Original article

Long-term survival of patients undergoing liver resection for very large hepatocellular carcinomas

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Background: **This study aimed to assess long-term survival after liver resection for huge hepatocellular carcinoma (HCC).**

Methods: **Patients with stage I–III HCC who underwent hepatectomy from 2002 to 2010 were identified retrospectively from prospective national databases and followed until December 2012. Patients were assigned into four groups according to tumour size: less than 3·0 cm (small), 3·0–4·9 cm (medium), 5·0–10·0 cm (large) and over 10·0 cm (huge). The primary endpoint was overall survival. The Kaplan–Meier method and Cox proportional hazards model were used for survival analysis.**

Results: **A total of 11 079 patients with HCC (mean(s.d.) age 59·7 (12·0) years) were eligible for this study. Median follow-up was 72·5 months. Patients with huge HCC had the worst prognosis; overall survival rates for patients with small, medium, large and huge HCC were 72·0, 62·1, 50·8 and 35·0 per cent respectively at 5 years, and 52·6, 41·8, 35·8 and less than 20·0 per cent at 10 years ($P < 0·001$). Multivariable analysis showed that tumour size affected long-term survival (hazard ratio (HR) 1·31, 1·55 and 2·38 for medium, large and huge HCC respectively *versus* small HCC). Prognostic factors for huge HCC were surgical margin larger than 0·2 cm (HR 0·70; $P = 0·025$), poor differentiation (HR 1·34; $P = 0·004$), multiple tumours (HR 1·64; $P < 0·001$), vascular invasion (HR 1·52; $P = 0·008$), cirrhosis (HR 1·37; $P = 0·013$) and the use of nucleoside analogues (HR 0·69; $P = 0·004$).**

Conclusion: **Huge HCCs have a worse prognosis than smaller HCCs after liver resection. A wide resection margin and antiviral therapy with nucleoside analogues may be associated with favourable long-term survival.**

Paper accepted 16 March 2016

Published online 23 August 2016 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10196

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and is fatal unless treated with a curative intervention[1]. Surgery (transplantation or hepatectomy) remains the only potentially curative treatment for HCC[2]. Technical advances in liver surgery and perioperative management have expanded the surgical indications towards advanced cancers and have improved long-term survival for patients with HCC[3,4]. However, the long-term prognosis after resection of HCC with curative intent remains unsatisfactory because of a high tumour recurrence rate (up to 70 per cent at 5 years)[5]. Among the prognostic factors for survival and recurrence, tumour size is important, and it may guide HCC treatment and form the basis of tumour staging systems.

To facilitate the interpretation of treatment effect or disease severity, tumour size in HCC has been categorized into several groups. The cut-off of tumour size at 2 and 5 cm was introduced as a criterion of the traditional TNM system. The Milan criteria[6] provided guidelines on liver transplantation for patients with HCC according to a tumour size of 3 and 5 cm (single tumour 5 cm or smaller, or two or three tumours with none larger than 3 cm). The effect of radiofrequency ablation for HCC was considered effective for small liver tumours (no larger than 3 cm) but controversial for tumours sized 3–5 cm[7]. For tumour sizes larger than 5 cm, the prognostic significance varied, with

inconsistent conclusions. Some studies[8,9] identified tumour size 5 cm or larger as a poor prognostic factor for overall survival, but others reported that size exceeding 5 cm had no significant impact in patients who had undergone liver resection for HCC[10,11]. Although surgery for huge HCC (larger than 10 cm) was originally thought to be ineffective, several studies suggested that results were comparable to those of surgery for smaller tumours[12,13]. Furthermore, study samples of patients with huge HCC and large HCC (size 5–10 cm) were usually small, which might limit the interpretation and application of these results.

This study aimed to assess the long-term survival of patients with huge HCCs and compared the survival of patients with huge HCCs with that of other groups according to tumour size in a population-based study. Prognostic factors were also investigated in relation to tumour size.

Methods

This study investigated the long-term outcome of patients with HCC who underwent liver surgery in Taiwan, an area where HCC is highly prevalent. Candidates included patients with a new diagnosis of HCC registered in the Taiwan Cancer Database (TCDB) from January 2002 to December 2006 and the Taiwan Cancer Registry (TCR) from January 2007 to December 2010. The TCDB and the TCR are national prospective databases (covering different time intervals) that aim to make national cancer health statistics available and to facilitate research. Both are nationwide databases with annual registration of newly diagnosed patients with HCC; they provide pathology reports, cancer staging, treatment profile and follow-up status for each patient. The institutional review board at Buddhist Xindian Tzu Chi General Hospital approved this study and waived informed consent (01-X22-087).

Study cohort

Patients newly diagnosed with liver cancer (C22 in ICD-O-3) were identified retrospectively. Exclusion criteria were: patients aged below 25 years or over 85 years, those whose pathology report did not reveal HCC (ICD-O-3 histology code 8170), those who did not undergo liver surgery (hepatectomy or transplantation), those whose estimated survival was less than 1 month, and those who had stage IV disease. Patients whose tumour size was not known were also excluded. Study subjects were assigned to one of four groups depending on tumour size (from the pathology report): less than 3·0 cm (small HCC), 3·0–4·9 cm (medium HCC), 5·0–10·0 cm (large HCC) and over 10·0 cm (huge HCC).

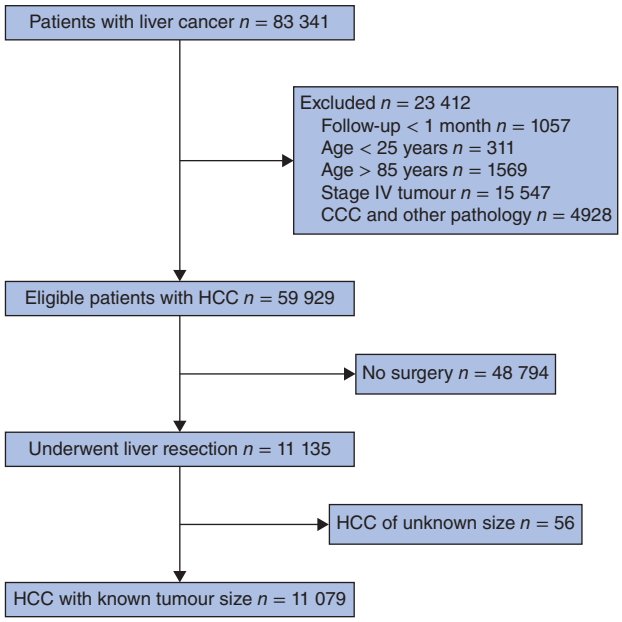
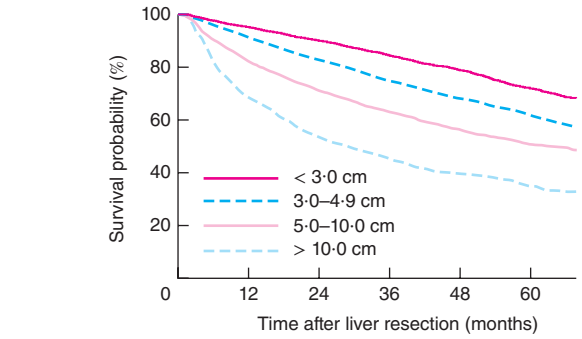


Fig. 1 Flow diagram of patients enrolled in this study. CCC, cholangiocarcinoma; HCC, hepatocellular carcinoma



No. at risk

< 3·0 cm	5070	4819	4468	3439	2575	1770
3·0–4·9 cm	2791	2545	2268	1622	1101	691
5·0–10·0 cm	2306	1894	1613	1139	766	500
> 10·0 cm	912	625	478	328	210	129

Fig. 2 Kaplan–Meier curves showing overall survival following liver resection for hepatocellular carcinoma according to tumour size. $P < 0·001$, less than 3·0 *versus* 3·0–4·9 cm, 3·0–4·9 *versus* 5·0–10·0 cm, and 5·0–10·0 *versus* more than 10·0 cm (log rank test)

Independent variables

Relevant demographic, clinical, pathological and therapeutic data for patients with HCC were retrieved from the TCDB and TCR. Potential prognostic variables included: patient details (year of cancer diagnosis, age,

Table 1 Demographic, clinical and therapeutic characteristics of patients undergoing liver resection for hepatocellular carcinoma in relation to tumour size

	Total ($n = 11\,079$)	< 3·0 cm ($n = 5070$)	3·0–4·9 cm ($n = 2791$)	5·0–10·0 cm ($n = 2306$)	> 10·0 cm ($n = 912$)	P‡
Year of cancer diagnosis						< 0·001
2002–2006	3524 (31·8)	1828 (36·1)	734 (26·3)	701 (30·4)	261 (28·6)	
2007–2010	7555 (68·2)	3242 (63·9)	2057 (73·7)	1605 (69·6)	651 (71·4)	
Age (years)						< 0·001
< 50·0	2446 (22·1)	1066 (21·0)	542 (19·4)	533 (23·1)	305 (33·4)	
50·0–59·9	3161 (28·5)	1601 (31·6)	741 (26·5)	598 (25·9)	221 (24·2)	
60·0–69·9	3222 (29·1)	1508 (29·7)	885 (31·7)	633 (27·5)	196 (21·5)	
70·0–79·9	2000 (18·1)	823 (16·2)	549 (19·7)	461 (20·0)	167 (18·3)	
≥ 80·0	250 (2·3)	72 (1·4)	74 (2·7)	81 (3·5)	23 (2·5)	
Sex						< 0·001
M	8368 (75·5)	3647 (71·9)	2141 (76·7)	1830 (79·4)	750 (82·2)	
F	2711 (24·5)	1423 (28·1)	650 (23·3)	476 (20·6)	162 (17·8)	
Tumour differentiation grade						
Well/moderate	7436 (67·1)	3627 (71·5)	1902 (68·1)	1411 (61·2)	496 (54·4)	< 0·001
Poor/none	3184 (28·7)	1219 (24·0)	782 (28·0)	799 (34·6)	384 (42·1)	
Not specified	459 (4·1)	224 (4·4)	107 (3·8)	96 (4·2)	32 (3·5)	
Resection margin (cm)						
≤ 0·2	1009 (9·1)	445 (8·8)	219 (7·8)	236 (10·2)	109 (12·0)	< 0·001
> 0·2	8597 (77·6)	3868 (76·3)	2259 (80·9)	1780 (77·2)	690 (75·7)	
Not specified	1473 (13·3)	757 (14·9)	313 (11·2)	290 (12·6)	113 (12·4)	
Initial treatment						
Minor hepatectomy*	8550 (77·2)	4406 (86·9)	2318 (83·1)	1505 (65·3)	321 (35·2)	< 0·001
Right/extended right lobectomy	1379 (12·4)	261 (5·1)	219 (7·8)	478 (20·7)	421 (46·2)	
Left/extended left lobectomy	758 (6·8)	204 (4·0)	174 (6·2)	254 (11·0)	126 (13·8)	
Lobectomy, unspecified	173 (1·6)	40 (0·8)	33 (1·2)	56 (2·4)	44 (4·8)	
Liver transplantation	219 (2·0)	159 (3·1)	47 (1·7)	13 (0·6)	0 (0)	
Tumour number						< 0·001
Single	8982 (81·1)	4791 (94·5)	2458 (88·1)	1354 (58·7)	379 (41·6)	
At least two	1889 (17·1)	236 (4·7)	296 (10·6)	872 (37·8)	485 (53·2)	
Not specified	208 (1·9)	43 (0·8)	37 (1·3)	80 (3·5)	48 (5·3)	
Vascular involvement						< 0·001
No invasion	5814 (52·5)	3376 (66·6)	1434 (51·4)	813 (35·3)	191 (20·9)	
Invasion	5057 (45·6)	1651 (32·6)	1320 (47·3)	1413 (61·3)	673 (73·8)	
Not specified	208 (1·9)	43 (0·8)	37 (1·3)	80 (3·5)	48 (5·3)	
pN category†						< 0·001
pN0	899 (8·1)	288 (5·7)	212 (7·6)	246 (10·7)	153 (16·8)	
pN1	65 (0·6)	12 (0·2)	8 (0·3)	26 (1·1)	19 (2·1)	
Not specified	10 115 (91·3)	4770 (94·1)	2571 (92·1)	2034 (88·2)	740 (81·1)	
Hepatitis viral status						< 0·001
HBV	5520 (49·8)	2425 (47·8)	1360 (48·7)	1221 (52·9)	514 (56·4)	
HCV	2492 (22·5)	1390 (27·4)	667 (23·9)	360 (15·6)	75 (8·2)	
HBV and HCV	1354 (12·2)	751 (14·8)	348 (12·5)	205 (8·9)	50 (5·5)	
Negative	1713 (15·5)	504 (9·9)	416 (14·9)	520 (22·5)	273 (29·9)	
Background liver						< 0·001
Cirrhosis	1280 (11·6)	465 (9·2)	331 (11·9)	318 (13·8)	166 (18·2)	
Hepatitis	6949 (62·7)	3336 (65·8)	1810 (64·9)	1331 (57·7)	472 (51·8)	
No cirrhosis or hepatitis	2850 (25·7)	1269 (25·0)	650 (23·3)	657 (28·5)	274 (30·0)	
Co-morbidity index‡						
≤ 2	5347 (48·3)	2226 (43·9)	1298 (46·5)	1259 (54·6)	564 (61·8)	< 0·001
3–4	2491 (22·5)	1253 (24·7)	630 (22·6)	451 (19·6)	157 (17·2)	
> 4	3241 (29·3)	1591 (31·4)	863 (30·9)	596 (25·8)	191 (20·9)	
Use of nucleoside analogues	2243 (20·2)	1128 (22·2)	562 (20·1)	402 (17·4)	151 (16·6)	< 0·001
Death from all causes	4023 (36·3)	1404 (27·7)	991 (35·5)	1067 (46·3)	561 (61·5)	< 0·001

Values in parentheses are percentages. Because of rounding, percentages may not add up to 100 per cent. *Three or fewer segments. †Tumours were staged according to the sixth edition of the American Joint Committee on Cancer TNM classification for liver cancer. ‡According to Charlson Co-morbidity Index (Deyo version). HBV, hepatitis B virus; HCV, hepatitis C virus. ‡χ^2 test.

Table 2 Univariable and multivariable Cox regression analyses of prognostic factors for long-term survival in 11 079 patients undergoing liver resection for hepatocellular carcinoma

	Univariable		Multivariable	
	Hazard ratio	*P*	Hazard ratio	*P*
Year of diagnosis (*versus* 2002–2006*)		0·014		0·785
2007–2010	0·92 (0·86, 0·98)		1·01 (0·93, 1·10)	
Age (*versus* < 50·0 years)		< 0·001		< 0·001
50·0–59·9	0·90 (0·82, 0·98)		0·92 (0·83, 1·01)	
60·0–69·9	1·08 (0·99, 1·18)		1·03 (0·94, 1·13)	
70·0–79·9	1·32 (1·20, 1·45)		1·12 (1·00, 1·24)	
≥ 80·0	1·75 (1·45, 2·11)		1·32 (1·08, 1·61)	
Sex (*versus* M)		0·058		0·378
F	0·93 (0·87, 1·00)		0·97 (0·90, 1·04)	
Tumour differentiation grade (*versus* well/moderate)		< 0·001		< 0·001
Poor/none	1·59 (1·49, 1·70)		1·33 (1·25, 1·43)	
Not specified	1·34 (1·16, 1·54)		1·17 (1·01, 1·35)	
Surgical margin (*versus* ≤ 0·2 cm)		< 0·001		< 0·001
> 0·2	0·64 (0·58, 0·70)		0·69 (0·63, 0·76)	
Not specified	0·76 (0·68, 0·85)		0·82 (0·73, 0·92)	
Primary tumour size (*versus* < 3·0 cm)		< 0·001		< 0·001
3·0–4·9	1·48 (1·36, 1·60)		1·31 (1·21, 1·42)	
5·0–10·0	2·15 (1·98, 2·33)		1·55 (1·42, 1·69)	
> 10·0	3·63 (3·29, 4·00)		2·38 (2·13, 2·67)	
pN category (*versus* pN0)		< 0·001		< 0·001
pN1	5·23 (3·94, 6·95)		2·69 (1·90, 3·81)	
Not specified	0·77 (0·70, 0·86)		0·95 (0·86, 1·06)	
Tumour number (*versus* single)		< 0·001		< 0·001
≥ 2	2·79 (2·60, 2·98)		1·55 (1·42, 1·69)	
Vascular invasion (*versus* no)		< 0·001		< 0·001
Yes	2·25 (2·11, 2·40)		1·57 (1·46, 1·70)	
Background liver (*versus* cirrhosis)		< 0·001		< 0·001
Chronic hepatitis	0·61 (0·56, 0·66)		0·69 (0·64, 0·76)	
No cirrhosis or hepatitis	0·65 (0·59, 0·71)		0·69 (0·62, 0·76)	
Hepatitis viral status (*versus* HBV)		< 0·001		< 0·001
HCV	1·18 (1·09, 1·27)		1·25 (1·14, 1·37)	
HBV and HCV	1·06 (0·96, 1·17)		1·14 (1·03, 1·27)	
Negative	1·46 (1·34, 1·59)		1·08 (0·98, 1·19)	
Use of nucleoside analogues (*versus* no)		< 0·001		0·683
Yes	0·83 (0·77, 0·91)		0·98 (0·89, 1·08)	

Values in parentheses are 95 per cent confidence intervals unless indicated otherwise. *Reference groups are shown in parentheses. Parameter estimates for multivariable analysis were adjusted for co-morbidity. HBV, hepatitis B virus; HCV, hepatitis C virus.

sex, co-morbidity, viral hepatitis status), disease characteristics (tumour size, tumour number, histological grade of differentiation, vascular invasion, tumour stage) and treatment characteristics (surgical procedure, nucleoside analogue (NA) therapy). Tumour stage was determined according to the sixth edition of the American Joint Committee on Cancer (AJCC) staging system for HCC[14]. The use of NAs referred to lamivudine, entecavir or telbivudine as oral antiviral therapy for chronic hepatitis B virus (HBV) infection[15]. The Charlson Co-morbidity Index (Deyo version)[16] was used for evaluation of concurrent illnesses. This is a composite score of co-existing diseases including myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, diabetes without complications, diabetes with chronic complications, hemiplegia/paraplegia, moderate/severe renal disease, cancer without metastasis, moderate/severe liver disease and metastatic solid tumours. Acquired immune deficiency syndrome was not included as only three patients had this condition. Information regarding co-morbidities and prescription of NAs required connection with the National Health Insurance Research Database (NHIRD). The NHIRD (from the National Health Insurance Administration) contains data for all patients including ICD-9-CM diagnostic codes and prescription details.

Dependent variable

The primary endpoint was overall survival, which represented the survival time after surgery with curative intent

Table 3 Multivariable Cox regression analysis examining effect of tumour size on long-term survival of patients operated on for hepatocellular carcinoma

	Hazard ratio			
	Size < 3·0 cm (*n* = 5070)	Size 3·0–4·9 cm (*n* = 2791)	Size 5·0–10·0 cm (*n* = 2306)	Size > 10·0 cm (*n* = 912)
Year of diagnosis (*versus* 2002–2006*)				
2007–2010	1·04 (0·91, 1·20)	1·12 (0·94, 1·34)	0·93 (0·79, 1·10)	0·90 (0·72, 1·13)
Age (*versus* < 50·0 years)				
50·0–59·9	1·08 (0·91, 1·28)	0·83 (0·68, 1·01)	0·94 (0·79, 1·13)	0·84 (0·67, 1·06)
60·0–69·9	1·29 (1·09, 1·53)§	0·92 (0·75, 1·11)	1·06 (0·88, 1·26)	0·80 (0·62, 1·03)
70·0–79·9	1·56 (1·29, 1·89)§	0·99 (0·79, 1·23)	1·04 (0·84, 1·27)	0·81 (0·61, 1·08)
≥ 80·0	1·89 (1·27, 2·80)§	1·72 (1·19, 2·49)§	1·11 (0·78, 1·58)	0·63 (0·33, 1·19)
Sex (*versus* M)				
F	0·89 (0·79, 1·01)	0·93 (0·80, 1·09)	1·04 (0·90, 1·22)	1·07 (0·86, 1·34)
Tumour differentiation grade (*versus* well/moderate)				
Poor or none	1·35 (1·19, 1·52)§	1·36 (1·19, 1·57)§	1·30 (1·15, 1·48)§	1·34 (1·12, 1·59)‡
Surgical margin (*versus* ≤ 0·2 cm)				
> 0·2	0·66 (0·56, 0·78)§	0·65 (0·53, 0·81)§	0·76 (0·63, 0·93)†	0·70 (0·54, 0·91)†
pN category (*versus* N0)				
N1	4·58 (1·92, 10·93)§	1·55 (0·55, 4·41)	3·10 (1·79, 5·36)§	1·71 (0·84, 3·50)
Not specified	0·95 (0·76, 1·20)	0·96 (0·76, 1·22)	1·05 (0·86, 1·28)	0·87 (0·70, 1·09)
Tumour number (*versus* single)				
≥ 2	1·33 (1·08, 1·64)‡	1·44 (1·20, 1·73)§	1·78 (1·51, 2·10)§	1·64 (1·30, 2·06)§
Vascular invasion (*versus* no)				
Yes	1·54 (1·38, 1·73)§	1·82 (1·58, 2·10)§	1·26 (1·05, 1·51)†	1·52 (1·12, 2·07)‡
Background liver (*versus* cirrhosis)				
Chronic hepatitis	0·68 (0·58, 0·81)§	0·73 (0·61, 0·88)§	0·69 (0·59, 0·82)§	0·73 (0·59, 0·91)§
No cirrhosis or hepatitis	0·69 (0·58, 0·84)§	0·75 (0·61, 0·92)§	0·63 (0·52, 0·76)§	0·73 (0·57, 0·94)†
Hepatitis viral status (*versus* HBV)				
HCV	1·40 (1·21, 1·62)§	1·41 (1·18, 1·69)§	1·10 (0·91, 1·32)	0·89 (0·63, 1·24)
HBV and HCV	1·29 (1·10, 1·52)§	1·09 (0·88, 1·36)	1·00 (0·80, 1·26)	1·22 (0·85, 1·74)
Negative	1·23 (1·01, 1·49)†	1·11 (0·91, 1·37)	1·04 (0·88, 1·23)	1·02 (0·82, 1·27)
Use of nucleoside analogues (*versus* no)				
Yes	1·03 (0·88, 1·20)	1·15 (0·95, 1·37)	1·01 (0·85, 1·20)	0·69 (0·54, 0·88)‡

Values in parentheses are 95 per cent confidence intervals unless indicated otherwise. *Reference groups are shown in parentheses. Parameter estimates for multivariable analysis were adjusted for co-morbidity. HBV, hepatitis B virus; HCV, hepatitis C virus. †$P < 0·050$, ‡$P < 0·010$, §$P < 0·001$.

for HCC. Individual survival status was retrieved through linkage to the National Register of Deaths from 2002 to 2012 (from the Ministry of Health and Welfare), in which date and cause of death were recorded.

Statistical analysis

Categorical variables were compared by χ^2 test. Kaplan–Meier analysis was used to calculate survival estimates, and pairwise comparisons among groups were made with the log rank test to identify significant differences. A univariable Cox proportional hazards model was analysed for all potential prognostic variables. Variables that were identified as statistically significant ($P < 0·100$) in univariable analyses were subsequently examined in a multivariable Cox hazards model. Subgroup multivariable analyses according to tumour size were also conducted to explore the significance of prognostic factors. Hazard ratios (HRs) with 95 per cent confidence intervals (c.i.) are reported. Statistical software programmes included SAS® version 9.2 (SAS Institute, Cary, North Carolina, USA) for the initial database merging process, and SPSS® version 20 (IBM, Armonk, New York, USA) for data management and statistical analyses. All *P* values were two-sided and the significance level was specified as $P < 0·050$. Given a statistical power of 0·90 and a type I error rate of 0·05, the superiority margin was estimated to be 0·1864 (HR 0·83 or 1·20).

Results

During the study interval, 83 341 patients with newly diagnosed liver cancer were identified. A total of 11 097 patients who had surgery for non-stage IV HCC were eligible for this study (*Fig. 1*). At the end of the study, 63·7 per cent of the patients (7056 of 11 079) were still alive. The demographic, clinical and interventional characteristics are

shown in *Table 1*. The age of this cohort ranged from 25 to 85 years with a mean(s.d.) of 59·7(12·0) years. The male to female ratio was 3·09. Stage I, II and III disease accounted for 52·5, 28·6 and 18·5 per cent of the cohort respectively. Most patients underwent partial hepatectomy (minor hepatectomy, 77·2 per cent; right hepatectomy, 12·4 per cent; left hepatectomy, 6·8 per cent) and only 2·0 per cent underwent liver transplantation. The most common tumour size was smaller than 3·0 cm (45·8 per cent), followed by 3·0–4·9 cm (25·2 per cent), 5·0–10·0 cm (20·8 per cent) and over 10·0 cm (8·2 per cent). Chronic infection with HBV and hepatitis C virus (HCV) was found in 62·0 and 34·7 per cent of the cohort respectively. In addition to liver disease, common co-morbidities were diabetes mellitus (28·2 per cent) and peptic ulcer disease (26·7 per cent). Some 20·2 per cent of patients in this cohort received NAs as antiviral therapy.

The median follow-up time was 72·5 (range 1–122) months. *Fig. 2* illustrates Kaplan–Meier survival curves for patients with HCC according to tumour size. Tumour size had a significant impact on the survival rate ($P < 0·001$ for all pairwise comparisons). Huge HCCs had the worst prognosis. Overall survival rates for patients with small, medium, large and huge HCCs were 95·1, 91·2, 82·1 and 68·5 per cent respectively at 1 year; 84·5, 74·9, 63·1 and 45·3 per cent at 3 years; 72·0, 62·1, 50·8 and 35·0 per cent at 5 years; and 52·6, 41·8, 35·8 and less than 20·0 per cent at 10 years ($P < 0·001$).

Both univariable and multivariable Cox proportional hazards models revealed tumour size as a prognostic factor ($P < 0·001$) (*Table 2*). Compared with tumour size smaller than 3·0 cm, the group with tumour size larger than 10·0 cm had the worst prognosis (HR 2·38, 95 per cent c.i. 2·13 to 2·67; $P < 0·001$) followed by those with tumour size 5·0–10·0 cm (HR 1·55, 1·42 to 1·69; $P < 0·001$) and 3·0–4·9 cm (HR 1·31, 1·21 to 1·42; $P < 0·001$). In multivariable analysis, other significant prognostic factors were: age, tumour differentiation, surgical margin, node status, tumour number, vascular invasion, cirrhosis and hepatitis viral status. Patients who used NAs as antiviral therapy had a better prognosis in the univariable model (HR 0·83, 0·77 to 0·91; $P < 0·001$) but not in the multivariable model (HR 0·98, 0·89 to 1·08; $P < 0·683$).

Table 3 summarizes prognostic factors for long-term survival of patients with HCC according to tumour size. Cirrhosis of the liver, tumour differentiation, surgical margin, tumour number and vascular invasion were significant factors regardless of tumour size ($P \leq 0·050$). Age and HBV infection were significant factors only for tumour size smaller than 5·0 cm ($P \leq 0·001$). Patients who received NAs as antiviral therapy had a better prognosis when tumour size was larger than 10·0 cm (HR 0·69, 95 per cent c.i. 0·54 to 0·88; $P = 0·004$).

Discussion

In this population-based study of 11 079 patients who underwent surgery for HCC with up to 10 years of follow-up, those with a tumour size larger than 10·0 cm had the worst prognosis. Factors such as tumour differentiation, surgical margin, single tumour, absence of vascular invasion and absence of cirrhosis predicted long-term survival regardless of tumour size. Factors such as age and virus-related profile predicted long-term survival only for small and medium HCCs. Antiviral therapy with NAs was associated with improved long-term survival in the huge HCC group alone. Considering the poor prognosis of this group, antiviral therapy with NAs may help improve survival in patients undergoing surgery for huge HCC.

Consistent with other studies[10,11,17], the present results showed that male sex, vascular invasion, multiple tumours, advanced differentiation grade and major hepatectomy were more common in patients with larger tumours. The lower incidence of chronic HCV infection in the huge HCC group in the present study was also similar to the findings of Lim and colleagues[11]. However, the finding of a higher incidence of chronic HBV infection in the huge HCC group in the present study was not significant in their study.

The 5-year overall survival rate for patients with huge HCCs after surgical resection was consistent with rates in recent large studies[17–19]. Notably, earlier large studies[20–22] investigating outcomes of patients with huge HCC reported lower 5-year overall survival rates. This might indicate that improvements have been made with use of multidisciplinary therapy for huge HCC. These studies, however, are based on survival results for patients with huge HCC treated in Asian countries. A geographical difference in survival might exist between Western and Eastern countries. In the USA, Shrager and co-workers[23] investigated 130 patients with huge HCC and showed a lower 5-year overall survival rate of 18·8 per cent. Regarding longer follow-up, several studies have reported 10-year overall survival rates ranging from 2·9 to 25·6 per cent in patients with huge HCC after partial hepatectomy[13,21,22,24].

The present finding of an inverse association between tumour size and long-term survival for patients with HCC is consistent with the results of a Japanese population-based study investigating over 25 000 patients with HCC undergoing hepatic resection[25]. That study reported overall survival rates in relation to tumour size slightly worse than the present results. This is probably because the Japanese

study included a higher percentage (more than 70 per cent) of chronic HCV infection. However, several studies have not indicated that huge HCC is an unfavourable prognostic factor. Allemann and colleagues[26] compared outcomes of patients with HCC after liver resection by tumour size, and found that patients with huge HCC had a longer median survival and better 5-year overall survival. Classifying patients with solitary HCC according to tumour size in three groups, Lim and co-workers[11] reported a better 5-year overall survival among patients with tumours smaller than 5 cm compared with those with lesions of 5–10 cm, or more than 10 cm in size. Because there was no significant difference in overall survival between patients with tumour sizes 5–10 cm and more than 10 cm, they concluded that, above 5 cm, tumour size did not matter for patients with HCC. Notably, the 5-year overall survival rates for patients with large HCC and huge HCC were higher than the rates in the present series, possibly because the latter study included both solitary and multiple tumours, and the groups with larger tumour size had a higher percentage of multiple tumours. In another study[27] using a similar classification of tumour size into three groups, overall survival rates in the huge HCC group and the large HCC group were similar.

Vascular invasion, multiple lesions and cirrhosis have previously been recognized as poor prognostic factors for patients with huge HCC after liver resection[11,18,21]. The present results support these findings. Other prognostic factors for patients with huge HCC after hepatectomy identified previously were α-fetoprotein (AFP) level, histopathological grade, surgical margin[17], intraoperative transfusion[19] and indocyanine green retention rate at 15 min (ICG-R15)[20].

Antiviral therapy with NAs is effective for suppressing DNA levels of HBV[28]. A high viral DNA load of HBV is the most important correctable risk factor for recurrence, and a previous study focusing on antiviral therapy showed that NAs decreased the recurrence rate after curative surgery for HBV-related HCC[29]. In a meta-analysis[30] evaluating the effectiveness of NAs after curative surgery in patients with HBV-related HCC, 5-year overall survival of the treatment group was better than that of the control group. Nishikawa and colleagues[28] demonstrated that use of NAs either before or after curative hepatectomy was a favourable predictor of overall survival. They suggested that maintaining viral suppression and reducing the risk of hepatic events, such as liver cirrhosis-related complications, by NA therapy could lead to improved survival after curative therapy. Many patients with HCC had a history of chronic HBV infection in the present study, and the percentage of HBV-related HCC was highest in the huge HCC group. This might partially explain why the use of NAs had a beneficial effect on the long-term survival of patients with huge HCC.

There are several limitations to this study. First, because not all databases provided molecular profiles such as preoperative AFP, viral load or serum ICG-R15, it was not possible to control for these in the survival analysis. Second, it was unclear which categorization of tumour size was the best to use in the survival analysis for patients with HCC. Comparison between different classifications of size of HCC was beyond the scope of this study. Finally, although the present study intended to analyse patients with HCC on a nationwide base, it covered only approximately 70 per cent of patients with newly diagnosed HCC annually in Taiwan.

Acknowledgements

The authors thank the Health and Welfare Data Science Centre, Ministry of Health and Welfare, Taiwan, for providing data for analyses.
Disclosure: The authors declare no conflict of interest.

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