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Original Article

Prognostic grade for resecting hepatocellular carcinoma: multicentre retrospective study

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Abstract

Background: Surgical treatment for hepatocellular carcinoma (HCC) is advancing, but a robust prediction model for survival after resection is not available. The aim of this study was to propose a prognostic grading system for resection of HCC.

Methods: This was a retrospective, multicentre study of patients who underwent first resection of HCC with curative intent between 2000 and 2007. Patients were divided randomly by a cross-validation method into training and validation sets. Prognostic factors were identified using a Cox proportional hazards model. The predictive model was built by decision-tree analysis to define the resection grades, and subsequently validated.

Results: A total of 16 931 patients from 795 hospitals were included. In the training set (8465 patients), four surgical grades were classified based on prognosis: grade A1 (1236 patients, 14.6 per cent; single tumour 3 cm or smaller and anatomical R0 resection); grade A2 (3614, 42.7 per cent; single tumour larger than 3 cm, or non-anatomical R0 resection); grade B (2277, 26.9 per cent; multiple tumours, or vascular invasion, and R0 resection); and grade C (1338, 15.8 per cent; multiple tumours with vascular invasion and R0 resection, or R1 resection). Five-year survival rates were 73.9 per cent (hazard ratio (HR) 1.00), 64.7 per cent (HR 1.51, 95 per cent c.i. 1.29 to 1.78), 50.6 per cent (HR 2.53, 2.15 to 2.98), and 34.8 per cent (HR 4.60, 3.90 to 5.42) for grades A1, A2, B, and C respectively. In the validation set (8466 patients), the grades had equivalent reproducibility for both overall and recurrence-free survival (all $P < 0.001$).

Conclusion: This grade is used to predict prognosis of patients undergoing resection of HCC.

Introduction

Liver resection has a leading role in the treatment of hepatocellular carcinoma (HCC). Worldwide data sets have confirmed improvement in patient outcomes, including 5-year survival rates of 50–70 per cent, operative mortality rates of 1–5 per cent, and declining global mortality[1–3]. Surgical practice for HCC has become better established by use of prognostic models[4,5]. Liver resection needs to be planned on an individual basis to maximize the surgical impact.

Representative clinical guidelines for treating HCC have proposed conflicting recommendations for surgery[6,7]. Liver resection can be indicated in patients who have up to three tumours of any size according to the Japanese algorithm[6], but is more restricted according to Western guidelines[7]. The newest TNM classification for HCC[8] categorizes patients based only on tumour-related factors, enabling suggestions for the prognosis of each patient. Nomograms are a feasible option for predicting patient survival[9], but an easy-to-use prognostic tool is preferable for surgical patients with HCC.

The aim of this study was to define and validate the prognostic value of resection grade for patients undergoing surgery for HCC.

Methods

This was a multicentre retrospective study with data collected by the Liver Cancer Study Group of Japan (LCSGJ). Since 1965, the

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LCSGJ has conducted biannual surveys for patients with HCC by using a standardized platform for reporting clinical measures[10]. The principal doctors from 795 hospitals throughout Japan answered 135 questionnaires regarding patient characteristics, diagnosis and treatment for HCC, and patient outcomes. HCC was diagnosed based on imaging studies, clinical data, and pathological studies. After registration, the patients were followed at each institute, according to the clinical practice guidelines for HCC[6].

Clinicopathological data for patients with primary liver cancer were collected from the 16th (2000–2001), 17th (2002–2003), 18th (2004–2005), and 19th (2006–2007) nationwide surveys by the LCSGJ[10]. For updating survival data[10], the principal doctor at each hospital was responsible for reporting 29 questionnaires biyearly regarding HCC recurrence and patient survival after surgery. Patients who underwent resection for HCC as the first treatment with curative intent, and with complete data regarding tumour status, liver function, and prognosis, were included. The patients were divided randomly into training and validation sets (1 : 1 ratio) by a cross-validation method.

Liver resection

According to the Japanese guidelines for HCC[6], liver resection was indicated for patients who had up to three tumours of any size. The surgical indication was based on hepatic functional reserve mainly according to Makuuchi's criteria[11], which included no accumulation of ascites, a total bilirubin level below 2.0 mg/dl, and indocyanine green retention rate at 15 min (ICG-R15) below 30 per cent. The use of these criteria resulted in an operative mortality rate (within 30 days) of less than 1 per cent in the LCSGJ surveys[10,11]. The acceptable hepatic volume to be resected was defined according to the patient's liver function: removal of approximately two-thirds of the liver was permitted when ICG-R15 was less 10 per cent (indicating normal background liver), removal of one-third when ICG-R15 was below 20 per cent (chronic hepatitis), and removal of one-sixth when ICG-R15 was less than 30 per cent (cirrhosis)[11]. Routine protocols for managing elective resection for HCC have been described elsewhere[12,13].

Anatomical resection was defined as complete resection of the target segment(s) harbouring HCC lesions, resulting in total exposure of landmark vessels that frame the segmental territory, such as the major hepatic vein(s)[11,13,14], including monosegmentectomy, disegmentectomy, trisegmentectomy, and hemihepatectomy (*Fig. S1*). After resection of HCC, residual tumour (R) was defined as R0 (no residual tumour) or R1 (macroscopic residual tumour)[4,15].

Decision-tree analysis

Grading for resection of HCC was determined as follows: prognostic factors for patient survival were identified by use of a Cox proportional hazards model in the training set, with $P < 0.050$ set as cut-off value for elimination, and a decision tree was built using significant factors. The software SPSS® Clementine version 12.0 (IBM, Armonk, New York, USA) was used to explore the data to search for optimal split variables, build a decision-tree structure, and classify the subjects into homogeneous groups based on the outcome of interest. The entire study population was investigated at every step of analysis to determine which variable(s) yielded the most significant division into two prognostic groups. The resulting final groups with 5-year overall survival in a tree-style form were most homogeneous for predicting the probability of survival.

Statistical analysis

Univariable and multivariable analyses were used to evaluate the effect of each tumour and surgical factor on prognosis. The results of multivariable analysis were expressed as coefficients, standard errors, and hazard ratios with 95 per cent confidence intervals. Overall survival was estimated using a Cox proportional hazards model to define the prognostic impact of the resection grade. Using a cross-validation method, patients were randomly divided in a 1 : 1 ratio into training and validation sets. The discriminatory power of the grading system was compared by using Harrell's concordance index (C-index) between training and validation sets[16]. $P < 0.050$ was considered statistically significant. All statistical analyses were conducted using SAS® version 9.2 (SAS Institute, Cary, North Carolina, USA).

Results

Of 77 268 patients registered with HCC, 16 931 patients from 795 hospitals were included in the study (*Fig. 1*). Median follow-up was 16.5 years. Patients were divided randomly into training (8465) and validation (8466) cohorts.

Training set

In the training cohort, 16 baseline characteristics were evaluated, and binary comparisons showed significant associations between all variables and 5-year survival, except for sex and age (*Table 1*). Univariable and multivariable analyses identified six tumour-related and surgical variables that were predictors of patient survival (all $P<0.001$) (*Table 2*). These included vascular invasion, multiple tumours, tumour size, residual tumour, non-anatomical resection, and positive surgical margin.

Decision-tree model

Using these predictors, the decision-tree analysis selected five variables to classify seven subgroups of patients (*Fig. 2*). Tumour residue was identified as the first predictor of patient survival, followed by vascular invasion, multiple tumours,

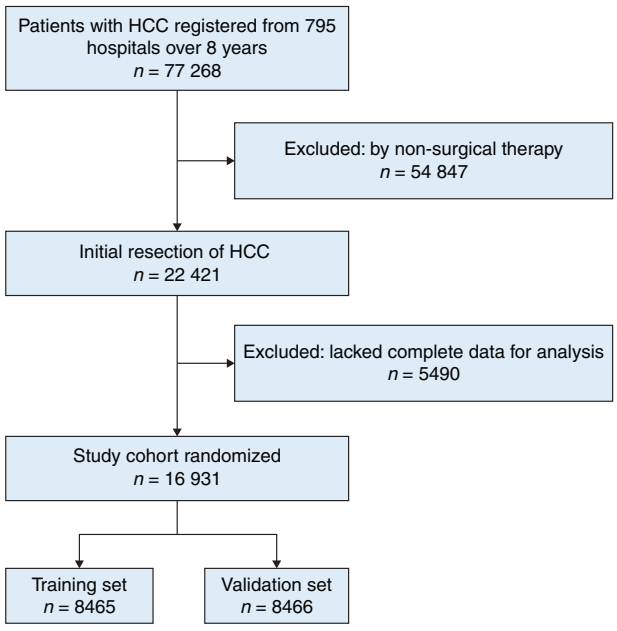


Fig. 1 Study flow chart

HCC, hepatocellular carcinoma.

Table 1 Patient characteristics in training set

	No. of patients	5-year survival (%)	Median survival (months)	P
Sex				0.921
M	6544	57.5	73.6	
F	1921	56.3	73.6	
Age (years)				0.456
<60	1957	57.9	84.0	
≥ 60	6019	56.8	71.7	
Hepatitis virus infection				< 0.001
HBsAg+/HCV-Ab–	1511	59.3	86.8	
HBsAg–/HCV-Ab+	4513	53.8	65.4	
HBsAg+/HCV-Ab+	145	57.2	72.8	
HBsAg–/HCV-Ab–	2003	64.1	n.r.	
Bilirubin (mg/dl)				< 0.001
<1.0	5994	58.7	82.4	
≥ 1.0	2311	53.8	65.4	
Albumin (g/dl)				< 0.001
<3.5	1465	43.0	51.0	
≥ 3.5	6769	60.6	83.9	
Platelet count (per μl)				< 0.001
$<10^5$	1892	53.1	62.1	
≥ 10^5	6358	58.8	83.9	
ICG-R15 (%)				< 0.001
<20	5591	60.7	91.4	
≥ 20	2198	49.4	58.2	
Child–Pugh grade				< 0.001
A	7335	59.3	81.4	
B	785	41.4	46.4	
Cirrhosis				< 0.001
No	3841	63.3	n.r.	
Yes	3595	51.9	63.3	
Tumour diameter (cm)				
≤ 2	1540	71.2	n.r.	< 0.001
>2	6856	54.6	69.4	
≤ 3	3637	66.9	91.4	< 0.001
>3	4759	50.5	61.0	
≤ 5	6040	62.8	84.3	< 0.001
> 5	2356	44.4	45.9	
Tumour number				< 0.001
Single	6111	63.0	93.2	
Multiple	2325	43.5	49.4	
Vascular invasion				< 0.001
No	6742	62.4	86.0	
Yes	1562	36.8	33.3	
α-Fetoprotein (ng/ml)				< 0.001
<20	3909	67.3	n.r.	
≥ 20	4221	48.2	57.1	
PIVKA-II (munits/ml)				< 0.001
<40	2717	68.3	91.4	
≥ 40	4248	54.2	69.6	
Surgical margin				< 0.001
Negative	7852	59.0	81.5	
Positive	579	38.6	39.8	
Tumour residue				< 0.001
No	7955	59.4	81.6	
Yes	510	26.0	22.6	

HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis V virus antibody; n.r., not reached; ICG-R15, indocyanine green retention rate at 15 min; PIVKA-II, protein induced by vitamin K antagonist II.

tumour size (over 3.0 cm), and non-anatomical resection as the final split. The model comprised seven subgroups of patients with 5-year mortality rates after surgery ranging from 14.5 to 49.8 per cent.

Resection grade

Prognostic data were integrated to classify patients with HCC into three independent resection grades (A, B, and C), with two subgrades (A1 and A2) (*Fig. 3*): grade A1—single tumour 3 cm or smaller without vascular invasion and anatomical R0 resection; grade A2—single tumour larger than 3 cm without vascular invasion, or non-anatomical R0 resection; grade B—multiple tumours, or single tumour with macroscopic vascular invasion, and R0 resection; and grade C—multiple tumours with vascular invasion and R0 resection, or any resulting in R1 resection.

Anatomical resection, including monosegmentectomy (23.4 per cent), bisegmentectomy/trisegmentectomy (20.7 per cent), or hemihepatectomy/extended hemihepatectomy (22.8 per cent), was performed in 11 323 patients (66.9 per cent), non-anatomical resection (limited or random resection) in 5352 patients (31.6 per cent), and an unknown procedure in 256 patients (1.5 per cent). The perioperative mortality rate was 0.8 per cent.

Table 2 Logistic regression analysis of tumour and surgical factors to identify predictors of survival

	Univariable analysis				Multivariable analysis			
	Coefficient	Standard error	Hazard ratio	P	Coefficient	Standard error	Hazard ratio	P
Tumour factors								
Vascular invasion	1.01	0.05	2.74 (2.50, 3.00)	< 0.001	0.69	0.05	2.00 (1.81, 2.21)	< 0.001
Multiple tumours	0.65	0.04	1.91 (1.76, 2.08)	< 0.001	0.46	0.05	1.58 (1.44, 1.73)	< 0.001
Tumour size (cm)	0.71	0.07	2.03 (1.78, 2.31)	< 0.001				
>2 versus ≤2	0.67	0.05	1.95 (1.78, 2.13)	< 0.001				
>3 versus ≤3	0.72	0.04	2.06 (1.89, 2.24)	< 0.001				
≤ 2							1.00 (reference)	
>2, ≤ 3					0.32	0.08	1.38 (1.18, 1.61)	< 0.001
>3, ≤ 5					0.56	0.08	1.75 (1.50, 2.03)	<0.001
>5					0.88	0.08	2.42 (2.08, 2.82)	< 0.001
Surgical factors								
Tumour residue	1.15	0.06	3.15 (2.79, 3.57)	< 0.001	0.61	0.08	1.83 (1.58, 2.13)	< 0.001
Surgical margin positive	0.74	0.06	2.10 (1.85, 2.37)	< 0.001	0.43	0.07	1.54 (1.34, 1.76)	< 0.001
Non-anatomical resection*	–0.19	0.05	1.21 (1.11, 1.33)	< 0.001	0.20	0.05	1.21 (1.09, 1.35)	< 0.001

Values in parentheses are 95 per cent confidence intervals. *Including any type of non-systematic resection, leaving a part of the tumour-bearing portal region (5352, 31.6 per cent). Others were anatomical resection, achieving systematic resection of the target segment(s) or hemiliver (11 323, 66.9 per cent), and unknown procedure (256, 1.5 per cent).

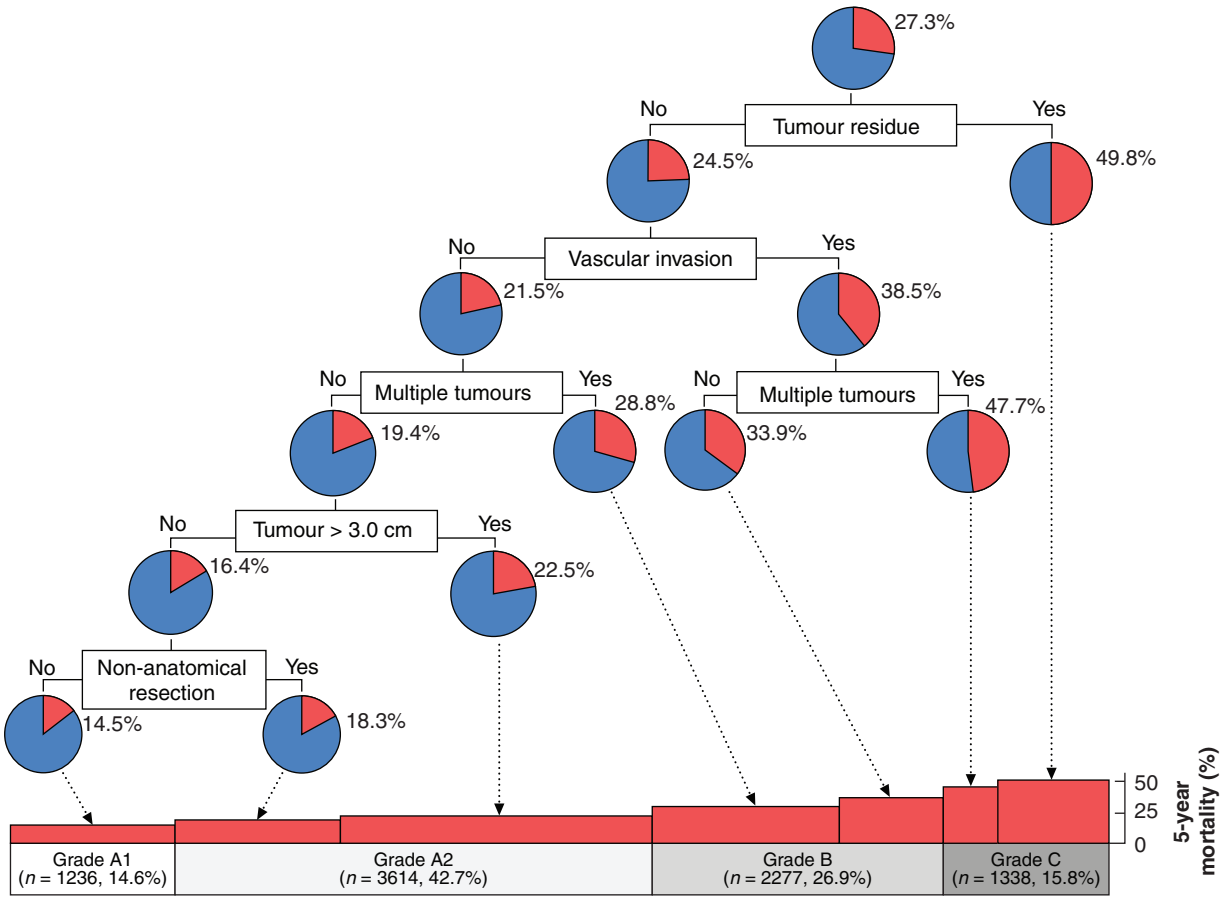


Fig. 2 Decision-tree analysis

The analysis selected five predictors to classify seven patient subgroups. The factor 'surgical margin' was not included owing to collinearity with tumour residue.

Validation set

Overall survival differed according to resection grade in the validation set (*Fig. 4*). In both sets, estimated 5-year survival rates and hazard ratios for mortality were related to resection grade and were very similar (all $P<0.001$) (*Table 3*). The C-index was the same in the two sets (both 0.62).

Resection grade could also differentiate recurrence-free survival. Five-year recurrence-free survival rates were 45.2, 36.9,

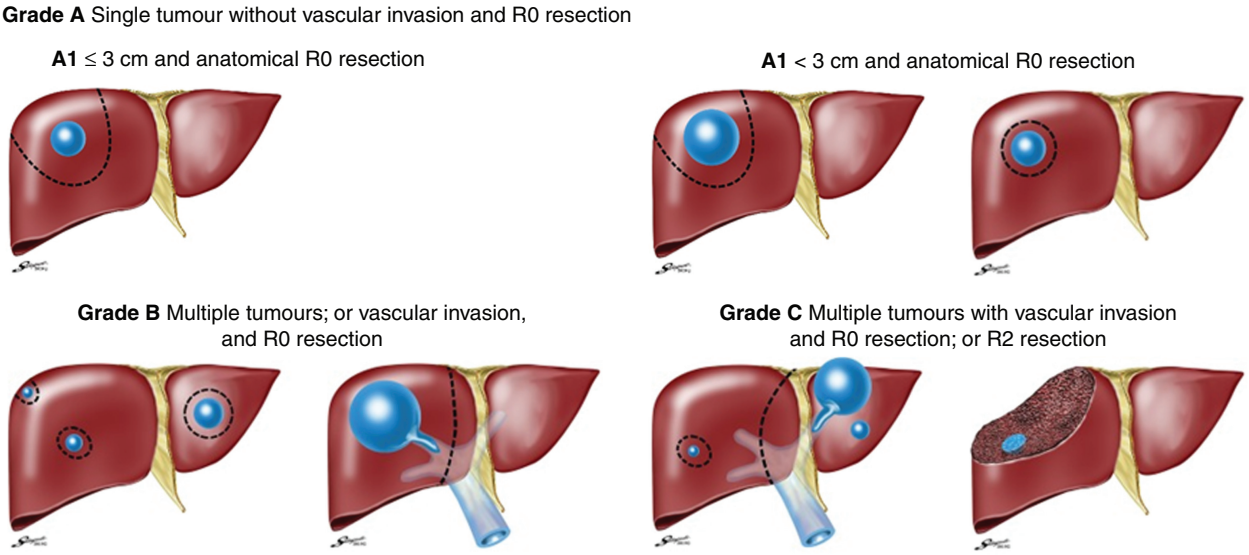
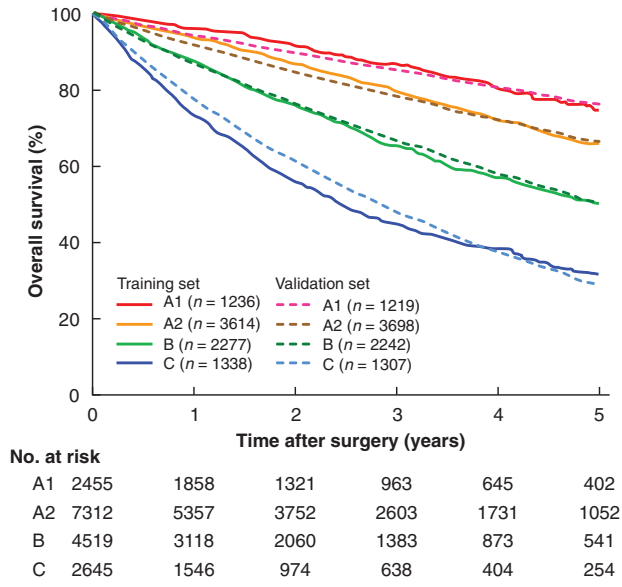


Fig. 3 Resection grades



No. at risk

A1	2455	1858	1321	963	645	402
A2	7312	5357	3752	2603	1731	1052
B	4519	3118	2060	1383	873	541
C	2645	1546	974	638	404	254

Fig. 4 Overall survival according to resection grade in training and validation sets

P<0.001 for comparison of survival across resection grades in training and validation sets combined (log rank test).

24.4, and 13.8 per cent for patients with resection grades A1, A2, B, and C, respectively (*Fig. 5*).

Discussion

Resection grade has been designed to guide optimal liver resection, resulting in good prediction of patient survival after resection of HCC. The model based on the training set stratified patients into four groups (grades A1, A2, B, and C) according to estimated survival after surgery. This was reproducible in the validation set, and resection grade may therefore be of clinical use.

This model involved only five factors. Excluded variables were tumour markers, microvascular invasion, and tumour cellular differentiation. These have been shown to be rather more accurate predictors of poor prognosis than decision-making tools for surgery[17]. Nomograms with more than ten variables are complicated but also may have better predictability than the present prediction model[9]. The advantage of resection grade, however, is that it is based only on clinically solid and indispensable variables. Resection grade can be applied simply to real-time practice in HCC resection.

Tumour size was the only continuous variable, and the 3-cm cut-off would be best suited as threshold based on evidence-based guidelines[6,7], whereas the 2-cm value led to overestimation of the prognostic forecast because such small tumours are frequently (25 per cent) precursor lesions of HCC[18,19]. As regards surgical factors, tumour residue was selected as the most important determinant, and surgical margin was not included because of its collinearity with tumour residue.

The resection grade system links prognostic prediction to surgical decision-making. Grade A1 requires anatomical resection for a single HCC 3 cm or smaller without vascular invasion, leading to the highest probability of 5-year survival. These tumour and surgical factors for grade A1 extracted from the decision-tree analysis are further supported by the findings of the LCSGJ study (5781 patients)[20], which showed the value of anatomical resection of single and small (3 cm or less) HCC, and a meta-regression analysis[21] that demonstrated the prognostic benefits of anatomical resection for non-invasive HCC. Moreover, anatomical resection of tumours in this grade will be better than non-anatomical resection, as suggested by a propensity score matching study[22] and systematic review[23]. If these conditions are not met, the tumour falls into the grade A2 group. In grade A as a whole, 5-year survival rates of around 70 per cent indicate a potential surgical cure[18,19,24] for the target HCC, unless multicentre recurrence develops in the remnant liver.

Grades B and C are associated with advanced HCC with multiple tumours or/and vascular invasion. The 5-year survival rate for grade B is within a standard international range[4,7,10], whereas that for grade C is dismal because of coexisting unfavourable tumour factors or tumour residue. Recent LCSGJ studies have shown that patients with multiple (up to 3) tumours[25] and those with portal or hepatic vein invasion[5,26] could benefit from liver resection, with longer survival outcomes than achieved with non-surgical treatment. Although resection of such advanced HCCs would not usually lead to cure, surgeons need to strive for

Table 3 Validation of resection grade

	Training set (n = 8465)					Validation set (n = 8466)				
	No. of patients*	Deaths	5-year survival (%)	Hazard ratio†	P	No. of patients*	Deaths	5-year survival (%)	Hazard ratio†	P
Resection grade										
A1	1236 (14.6)	179	73.9	1.00 (reference)		1219 (14.4)	183	74.8	1.00 (ref.)	
A2	3614 (42.7)	760	64.7	1.51 (1.29, 1.78)	< 0.001	3698 (43.7)	739	66.0	1.43 (1.21, 1.68)	< 0.001
B	2277 (26.9)	712	50.6	2.53 (2.15, 2.98)	< 0.001	2242 (26.5)	724	50.4	2.52 (2.14, 2.96)	< 0.001
C	1338 (15.8)	662	34.8	4.60 (3.90, 5.42)	< 0.001	1307 (15.4)	667	31.5	4.71 (4.00, 5.55)	< 0.001
C-index				0.62 (0.60, 0.63)					0.62 (0.60, 0.63)	

Values in parentheses are * percentages and † 95 per cent confidence intervals. C-index, concordance index. $P < 0.001$ (test for trend in both training and validation tests).

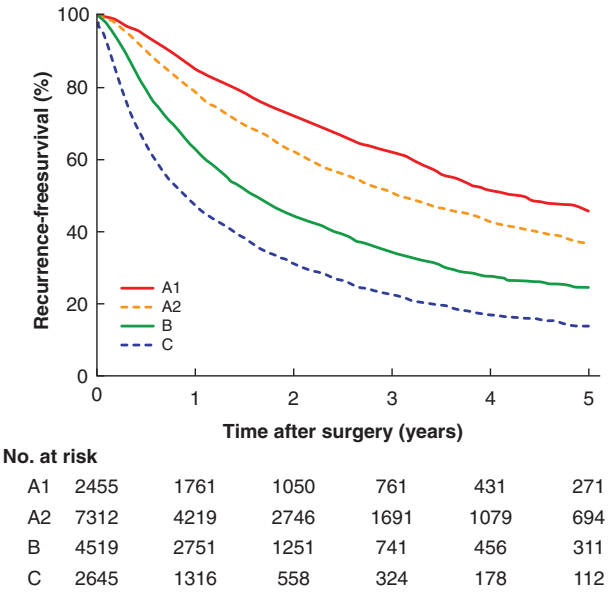


Fig. 5 Recurrence-free survival according to resection grade

$P < 0.001$ (log rank test).

R0 resection whenever possible[15]. Consequently, liver resection is tailored according to the resection grading system to maximize the surgical efficacy.

The C-index for the validation set was similar to that of the Barcelona Clinic Liver Cancer (BCLC) system (0.64)[7,27]. In the present study, patients were selected according to Makuuchi's criteria. This may have led to a cohort of patients with a favourable prognosis (BCLC stage 0 or A)[2,24,28]. This study, however, also included those with multiple tumours (stage B) and vascular invasion (stage C). Recent evidence supports expanded use of surgery[2,4,5,25,26,28]. The present grading system can be used for a wider surgical indication than BCLC stage. Limitations of the present study include the retrospective design and lack of validation in a cohort outside Japan.

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Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

References

1. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med* 2007;**356**:1545–1559
2. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G *et al.* A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to EASL/AASLD recommendations?: An observational study of study of the HCC East–West Study Group. *Ann Surg* 2013;**257**:929–937
3. Bertuccio P, Turati F, Carioli G, Rodriguez T, Vecchia CL, Malvessi M *et al.* Global trends and predictions in hepatocellular carcinoma mortality. *J Hepatol* 2017;**67**:302–309
4. Tsilimigras DI, Moris D, Hyer JM, Bagante F, Sahara K, Moro A *et al.* Hepatocellular carcinoma tumour burden score to stratify prognosis after resection. *Br J Surg* 2020;**107**:854–864
5. Zhang XP, Wang K, Gao YZ, Wei XB, Lu CD, Chai ZT *et al.* Prognostic model for identifying candidates for hepatectomy among patients with hepatocellular carcinoma and hepatic vein invasion. *Br J Surg* 2020;**107**:865–877
6. Kokudo N, Hasegawa K, Akahane M, Igaki H, Izumi N, Ichida T *et al.* Evidence-based clinical guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2013 *Update*. *Hepatol Res* 2015;**45**:123–127
7. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 2016;**150**:835–853
8. Kamarajah SK, Frankel TL, Sonnenday C, Cho CS, Nathan H. Critical evaluation of the American Joint Commission on Cancer (AJCC) 8th edition staging system for patients with hepatocellular carcinoma (HCC): a Surveillance, Epidemiology, End Results (SEER) analysis. *J Surg Oncol* 2018;**117**:644–650
9. Burkhart RA, Pawlik TM. Staging and prognostic models for hepatocellular carcinoma and intrahepatic cholangiocarcinoma. *Cancer Control* 2017;**24**:1–11
10. Kudo M, Izumi N, Sakamoto M, Matsuyama Y, Ichida T, Nakashima O *et al.* Survival analysis over 28 years of 173 378

patients with hepatocellular carcinoma in Japan. *Liver Cancer* 2016;**5**:190–197
11. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S *et al.* Surgery for small liver cancers. *Semin Surg Oncol* 1993;**9**:298–304
12. Yamazaki S, Takayama T, Moriguchi M, Mitsuka Y, Okada S, Midorikawa Y *et al.* Criteria for drain removal following liver resection. *Br J Surg* 2012;**99**:1584–1590
13. Takayama T, Midorikawa Y, Higaki T, Nakayama H, Moriguchi M, Aramaki O *et al.* Algorithm for resecting hepatocellular carcinoma in the caudate lobe. *Ann Surg* 2019; DOI: 10.1097/SLA.0000000000003384 [Epub ahead of print]
14. Shindoh J, Makuuchi M, Matsuyama Y, Mise Y, Arita J, Sakamoto Y *et al.* Complete removal of the tumor-bearing portal territory decreases local recurrence and improves disease-specific survival of patients with hepatocellular carcinoma. *J Hepatol* 2016;**64**:594–600
15. Aoki T, Kubota K, Hasegawa K, Kubo S, Izumi N, Kokudo N *et al.* Significance of the surgical hepatic resection margin in patients with a single hepatocellular carcinoma. *Br J Surg* 2020;**107**:113–120
16. Harrell FE Jr, Califf RM, Pryor DB, Lee KL, Rosani RA. Evaluating the yield of medical tests. *JAMA* 1982;**247**:2543–2546
17. Erstad DJ, Tanabe KK. Prognostic and therapeutic implications of microvascular invasion in hepatocellular carcinoma. *Ann Surg Oncol* 2019, **26**:1474–1493
18. Takayama T, Makuuchi M, Hirohashi S, Sakamoto M, Yamamoto J, Shimada K *et al.* Early hepatocellular carcinoma as an entity with a high rate of surgical cure. *Hepatology* 1998;**28**:1241–1246
19. Midorikawa Y, Takayama T, Shimada K, Nakayama H, Higaki T, Moriguchi M *et al.* Marginal survival benefit in the treatment of early hepatocellular carcinoma. *J Hepatol* 2013;**58**:306–311
20. Eguchi S, Kanematsu T, Arii S, Okazaki M, Okita K, Omata M *et al.* Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. *Surgery* 2008;**143**:469–475
21. Cucchetti A, Cescon M, Ercolani G, Bigonzi E, Torzilli G, Pinna AD. A comprehensive meta-regression analysis on outcome of anatomic resection *versus* nonanatomic resection for hepatocellular carcinoma. *Ann Surg Oncol* 2012;**19**:3697–3705
22. Kaibori M, Kon M, Kitawaki T, Kawaura T, Hasegawa K, Kokudo N *et al.* Comparison of anatomic and non-anatomic hepatic resection for hepatocellular carcinoma. *J Hepatobiliary Pancreat Sci* 2017;**24**:616–626
23. Moris D, Tsilimigras DI, Kostakis ID, Ntanasis-Stathopoulos I, Shah KN, Felekouras E *et al.* Anatomic *versus* non-anatomic resection for hepatocellular carcinoma: a systematic review and meta-analysis. *Eur J Surg Oncol* 2018;**44**:927–938
24. Lim C, Bhangui P, Salloum C, Gómez-Gavara C, Lahat E, Luciani A *et al.* Impact of time to surgery in the outcome of patients with liver resection for BCLC 0-A stage hepatocellular carcinoma. *J Hepatol* 2018;**68**:100–108
25. Fukami Y, Kaneoka Y, Maeda A, Kumada T, Tanaka J, Akita T *et al.* Liver resection for multiple hepatocellular carcinomas: a Japanese nationwide survey. *Ann Surg* 2020;**272**:145–154
26. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M *et al.* Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. *J Hepatol* 2016;**65**:938–943
27. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul JL *et al.* EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2018;**69**:182–236
28. Kim H, Ahn SW, Hong SK, Yoon KC, Kim HS, Choi YR *et al.* Survival benefit of liver resection for Barcelona Clinic Liver Cancer stage B hepatocellular carcinoma. *Br J Surg* 2017;**104**:1045–1052