular tumor invasion (MVI). Operative factors were type of hepatectomy, resection margin, intraoperative blood loss, requirement of blood transfusion and severe postoperative complications (grade III or above according to Clavien-Dindo classification[15]).

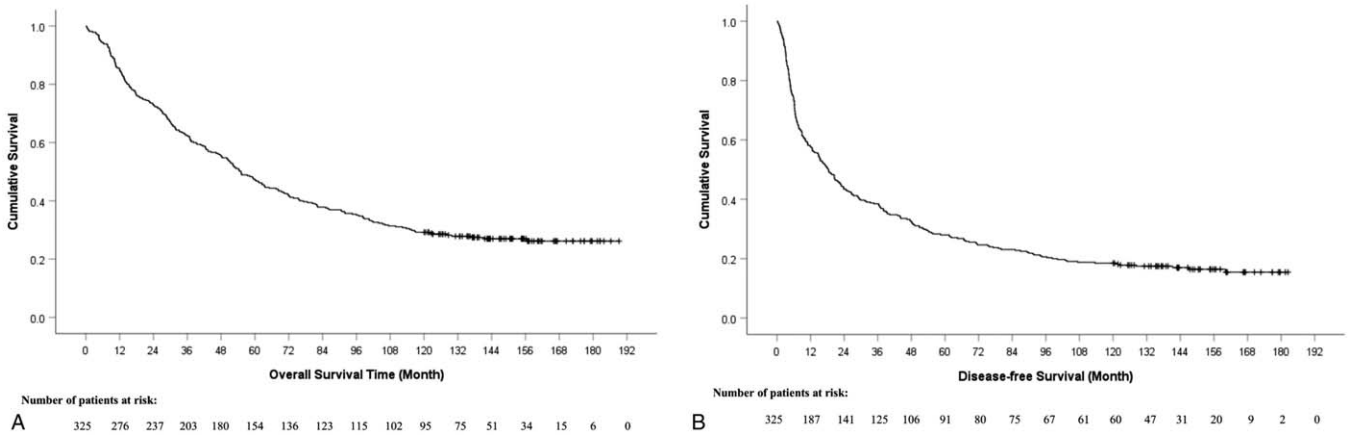

Figure 1. Actual overall (A) and disease-free (B) survival of the whole cohort of patients.

2.4. Statistical analysis

Statistical comparisons of baseline characteristics were performed by Chi-square test with Yates' correction or the Fisher's exact test for categorical variables, and Mann–Whitney *U* test for continuous variables. Univariate and multivariate analyses by logistic regression model were adopted to identify significant prognostic factors for mid-term (group 1 vs group 2) and long-term (group 1 vs group 3) overall survival. Overall survival was defined as the time interval from hepatectomy until death from any cause, or until the time of analysis of the present study. Recurrence-free survival was defined as the time interval from hepatectomy until tumor recurrence, or until the time of analysis of the present study. All statistical tests were two-sided and a significant difference was considered when $P < .05$. SPSS version 24.0 statistical software (SPSS, Chicago, IL) was used for statistical analyses.

3. Results

3.1. Actual survival outcome of whole cohort

With a median follow-up of 144 months (range: 8–230 months), there were 171 patients (52.7%) in group 1, 59 patients (18.1%) in group 2 and 95 patients (29.2%) in group 3 out of the whole cohort (n = 325). The actual overall survival rates were 84.9%, 62.5%, 47.4%, and 29.2% at 1, 3, 5, and 10 years (Fig. 1A). The actual disease-free survival rates were 57.5%, 38.5%, 28%, and 18.5% at 1, 3, 5, and 10 years (Fig. 1B). Out of the154 patients who survived more than 5 years, 95 patients (61.6%) could survive 10 years or more. The hospital mortality for group 1 was 2.9% (n = 5) due to post-operative liver failure and severe sepsis. There were no hospital mortalities in groups 2 and 3.

3.2. Clinico-pathologic characteristics of patients

The baseline characteristics among the three groups were shown in Table 1. When comparing groups 1 and 2, the baseline demographic characteristics were similar between the two groups. However, group 2 had a higher ratio of minor hepatectomy (72.8% vs 53.8%), lower intra-operative blood loss (median: 0.3 L vs 0.5 L), smaller tumor size (median: 3 cm vs 5.5 cm), lower incidence of microvascular tumor invasion (13.6% vs 45%), and tumor rupture (5.1% vs 18.1%) than group 1. There was more liver cirrhosis on histology in group 2 than group 1 (71.2% vs 56.7%).

When comparing groups 1 and 3, the patients in group 3 were younger, had a higher incidence of hepatitis B virus infection (90.5% vs 78.9%), better general health (low ASA grading), higher serum albumin levels (median: 42 g/L vs 40 g/L), lower serum AFP level (median: 15ηg/mL vs 88 ηg/mL), lower intra-operative blood loss (median: 0.25 L vs 0.45 L) and blood transfusion requirement, smaller tumor size (median: 3.2 cm vs 5.5 cm), more solitary tumors (87.3% vs 64.9%), and lower incidence of microvascular tumor invasion (11.6% vs 45%), satellite nodules (6.3% vs 26.9%) and tumor rupture (4.2% vs 18.1%) than group 1.

3.3. Postoperative complications

There was a decreasing trend in overall complication rates between groups 1, 2, and 3 (Table 2). Group 3 had significantly less overall complications than group 1 (20% vs 35.7%). There was no statistically significant difference in severe complication rate between groups. Although not statistically significant, group 1 had more intra-abdominal bleeding, liver failure, wound complications, and biliary complications than groups 2 and 3.

3.4. Tumor recurrence pattern

There were 57 of 95 patients (60%) in group 3 and 5 of 59 patients (9.1%) in group 2, who remained recurrence-free at the time of analysis. The tumor recurrence pattern was illustrated in Table 3. Compared with group 1, group 2 had more intrahepatic recurrence (69.5% vs 42.1%). The incidence of extrahepatic recurrence was however similar between groups 1 and 2. Nonetheless, group 3 had less extrahepatic recurrence than group 1 (0% vs 12.3%), even though the incidence of intrahepatic recurrence was similar between them. The time interval to tumor recurrence was significantly longer in groups 2 and 3 than group 1. For treatment modality for recurrent tumor, more patients in group 2 could receive local ablation therapy than those in group 1 (18.6% vs 8.2%). Likewise, more patients in group 3 could receive hepatic re-resection than those in group 1 (18.9% vs 8.8%). There were larger proportion of patients in group 1 than

Table 1

Patient demographics and tumor characteristics of Group 1 (survival <5 years), Group 2 (5 years ≤survival <10 years) and Group 3 (survival ≥10 years).

Characteristics	Group 1 (n=171)	Group 2 (n=59)	Group 3 (n=95)	P*	P†
Age	57 (21–85)	61 (43–81)	53 (29–72)	.092	<.001
Male: female	152: 19	49: 10	80: 15	.244	.274
Hepatitis B viral infection	135 (78.9)	47 (79.7)	86 (90.5)	.907	.016
Hepatitis C viral infection	11 (6.4)	4 (6.8)	2 (2.1)	1.000	.145
ASA grading					
≤2: 3	127: 44	47: 12	88: 7	.405	<.001
Child-Pugh classification					
Class A: Class B: Class C	165: 6: 0	54: 4: 1	94: 1: 0	.122	.427
ICG – 15 (%)	4.3 (0.1–40.7)	5.3 (1.0–32.0)	3.2 (0.4–15.2)	.123	.094
Bilirubin (mmol/L)	11 (3–57)	11 (3–33)	10 (5–32)	.356	.332
Albumin (g/L)	40 (22–49)	41 (27–47)	42 (30–50)	.939	<.001
INR	1.06 (0.84–1.55)	1.07 (0.91–1.43)	1.07 (0.90–1.29)	.149	.625
Creatinine (μmol/L)	83 (46–286)	85 (54–859)	84 (55–139)	.393	.601
Serum AFP level (ηg/ml)	88 (1–625,000)	52 (1–46,000)	15 (1–161,000)	.382	.014
Type of hepatectomy					
Major: Minor	79: 92	16: 43	43: 52	.010	.883
Intraoperative blood loss (L)	0.45 (0.02–11.30)	0.30 (0.02–6.07)	0.25 (0.01–3.6)	.022	<.001
No. of patients required blood transfusion	24 (14.0)	4 (6.8)	5 (5.2)	.142	.028
Severe postoperative complication‡	21 (12.3)	6 (10.2)	8 (8.4)	.664	.333
Size of largest tumor (cm)	5.5 (0.8–24.0)	3.0 (1.0–13.0)	3.2 (1.5–20.0)	<.001	<.001
No. of tumor nodules					
Single: multiple	111: 60	45: 14	83: 12	.107	<.001
Tumor differentiation				.663	.201
Well-differentiated	15 (8.8)	7 (11.9)	14 (14.7)		
Moderate-differentiated	138 (80.7)	46 (78.0)	75 (78.9)		
Poor-differentiated	14 (8.2)	6 (10.2)	3 (3.2)		
Undifferentiated	4 (2.3)	0 (0.0)	3 (3.2)		
Microvascular invasion	77 (45.0)	8 (13.6)	11 (11.6)	<.001	<.001
Presence of satellite nodules	46 (26.9)	12 (20.3)	6 (6.3)	.317	<.001
Ruptured tumor	31 (18.1)	3 (5.1)	4 (4.2)	.015	.001
Cirrhosis on histology	97 (56.7)	42 (71.2)	46 (48.4)	.050	.193

AFP = alpha fetoprotein, ASA = American Society of Anesthesia, ICG – 15 = Indocyanine-green retention at 15 min.

* Comparison between group 1 and 2.

† Comparison between group 1 and 3.

‡ Severe postoperative complication according to Clavian-Dindo grade III or above.

Table 2

Comparison of short-term perioperative outcome between groups.

Characteristics	Group 1 (n=171)	Group 2 (n=59)	Group 3 (n=95)	P*	P†
Overall complication	61 (35.7)	20 (33.9)	19 (20.0)	.806	.008
Pulmonary complications	20 (11.7)	13 (22.0)	6 (6.3)	.051	.157
Wound complications	19 (11.1)	2 (3.4)	4 (4.2)	.076	.055
Intraabdominal collection	3 (1.8)	2 (3.4)	4 (4.2)	.605	.252
Intraabdominal bleeding	2 (1.2)	0 (0.0)	0 (0.0)	.448	.539
Liver failure	5 (2.9)	1 (1.7)	1 (1.1)	1.000	.426
Renal failure	3 (1.8)	1 (1.7)	0 (0.0)	1.000	.555
Biliary complications	5 (2.9)	0 (0.0)	1 (1.1)	.332	.426
Vascular complications	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Sepsis	4 (2.3)	0 (0.0)	2 (2.1)	.575	1.000
Others	28 (16.3)	11 (18.6)	3 (3.1)	.689	.001
Severe complications‡	21 (12.3)	6 (10.2)	8 (8.4)	.664	.333
Hospital mortality	5 (2.9)	0	0	.332	.164

* Comparison between group 1 and 2.

† Comparison between group 1 and 3.

‡ Severe postoperative complication according to Clavian-Dindo grade III or above.

Table 3

Comparison of tumor recurrence pattern and follow-up treatment between groups.

Characteristics	Group 1 (n = 171)	Group 2 (n = 59)	Group 3 (n = 95)	P*	P†
Intrahepatic recurrence	72 (42.1)	41 (69.5)	37 (38.9)	<.001	.616
Extrahepatic recurrence	21 (12.3)	3 (5.1)	0 (0.0)	.119	<.001
Intrahepatic and extrahepatic recurrence	62 (36.3)	10 (16.9)	1 (1.1)	.006	<.001
Time to tumor recurrence (months)	6 (1 – 50)	36 (1 – 100)	45 (1 – 160)	<.001	<.001
Treatment of recurrence					
Hepatic re-resection	15 (8.8)	8 (13.6)	18 (18.9)	.291	.016
Local ablation (RFA or MWA)	14 (8.2)	11 (18.6)	8 (8.4)	.026	.947
TACE/PEI	58 (33.9)	24 (40.7)	11 (11.6)	.350	<.001
Radiotherapy	3 (1.8)	0	0	.571	.555
Lung resection	3 (1.8)	0	0	.571	.555
Nephrectomy	1 (0.6)	0	0	1.000	1.000
Systemic treatment	31 (18.1)	5 (8.5)	0 (0.0)	.078	<.001
Supportive care	30 (17.5)	6 (10.2)	1 (1.1)	.179	<.001

MWA = microwave ablation, PEI = percutaneous ethanol injection, RFA = radiofrequency ablation, TACE = transarterial chemoembolization.
* Comparison between group 1 and 2.
† Comparison between group 1 and 3.

those in groups 2 and 3, who could only receive palliative TACE, systemic treatment or supportive care.

3.5. Prognostic factors for mid-term overall survival

Univariate analysis showed that tumor size (odds ratio [OR] 0.818, 95% confidence interval [CI] 0.734–0.911), microvascular tumor invasion (OR 0.191, 95% CI 0.086–0.428), tumor rupture (OR 0.242, 95% CI 0.071–0.824), and major hepatectomy (OR 0.433, 95% CI 0.227–0.828) were poor prognostic factors. Multivariate analysis showed that only microvascular tumor invasion was an independent poor prognostic factor for mid-term survival (OR 0.271, 95% CI 0.115–0.64) (Table 4).

3.6. Prognostic factors for long-term overall survival

Univariate analysis showed that age (OR 0.951, 95% CI 0.926–0.976), ASA ≤2 (OR 5.139, 95% CI 2.1–12.577), hepatitis B

Table 4

Univariate and multivariate analyses of prognostic factors of mid-term overall survival (group 1 vs group 2).

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	P	OR (95% CI)	P
Age	1.027 (0.998– .057)	.064		
Gender (male)	0.613 (0.267–1.406)	.247		
ASA grade ≤2	1.357 (0.660–2.790)	.406		
Hepatitis B viral infection	1.044 (0.502–2.173)	.907		
Hepatitis C viral infection	1.058 (0.324–3.459)	.926		
Child-Pugh grade A	0.393 (0.115–1.338)	.135		
ICG – 15	1.030 (0.978–1.086)	.265		
Bilirubin	0.968 (0.919–1.021)	.230		
Albumin	1.002 (0.937–1.071)	.963		
Creatinine	1.006 (0.999–1.014)	.098		
Platelet	0.999 (0.995–1.002)	.520		
Serum AFP level	1.00 (1.00–1.00)	.229		
Cirrhosis on histology	1.885 (0.994–3.573)	.052		
Tumor size	0.818 (0.734–0.911)	<.001		
Solitary tumor	1.737 (0.883–3.419)	.110		
Tumor differentiation				
Well-differentiated	1.089 (0.293–4.041)	.899		
Moderate-differentiated	0.778 (0.282–2.142)	.627		
Microvascular invasion	0.191 (0.086–0.428)	<.001	0.271 (0.115–0.640)	.003
Tumor ruptured	0.242 (0.071–0.824)	.023		
Intraoperative blood loss	0.864 (0.601–1.244)	.433		
Blood transfusion required	0.445 (0.148–1.342)	.151		
Type of hepatectomy				
Major resection	0.433 (0.227–0.828)	.011		
Minor resection	–			
Severe postoperative complications*	0.809 (0.310–2.112)	.664		

ASA = American Society of Anesthesia, ICG – 15 = Indocyanine-green retention at 15 min, AFP = alpha fetoprotein.
* Severe postoperative complication according to Clavian-Dindo grade III or above.

Table 5

Univariate and multivariate analyses of potential prognostic factors of long-term overall survival (Group 1 vs Group 3).

	Univariate analysis		Multivariate analysis	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Age	0.951 (0.926–0.976)	<.001	0.952 (0.920–0.986)	.006
Gender (male)	0.667 (0.322–1.382)	.276		
ASA grade <2	5.139 (2.100–12.577)	<.001	3.746 (1.325–10.587)	.013
Hepatitis B viral infection	2.548 (1.169–5.553)	.019		
Hepatitis C viral infection	0.313 (0.068–1.442)	.136		
Child-Pugh grade A	3.418 (0.405–28.824)	.259		
ICG -15	0.913 (0.835–0.999)	.047		
Bilirubin	0.970 (0.929–1.014)	.182		
Albumin	1.178 (1.096–1.266)	<.001	1.099 (1.008–1.199)	.032
Creatinine	0.999 (0.987–1.010)	.801		
Platelet	1.002 (0.999–1.005)	.190		
Serum AFP level	1.000 (1.000–1.000)	.294		
Cirrhosis on histology	0.716 (0.433–1.185)	.194		
Tumor size	0.854 (0.787–0.927)	<.001		
Solitary tumor	3.739 (1.890–7.394)	<.001	3.289 (1.419–7.625)	.006
Tumor differentiation				
Well-differentiated	4.356 (1.028–18.459)	.046		
Moderate-differentiated	2.536 (0.706–9.106)	.154		
Microvascular invasion	0.160 (0.080–0.321)	<.001	0.203 (0.090–0.456)	<.001
Tumor ruptured	0.199 (0.068–0.581)	.003		
Intraoperative blood loss	0.326 (0.168–0.632)	<.001		
Blood transfusion required	0.340 (0.125–0.924)	.034		
Type of hepatectomy				
Major resection	0.963 (0.582–1.593)	.883		
Minor resection	–			
Severe postoperative complications*	0.657 (0.279–1.546)	.336		

AFP = alpha fetoprotein, ASA = American Society of Anesthesia, ICG – 15 = Indocyanine-green retention at 15 min.
* Severe postoperative complication according to Clavian-Dindo grade III or above.

virus infection (OR 2.548, 95% CI 1.169–5.553), albumin level (OR 1.178, 95% CI 1.096–1.266), tumor size (OR 0.854, 95% CI 0.787–0.927), solitary tumor (OR 3.739, 95% CI 1.89–7.394), well-differentiated tumor (OR 4.356, 95% CI 1.028–18.459), microvascular tumor invasion (OR 0.160, 95% CI 0.08–0.321), tumor rupture (OR 0.199, 95% CI 0.068–0.581), intra-operative blood loss (OR 0.326, 95% CI 0.168–0.632), and blood transfusion requirements (OR 0.34, 95% CI 0.125–0.924) were prognostic factors. Multivariate analysis showed that age (OR 0.952, 95% CI 0.92–0.986), ASA ≤2 (OR 3.746, 95% CI 1.325–10.587), albumin levels (OR 1.099, 95% CI 0.92–0.986), solitary tumor (OR 3.289, 95% CI 1.149–7.625), and microvascular tumor invasion (OR 0.203, 95% CI 0.09–0.456) were independent prognostic factors for long-term survival (Table 5).

4. Discussion

The present study demonstrated that curative hepatectomy for HCC results in bimodal actual survival outcome with very favorable long-term survival rate of 29.2%. Out of those who survived more than five years after surgery, 61.6% could live longer than 10 years. Absence of microvascular invasion was a good prognostic factor for both mid and long-term overall survival, whereas young age, ASA grade ≤2, high albumin level and solitary tumor were good prognostic factors for long-term overall survival. This study is also one of the largest cohorts of HCC patients with comprehensive follow-up for more than ten years. Such information will help patient counselling and stratifying high and low risk patients for modification of recurrent tumor surveillance and adjuvant therapy.

Actual long-term survival after curative hepatectomy for HCC is rarely reported in the literature. Li et al[11] reported an actual 10-year survival rate of 16.6% in 1016 Chinese patients with HCC. The independent risk factors for long-term survival were cirrhosis, pre-operative HBV viral load $>10^4$ copies/mL, tumor size greater than 5 cm, multiple tumors, vascular invasion, post-operative HBV reactivation and early recurrent disease within 2 years. Similarly, Eguchi et al[7] reported a 10-year recurrence-free survival of 22.4% after liver resection, and the strongest predictor of death from recurrent HCC was tumor differentiation. Long-term survival data from Western centers have shown inferior outcomes after curative hepatectomy. Data from the Memorial Sloan Kettering Center[12] showed that small tumors (<5 cm), solitary tumors and absence of vascular invasion were independently associated with actual 10-year survival. However, this study only had 50 patients with more than 10-years survival. A small cohort study from Germany showed an overall survival rate of 7.4% at 10-years, with age at resection and tumor staging as predictors of long-term survival.[4] Franssen's group[10] published 10-year survival rate of 15%, and demonstrated that the absence of vascular invasion, no peri-operative blood transfusion and recurrent disease within 2 years of primary resection were predictive of 10-year survival. Finally, a systematic review of actual 10-year survival concluded that poor liver function, close surgical resection margins and presence of satellite lesions were poor prognostic factors.[9] The overall 10-year survival rate in the review was 7.2%. In the present study, there

was coherent and comprehensive follow-up of the whole cohort, with a favorable actual 10-year survival rate of 29.2%. These high overall survival rates compared to other published series of long-term survival after curative hepatectomy reflected the aggressive treatment strategy and meticulous surgical techniques for HCC in the authors' center.

Unfavorable tumor pathology is directly linked to poor patient survival after hepatectomy. Microvascular tumor invasion was a prognostic factor on multivariate analysis for both mid and long-term survival. Microvascular tumor invasion is defined as the presence of tumor cells in portal veins, in large capsule vessels or in the vascular space between endothelial cells and is only detected under microscopic examination.[16] It is often present in large tumors (size >5 cm) and multifocal disease[17] and is associated with early recurrent disease.[18] Previous studies have already shown that it was a poor prognostic factor following curative hepatectomy[7,8,10–12,16], even for solitary small HCC (size <5 cm),[19] Post-operative TACE has been suggested as adjuvant treatment for HCC with microvascular tumor invasion, with improved survival outcomes.[20,21] Microvascular tumor invasion-positive patients are more likely to have intrahepatic metastases, and TACE can treat the haematogenous spread of residual tumor and delay recurrent disease.[22,23] Large tumor size is a risk factor for recurrent HCC after hepatectomy.[24] Patients with tumor smaller than 3 cm have longer overall and disease-free survival than those with large tumor.[4,25] Large tumor is also associated with vascular invasion, multiple tumors, poor differentiation and major hepatectomy.[26,27] Tumor rupture is associated with poor overall survival compared to non-ruptured cases, although the published literature has shown conflicted results.[28]

Liver cirrhosis and other markers of liver dysfunction such as thrombocytopenia, elevated alanine aspartate and hypoalbuminemia have been reported as prognostic factors for overall survival.[29] In the present study, only serum albumin level is prognostic. Wayne et al[30] identified 249 patients who underwent curative hepatectomy for HCC that were 5 cm or smaller. On multivariate analysis, fibrosis score, Edmondson-Steiner grade and Child-Pugh score were significant predictors of survival after hepatectomy. The presence of liver fibrosis has been shown to affect survival after hepatectomy. The risk of death from HCC beyond five years after resection was reported to be 7% in patients with normal liver or minimal fibrosis, compared to 58% in patients with liver fibrosis.[31] These results highlighted the importance of underlying chronic liver disease as a major contributor to overall survival after curative hepatectomy for HCC.

Some of operative parameters are crucial for patient survival after hepatectomy. Intra-operative blood loss and the need for blood transfusion were independent prognostic factors for long-term survival. The prognostic value of perioperative blood transfusion has been reported previously.[2,4,10] Blood transfusion has an immunomodulatory role[32] and there are published reports of recurrent HCC after perioperative transfusions.[33] Minor hepatectomy was a positive prognostic factor, possibly because the future liver remnant is more likely to tolerate repeat liver resection for intrahepatic recurrence.[34] Furthermore, large future liver remnant following minor hepatectomy might be beneficial for the oncological treatment of possible recurrent HCC.[32]

The association between baseline demographic factors and overall survival is interesting. Young patient has a survival advantage because of fewer significant comorbidities[35,36] and can tolerate more radical treatments for HCC, such as repeat hepatectomy.[4,7] This is an intuitive finding as life expectancy is naturally lower in elderly patients. The impact of hepatitis serology status and HCC survival has been investigated in several studies. Yamanaka et al[37] reported that patients with hepatitis B related HCC have better overall survival rates compared to those with hepatitis C related HCC, whereas Haratake et al[38] found contrasting results. The long-term prognosis after curative hepatectomy appears to be more affected by tumor and liver disease factors rather than hepatitis serology status.[39]

The time interval to tumor recurrence and the pattern of tumor recurrence determine patient prognosis to some extent. Tumor recurrence within 2 years of curative hepatectomy is an adverse prognostic factor for overall survival.[10–12] The authors' center has previously shown that recurrence within nine months of hepatectomy had inferior overall survival. Multivariate analysis showed that tumor diameter >3.5 cm and tumor rupture were risk factors for tumor recurrence.[40] In the present study, mid- and long-term survivors had predominantly intrahepatic recurrences (69.5% and 38.9%), which were amenable for curative liver-directed therapies (hepatic re-resection and local ablation therapy). In contrast, short-term survivors had more extrahepatic recurrence (12.3%), which could only be treated by systemic therapy or symptomatic care.

This study contributes to the limited published data on actual long-term survival outcomes after curative hepatectomy for HCC. Whilst the reported prognostic factors in this study are well known, there was a bimodal distribution of post-hepatectomy survival outcomes, which to our knowledge, has not been previously described. This new point of view will have important clinical implications on how to identify patients within the bimodal distribution and guide the appropriate recurrent HCC surveillance strategies.

The major limitation of the present study was its retrospective nature. The major aetiology of HCC in this study was hepatitis B virus infection, thus the long-term outcomes for HCC caused by hepatitis C or alcoholism might differ. Second, only individual poor prognostic factors were investigated in the present study. It would be desirable that a constructive user-friendly prediction model can be derived to accurately predict the chance of actual mid- and long-term survival of patients with HCC. Third, the prognostic factors for long-term recurrence-free survival were not studied in the present study.

In conclusion, curative hepatectomy results in bimodal actual survival outcome with favorable actual 10-year survival rate of 29.2%. Absence of microvascular invasion was good prognostic factor for both mid and long-term overall survival, whereas young age, ASA grade ≤2, high albumin level and solitary tumor were good prognostic predictors for long-term overall survival.

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