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Significant Improvement in Long-Term Survival after Liver Resection for Hepatocellular Carcinoma: Evolving Outcomes over 20 Years

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Purpose: Advanced techniques and multidisciplinary approaches have improved hepatocellular carcinoma (HCC) surgical outcomes. This study updates the long-term survival after liver resection (LR) for HCC based on over 20 years of experience.
Materials and Methods: Between 1996 and 2017, 1963 patients with HCC underwent LR. After excluding 185 patients who received preoperative therapy, 1778 treatment-naïve HCC patients were included. Clinicopathological characteristics and surgical outcomes were compared across three periods: 1 (1996–2007), 2 (2008–2012), and 3 (2013–2017). Prognostic factors for overall survival (OS) and disease-free survival (DFS) were analyzed using Cox regression analysis.
Results: Recent trends indicate increased diagnoses at older ages, number of non-B and non-C HCC cases and decreased incidence of cirrhosis. Minor, non-anatomical, and minimally invasive LR have become more prevalent. In period 3, short-term outcomes improved, as 90-day mortality decreased to 0.3% and major complications to 5.0%. Long-term outcomes improved (5-year OS: 68.1% vs. 80.7% vs. 90.5%, $p<0.001$; 5-year DFS: 41.4% vs. 50.7% vs. 61.1%, $p<0.001$), and early recurrence rates decreased in period 3 (34.0% vs. 34.0% vs. 25.8%, $p<0.001$). Factors such as smaller tumor size, decreased incidence of cirrhosis, fewer intraoperative transfusions, and fewer major complications have contributed to improved OS and DFS.
Conclusion: Remarkable improvements in 5-year OS and DFS were observed after curative LR for HCC, particularly in period 3. Advancements in surgical outcomes, including very low short-term mortality, along with improved surgical techniques, early detection, and refined patient selection, are likely key factors in this progress.

Key Words: Hepatocellular carcinoma, long-term outcomes, liver resection

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most prevalent type of cancer worldwide.[1] HCC is one of the most lethal malignancies and the second leading cause of cancer-related death in Korea.[2] Liver resection (LR) is the mainstay of curative treatment according to current treatment guidelines for HCC, considering the shortage of liver transplantation donors. Over the past few decades, several studies have reported significant improvements in survival, operative mortality, and morbidity rates after LR for HCC.[3-5] Several factors, including advancements in surgical techniques as a major contributor, have been implicated in these improvements.[5,6]

A decade ago, Han, et al.[7] reported surgical and long-term oncological outcomes of LR for HCC at our institution, demonstrating a 5-year overall survival (OS) rate of 64.4% and an improvement in OS after 2003. Minimally invasive surgery has been globally adopted, including in the field of LR, and has advanced to enable the execution of complex minimally invasive LR.[8] Our institution has adopted laparoscopic and robotic LR, in addition to open LR, as the primary surgical modalities over the past decade.[9,10] We aimed to provide an updated report, reflecting these changes, on the characteristics of patients with

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HCC, surgical outcomes, and long-term oncological outcomes based on our institution's 21-year experience with LR for HCC.

MATERIALS AND METHODS

Study population

Between January 1996 and December 2017, data from 1963 patients who underwent LR for HCC at Severance Hospital in Seoul, Korea, were retrospectively reviewed. Among these patients, 185 who had received preoperative treatment for HCC, such as transarterial chemoembolization (TACE) or radiofrequency ablation (RFA), were excluded. Surgical and long-term outcomes were analyzed for 1778 treatment-naïve patients who underwent primary curative LR for HCC. Curative resection was defined as grossly complete tumor resection without any microscopic involvement of the resection margin.

This study was reviewed and approved by the Yonsei University Institutional Review Board, which waived the requirement for informed consent (No. 4-2023-0806).

Surgical indication and postoperative follow-up for HCC

At our institution, patients with HCC were managed by a multidisciplinary team. LR was recommended for patients with preserved liver function, if the tumor was considered resectable with an adequate future liver remnant volume. Patients underwent postoperative evaluation for serum tumor markers [alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II)] and regular dynamic computed tomography (CT). The follow-up schedule included evaluations every 3 months in the first year, every 3–6 months in the second year, and every 6 months thereafter. In cases where CT scans indicated potential recurrence, magnetic resonance imaging was performed. A multidisciplinary team determined the appropriate treatment for recurrent lesions, including TACE, RFA, repeated resection, or liver transplantation.

Surgical procedures

Our institution initiated laparoscopic wedge resection of the liver in 2002, commencing our implementation of minimally invasive LR. In 2006, we introduced laparoscopic left lateral sectionectomy, an anatomic LR procedure. In 2007, we expanded our capabilities to perform major LRs, including laparoscopic left and right hepatectomies. The first robotic LR for HCC in the left lateral section was performed in 2007,[9] and major robotic LRs became more common in 2009.[11]

Parenchymal transection was mainly performed using a Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab, Boulder, CO, USA) using open and laparoscopic approaches. Surgical techniques for robotic LR have been reported previously.[11] During robotic LR, the liver parenchyma was transected using a harmonic scalpel and Maryland bipolar forceps. Our institution has employed the standardized rubber band traction technique during parenchymal dissection, initially in open LRs, and subsequently in robotic and laparoscopic approaches.[10,12] The Pringle maneuver was selectively applied, and low central venous pressure was maintained during LR through balanced fluid management.

The surgical type was categorized as anatomic or non-anatomic LR, and further classified based on the extent of LR (minor or major). Anatomic LR involves the resection of at least one liver segment as defined by Couinaud's classification.[13] Non-anatomic LR was defined as LR regardless of Couinaud's classification. Depending on the extent of the operation, minor LR included two or fewer segments, and major LR included three or more segments.[14,15] Recently, there has been a shift toward a tailored surgical approach for determining the extent of LR, considering the tumor size, features, and location, with a focus on preserving liver volume. Intraoperative ultrasonography was routinely used for non-anatomic LR.

Clinical and histopathologic characteristics

Preoperative clinical and histopathological data were retrospectively collected. Demographic and medical information, including age, sex, body mass index, etiology of liver disease [hepatitis B virus (HBV), hepatitis C virus (HCV), and non-B, non-C (NBNC) hepatitis], AFP, and PIVKA-II, was collected from electronic medical records (EMRs). We examined whether any other treatments were performed prior to surgery and whether antiviral agents were prescribed after surgery. Whether repeat LR or liver transplantation was performed for recurrent HCC during follow-up after hepatectomy was also reviewed.

The following pathological information was extracted from pathology reports and evaluated: tumor size (cm), tumor number (single or multiple), histologic tumor grade based on the Edmondson-Steiner criteria (I–II/III–IV), presence of cirrhosis in background liver tissue, microscopic vascular invasion (MVI), and surgical margin (cm). The HCC staging classification was determined using the 8th edition of the American Joint Committee on Cancer (AJCC) staging system.

Surgical and long-term oncologic outcomes

OS was defined as the time from surgery to death (all causes) or the date of the last follow-up. Disease-free survival (DFS) was defined as the time during which a patient remained free from HCC recurrence after surgery. In addition, subgroup analyses of OS and DFS were performed according to the AJCC staging system. Early HCC recurrence was defined as recurrence within 2 years. The following variables were analyzed to compare surgical outcomes across periods: operative time, estimated blood loss (EBL), intraoperative transfusion, length of postoperative hospital stay, 30-day mortality, 90-day mortality, in-hospital mortality, and postoperative complications. Complications were graded using the Clavien–Dindo classification system.[16] Major complications were defined as complications greater than grade III.

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Statistical analysis

To compare changes in clinical features and outcomes over time for more than 20 years in patients with HCC who underwent LR at our institution, the total cohort was divided into three periods: an initial period of over 10 years (period 1: 1996–2007), a subsequent 5-year period (period 2: 2008–2012), and a recent 5-year period (period 3: 2013–2017). Results are expressed as mean±standard deviation, median (interquartile range, IQR), or, when appropriate, as frequencies and percentages. Parameters were compared between subgroups using a two-sided t-test or analysis of variance for parametric variables and the Mann–Whitney U test or the Kruskal–Wallis test for non-parametric variables. Categorical data were evaluated using Fisher's exact test or the chi-squared test. The Mantel–Haenszel linear trend test was performed to evaluate linear associations across periods 1 to 3, based on their sequential order. The Kaplan–Meier method was used to estimate survival probabilities, and differences in survival were assessed using the log-rank test. Univariable analysis was performed using Cox proportional hazards (PH) regression analysis. For multivariable analysis, factors were selected based on clinical relevance and statistical significance in univariable analysis (p<0.1). The PH assumption was evaluated for the period variable, the most critical independent variable in our study. Log-log plots showed parallel curves, indicating that the PH assumption was met (Supplementary Fig. 1, only online).

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Statistical significance was set at p<0.05. Tukey's correction was applied to adjust the p-values for multiple comparisons.

RESULTS

The baseline clinicopathological characteristics of the patients are summarized in Table 1. Compared to those in period 1, patients in period 3 were significantly older (mean age, 53.3 years vs. 55.8 years vs. 58.1 years, p<0.001) and had a lower proportion of HBV, an increased incidence of NBNC HCC, a lower frequency of cirrhosis in background liver tissue, and a decreased proportion of preoperative serum AFP levels below 400 ng/mL. In terms of postoperative management, a higher proportion of patients received antiviral agents for HCC related to chronic viral infections in period 3 compared to previous periods.

Compared to periods 1 and 2, in period 3, the mean tumor size at the time of diagnosis in patients with HCC gradually decreased (4.7 cm vs. 3.7 cm vs. 3.6 cm, p<0.001), whereas the frequency of multiple tumors significantly increased (8.0% vs. 9.0% vs. 13.8%, p=0.001).

Surgical and long-term outcomes

The surgical characteristics and patient outcomes are summarized in Table 2. From periods 1 to 3, the use of minimally invasive surgery (laparoscopic and robotic LR) significantly increased (adjusted p<0.001). Minor and non-anatomic LRs became significantly more frequent over time (adjusted p=0.002 and adjusted p<0.001, respectively). Additionally, the mean EBL significantly decreased from period 1 to 2 and from period 1 to 3 (both adjusted p<0.001), whereas the reduction from period 2 to 3 was not significant (adjusted p=0.173) (1033.0 mL vs. 490.9 mL vs. 399.3 mL). Similarly, the frequency of intraoperative transfusion was lower in period 3 compared to those in periods 1 and 2 (43.6% vs. 13.0% vs. 9.8%, p<0.001). The mean postoperative hospital stay significantly decreased across periods (adjusted p=0.001 for period 1 vs. 2, and adjusted p<0.001 for period 1 vs. 3), but no significant difference was observed between periods 2 and 3 (adjusted p=0.071).

The mean surgical margin decreased significantly over time, particularly from period 1 to period 3 (adjusted p=0.002) and between periods 2 and 3 (adjusted p=0.015), yet consistently exceeded 1 cm across all periods (1.9 cm vs. 1.8 cm vs. 1.5 cm). Furthermore, the proportion of close surgical margins (<1 mm) significantly decreased from 3.7% in period 1 to 0.9% in period 2 and 1.0% in period 3 (p=0.007).

Short-term surgical outcomes also improved significantly, with 30-day mortality decreasing from 1.1% in period 1 to 0.1% in period 3 (p=0.031), and 90-day mortality decreasing from 2.3% to 0.3% (p=0.001). In-hospital mortality also significantly decreased from 1.8% to 0.1% (p=0.002). The rate of major complications significantly improved over the periods, decreasing from 9.4% in period 1 to 5.0% in period 3 (p=0.002).

The overall median follow-up duration was 71.0 months (IQR 46.0–101.0). The median follow-up durations by period were 69.0 months (29.0–98.0) for period 1, 101.0 months (44.0–132.0) for period 2, and 68.0 months (55.0–86.0) for period 3. Long-term outcomes showed substantial improvement, with 5-year OS increasing from 68.1% in period 1 to 80.7% in period 2 (adjusted p=0.003), and further to 90.5% in period 3 (adjusted p<0.001). Similarly, 5-year DFS increased from 41.4% in period 1 to 50.7% in period 2 (adjusted p=0.017), and further to 61.1% in period 3 (adjusted p<0.001). Additionally, early recurrence rates within 2 years significantly decreased, from 36.9% in period 1 to 30.6% in period 2, and further declined to 24.2% in period 3 (p<0.001).

Detailed pairwise comparison results for continuous variables, adjusted using Tukey's correction, are presented in Supplementary Table 1 (only online).

Prognostic factors

In the multivariable Cox regression analysis for OS, independent negative prognostic factors included male sex [hazard ratio (HR): 1.422; 95% confidence interval (CI): 1.101–1.837; p=0.007], tumor size >5 cm (HR: 1.681; 95% CI: 1.355–2.087; p<0.001), presence of cirrhosis (HR: 1.386; 95% CI: 1.134–1.695; p=0.001), MVI (HR: 1.912; 95% CI: 1.526–2.397; p<0.001), Ed-

Table 1. Comparison of Clinicopathologic Characteristics between Three Time-Period Groups of Patients Who Underwent Hepatectomy for Naïve Hepatocellular Carcinoma during 1996–2017

Variables	Total (n=1778)	Period 1 (1996–2007) (n=563)	Period 2 (2008–2012) (n=532)	Period 3 (2013–2017) (n=683)	*p*
Age (yr)	55.9±10.2	53.3±10.0	55.8±10.4	58.1±9.7	<0.001
Age					<0.001*
≤60 years	1173 (66.0)	406 (72.1)	349 (65.6)	418 (61.2)	
>60 years	605 (30.4)	157 (27.9)	183 (34.4)	265 (38.8)	
Sex					0.880*
Female	388 (21.8)	124 (22.0)	116 (21.8)	148 (21.7)	
Male	1390 (78.2)	439 (78.0)	416 (78.2)	535 (78.3)	
BMI (kg/m^2)	23.8±3.0	23.5±3.1	24.1±3.1	23.9±3.0	0.014
BMI					0.155*
≤25 kg/m^2	1206 (67.8)	399 (70.9)	350 (65.8)	457 (66.9)	
>25 kg/m^2	572 (32.2)	164 (29.1)	182 (34.2)	226 (33.1)	
Etiology					0.150*
NBNC	166 (9.3)	45 (8.0)	37 (7.0)	84 (12.3)	
HBV	1514 (85.2)	491 (87.2)	466 (87.6)	557 (81.6)	
HCV	98 (5.5)	27 (4.8)	29 (5.5)	42 (6.1)	
AFP					<0.001*
≤400 ng/mL	1407 (79.7)	408 (73.4)	426 (81.0)	573 (83.9)	
>400 ng/mL	358 (20.3)	148 (26.6)	100 (19.0)	110 (16.1)	
PIVKA-II					0.652*
≤100 ng/mL	895 (58.6)	221 (59.1)	285 (56.4)	389 (59.9)	
>100 ng/mL	633 (41.4)	153 (40.9)	220 (43.6)	260 (40.1)	
Anti-viral therapy (yes)	181 (10.2)	32 (5.7)	53 (10.0)	96 (14.1)	<0.001*
Pathologic findings					
Tumor size (cm)	4.0±2.5	4.7±2.8	3.7±2.3	3.6±2.4	<0.001
Tumor size					<0.001*
≤5 cm	1366 (76.8)	381 (67.7)	426 (80.1)	559 (81.8)	
>5 cm	412 (23.2)	182 (32.3)	106 (19.9)	124 (18.2)	
Tumor size					<0.001*
≤3 cm	831 (46.7)	197 (35.0)	265 (49.8)	369 (54.0)	
>3 cm	947 (53.3)	366 (65.0)	267 (50.2)	314 (46.0)	
Tumor number					0.001*
Single	1591 (89.5)	518 (92.0)	484 (91.0)	589 (86.2)	
Multiple	187 (10.5)	45 (8.0)	48 (9.0)	94 (13.8)	
Edmondson grade					0.006*
I–II	764 (45.0)	244 (49.3)	239 (45.8)	281 (41.3)	
III–IV	934 (55.0)	251 (50.7)	283 (54.2)	400 (58.7)	
MVI (yes)	867 (48.9)	280 (50.3)	264 (49.6)	323 (47.3)	0.288*
Cirrhosis (yes)	899 (50.6)	292 (51.9)	291 (54.7)	316 (46.3)	0.037*
Surgical margin (cm)†	1.6±1.8	1.9±1.4	1.8±2.4	1.5±1.5	0.001
Surgical margin (≥1 cm)†	763 (53.3)	189 (63.4)	247 (54.5)	327 (48.0)	<0.001*
Close surgical margin (<1 mm)†	22 (1.5)	11 (3.7)	4 (0.9)	7 (1.0)	0.007*
8th AJCC stage					0.005*
Stage 1A	305 (17.2)	72 (12.8)	99 (18.6)	134 (19.6)	
Stage 2B	595 (33.5)	207 (36.8)	170 (32.0)	218 (31.9)	
Stage 2	805 (45.3)	247 (43.9)	251 (47.2)	307 (44.9)	
Stage 3A	26 (1.5)	10 (1.8)	6 (1.1)	10 (1.5)	
Stage 3B	44 (2.5)	26 (4.6)	6 (1.1)	12 (1.8)	
Stage 4	3 (0.2)	1 (0.2)	0 (0.0)	2 (0.3)	

BMI, body mass index; NBNC, non-B, non-C; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; MVI, microscopic vascular invasion; AJCC, American Joint Committee on Cancer.
Data are presented as mean±standard deviation or frequency (%).
*A Mantel–Haenszel linear trend test was conducted for categorical variables to analyze sequential trends across periods 1 to 3. All multiplicity-adjusted *p*-values for continuous variables were calculated using Tukey's correction; †Surgical margin data were available for 1432 patients of all patients.

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Table 2. Comparison of Surgical Characteristics and Outcomes between Three Time-PeriodGroups of Patients Who Underwent Hepatectomy for Naïve Hepatocellular Carcinoma during 1996–2017

Variables	Total (n=1778)	Period 1 (1996–2007) (n=563)	Period 2 (2008–2012) (n=532)	Period 3 (2013–2017) (n=683)	*p*
Surgical approach					<0.001*
Open	1528 (85.9)	548 (97.3)	486 (91.4)	494 (72.3)	
Laparoscopic	210 (11.8)	15 (2.7)	34 (6.4)	161 (23.6)	
Robotic	40 (2.2)	0 (0)	12 (2.3)	28 (4.1)	
Extent of liver resection					0.002*
Minor	991 (55.7)	298 (52.9)	274 (51.5)	419 (61.3)	
Major	787 (44.3)	265 (47.1)	258 (48.5)	264 (38.7)	
Non-anatomic resection	668 (37.6)	199 (35.3)	175 (32.9)	294 (43.0)	<0.001*
Anatomic resection	1110 (62.4)	364 (64.7)	357 (67.1)	389 (57.0)	
Surgical outcomes					
Operation time (min)	270.9±108.5	278.9±101.0	252.2±96.6	278.9±120.9	<0.001
EBL (mL)	627.4±927.6	1033.0±1387.2	490.9±583.2	399.3±434.8	<0.001
EBL (>1 L)	289 (16.3)	178 (31.6)	58 (10.9)	53 (7.8)	<0.001*
Intraoperative transfusion (yes)	379 (21.4)	243 (43.6)	69 (13.0)	67 (9.8)	<0.001*
Hospital stay (days)	13.1±20.0	17.2±34.7	12.7±7.5	10.1±6.1	<0.001
Mortality					
30-day mortality	10 (0.6)	6 (1.1)	3 (0.6)	1 (0.1)	0.031*
90-day mortality	22 (1.2)	13 (2.3)	7 (1.3)	2 (0.3)	0.001*
In hospital mortality	16 (0.9)	10 (1.8)	5 (0.9)	1 (0.1)	0.002*
Postoperative complication					0.001*
Grade IIIA	100 (5.6)	41 (7.3)	30 (5.6)	29 (4.2)	
Grade IIIB	7 (0.4)	3 (0.5)	2 (0.4)	2 (0.3)	
Grade IV	6 (0.3)	0 (0)	4 (0.8)	2 (0.3)	
Grade V	14 (0.8)	9 (1.6)	4 (0.8)	1 (0.1)	
Major complication (≥grade III)	127 (7.1)	53 (9.4)	40 (7.5)	34 (5.0)	0.002*
Recurrence					<0.001*
No recurrence	893 (50.2)	245 (43.5)	245 (46.1)	403 (59.0)	
Early recurrence (≤2 years)	536 (30.1)	208 (36.9)	163 (30.6)	165 (24.2)	
Late recurrence (>2 years)	349 (19.6)	110 (19.5)	124 (23.3)	115 (16.8)	
Repeat liver resection	142 (8.0)	41 (7.3)	48 (9.0)	53 (7.8)	0.800*
Liver transplant after hepatectomy	62 (3.5)	10 (1.8)	30 (5.6)	22 (3.2)	0.226*

EBL, estimated blood loss.
Data are presented as mean±standard deviation or frequency (%). Complications were graded by the Clavien–Dindo classification system. Tukey's correction was applied to adjust the *p*-values for multiple comparisons.
*A Mantel–Haenszel linear trend test was conducted for categorical variables to analyze sequential trends across periods 1 to 3. All multiplicity-adjusted *p*-values for continuous variables were calculated using Tukey's correction.

mondson grade III/IV (HR: 1.272; 95% CI: 1.027–1.576; p=0.028), intraoperative transfusion (HR: 1.761; 95% CI: 1.406–2.207; p<0.001), and major complications (HR: 1.621; 95% CI: 1.185–2.217; p=0.002) (Table 3). Similarly, in the multivariable Cox regression analysis for DFS, factors associated with poor prognosis included male sex (HR: 1.493; 95% CI: 1.245–1.791; p<0.001), HCV (reference: NBNC, HR: 1.464; 95% CI: 1.032–2.077; p=0.033), tumor size >5 cm (HR: 1.524; 95% CI: 1.291–1.800; p<0.001), presence of cirrhosis (HR: 1.489; 95% CI: 1.289–1.721; p<0.001), MVI (HR: 1.523; 95% CI: 1.320–1.758; p<0.001), intraoperative transfusion (HR: 1.417; 95% CI: 1.186–1.692; p<0.001), and major complications (HR: 1.470; 95% CI: 1.140–1.865; p=0.003) (Table 4).

The period of resection had a positive impact on both OS and DFS, with improvement observed from periods 1 to 3 [period 3 (reference period 1); OS, HR: 0.351, 95% CI: 0.263–0.468, p<0.001; DFS, HR: 0.646, 95% CI: 0.537–0.777, p<0.001]. As shown in Supplementary Fig. 2 (onle online), subgroup analysis of patients with stages I, II, and III, based on the AJCC staging system, showed significantly improved OS and DFS from periods 1 to 3 in stages I and II, consistent with the trend observed in the total cohort (stage I OS, p<0.001; stage I DFS, p=0.008; stage II OS, p<0.001; stage II DFS, p=0.001). However, in advanced stage III, no significant differences in survival

Table 3. Univariable and Multivariable Cox Proportional Hazards Regression Analysis of Overall Survival in 1778 Patients Who Underwent Primary Curative Liver Resection for Hepatocellular Carcinoma during 1996–2017

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, >60 years	0.959 (0.783–1.174)	0.682		
Sex				
Female (ref)	1			
Male	1.291 (1.014–1.644)	0.038*	1.422 (1.101–1.837)	0.007*
BMI, >25 kg/m^2	1.051 (0.860–1.283)	0.628		
Etiology				
NBNC (ref)	1			
HBV	0.895 (0.650–1.232)	0.495		
HCV	1.042 (0.639–1.699)	0.870		
Antiviral agent, yes	0.637 (0.442–0.917)	0.015*		
AFP, >400 ng/mL	1.667 (1.352–2.055)	<0.001*		
PIVKA-II, >100 ng/mL	1.776 (1.432–2.202)	<0.001*		
Pathological findings				
Tumor size, >5 cm	2.206 (1.814–2.682)	<0.001*	1.681 (1.355–2.087)	<0.001*
Multiple tumors	0.868 (0.625–1.206)	0.400		
Cirrhosis	1.328 (1.099–1.606)	0.003*	1.386 (1.134–1.695)	0.001*
Microscopic vascular invasion	2.351 (1.926–2.869)	<0.001*	1.912 (1.526–2.397)	<0.001*
Edmonson grade (I–II/ III–IV)	1.522 (1.246–1.860)	<0.001*	1.272 (1.027–1.576)	0.028*
Surgical margin, <1 mm†	1.196 (0.533–2.684)	0.664		
Surgical findings				
Operation time, >300 min	1.923 (1.421–2.603)	<0.001*		
EBL, >1 L	2.184 (1.764–2.703)	<0.001*		
Intraoperative transfusion, yes	2.695 (2.219–3.273)	<0.001*	1.761 (1.406–2.207)	<0.001*
Major complication (≥grade III)	1.974 (1.462–2.664)	<0.001*	1.621 (1.185–2.217)	0.002*
Extent of liver resection				
Minor (ref)				
Major	1.136 (0.941–1.372)	0.185		
Anatomic resection, yes	1.131 (0.927–1.379)	1.131		
Period				
1 (1996–2007) (ref)	1		1	
2 (2008–2012)	0.524 (0.423–0.650)	<0.001*	0.694 (0.544–0.885)	0.003*
3 (2013–2017)	0.256 (0.196–0.333)	<0.001*	0.351 (0.263–0.468)	<0.001*

HR, hazard ratio; CI, confidence interval; NBNC, non-B, non-C; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; EBL, estimated blood loss.
Complications were graded by the Clavien–Dindo classification system.
*Statistically significant results from logistic regression analysis. Variables with $p<0.1$ in the univariable analysis were included in the multivariable analysis; †Surgical margin data were available for 1432 patients of all patients.

were observed over time (stage III OS, $p=0.274$; stage III DFS, $p=0.467$).

DISCUSSION

In this study, we demonstrated continuous improvement in both the 5-year OS and DFS after LR for HCC at our institution over the past 21 years (1996–2017). Over time, a gradual shift in the characteristics of patients with HCC has been observed. The average age at diagnosis has increased, and there is a higher prevalence of NBNC HCC compared to that of virus-related HCC. Additionally, the incidence of cirrhosis has decreased. This shift may be attributed to patients with NBNC HCC often being diagnosed at an older age.[17,18] Preoperative AFP levels are lower than those in the past, and the tumor size at the time of diagnosis is smaller due to early detection. There is also an increasing trend toward performing curative LR in patients with multiple HCCs. Additionally, postoperative management of patients with viral-related HCC includes a higher usage of antiviral agents.

The selection process for curative LR has improved over time,

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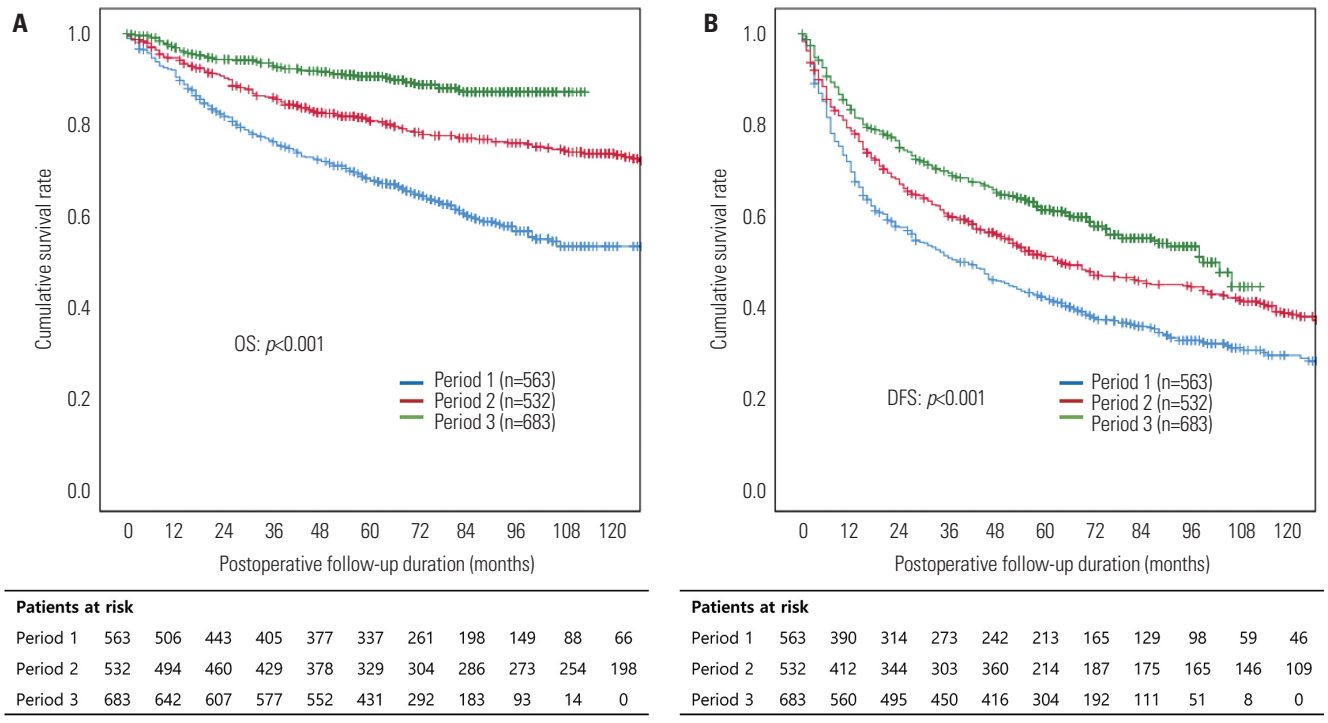
Table 4. Univariable and Multivariable Cox Proportional Hazards Regression Analysis of Disease-Free Survival in 1778 Patients Who Underwent Primary Curative Liver Resection for Hepatocellular Carcinoma during 1996–2017

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age, >60 years	1.021 (0.894–1.166)	0.755		
Sex				
Female (ref)				
Male	1.350 (1.149–1.585)	<0.001	1.493 (1.245–1.791)	<0.001*
BMI, >25 kg/m^2	1.033 (0.904–1.181)	0.633		
Etiology				
NBNC (ref)	1		1	
HBV	1.015 (0.816–1.264)	0.892	0.928 (0.725–1.188)	0.552
HCV	1.428 (1.040–1.961)	0.028	1.464 (1.032–2.077)	0.033*
Antiviral agent, yes	0.908 (0.734–1.123)	0.372		
AFP, >400 ng/mL	1.342 (1.155–1.558)	<0.001		0.128
PIVKA-II, >100 ng/mL	1.384 (1.207–1.588)	<0.001		0.133
Pathological findings				
Tumor size, >5 cm	1.493 (1.297–1.720)	<0.001	1.524 (1.291–1.800)	<0.001*
Multiple tumor	1.084 (0.886–1.328)	0.434		
Cirrhosis	1.317 (1.161–1.494)	<0.001	1.489 (1.289–1.721)	<0.001*
Microscopic vascular invasion	1.585 (1.396–1.799)	<0.001	1.523 (1.320–1.758)	<0.001*
Edmonson grade (I–II/ III–IV)	1.268 (1.113–1.444)	<0.001		0.132
Surgical margin, <1 mm†	0.982 (0.555–1.738)	0.952		
Operative findings				
Operation time, >300 min	1.132 (0.989–1.296)	0.072		0.858
EBL, >1 L	1.440 (1.228–1.689)	<0.001		0.923
Intraoperative transfusion, yes	1.633 (1.417–1.882)	<0.001	1.417 (1.186–1.692)	<0.001*
Major complication (≥grade III)	1.585 (1.268–1.980)	<0.001	1.470 (1.140–1.895)	0.003*
Extent of liver resection				
Minor (ref)				
Major	0.936 (0.824–1.062)	0.306		
Anatomic resection, yes	1.113 (0.976–1.270)	0.111		
Period				
1 (1996–2007) (ref)	1		1	
2 (2008–2012)	0.748 (0.643–0.870)	<0.001	0.798 (0.663–0.960)	0.017*
3 (2013–2017)	0.562 (0.482–0.656)	<0.001	0.646 (0.537–0.777)	<0.001*

HR, hazard ratio; CI, confidence interval; NBNC, non-B, non-C hepatitis; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; EBL, estimated blood loss.
Complications were graded using the Clavien–Dindo classification system.
*Statistically significant results from logistic regression analysis. Variables with $p<0.1$ in the univariable analysis were included in the multivariable analysis; †Among all patients, the surgical margin was reported in 1432 patients.

with a focus on a tailored surgical strategy based on tumor factors. The concept of parenchyma-sparing LR has contributed to increased use of minor or non-anatomic LR, further accelerated by the introduction of minimally invasive surgery. The growing use of laparoscopic and robotic LR has led to shorter postoperative hospital stays and significantly reduced EBL. This, in turn, has reduced the need for intraoperative transfusions and the incidence of major postoperative complications.[19] Furthermore, in terms of short-term surgical outcomes, the recent 5-year period showed very favorable results, with 90-day mortality in 2 cases (0.3%) and 30-day mortality in 1 case (0.1%).

In a study conducted by Han, et al.[7] at our institution a decade ago, involving approximately 600 patients with HCC from 1996 to 2007, the 5-year OS was 64.4%, and 5-year DFS was 45.8%. After 2003, improved survival was observed in patients with HCC and tumors larger than 3 cm.[7] The improvement was attributed to more appropriate patient selection and reduced perioperative transfusion due to enhanced surgical techniques. In the current study, spanning 1996 to 2017 and encompassing 21 years of experience, continuous improvement in survival was observed. Notably, long-term OS during



Patients at risk												
Period 1	563	506	443	405	377	337	261	198	149	88	66	
Period 2	532	494	460	429	378	329	304	286	273	254	198	
Period 3	683	642	607	577	552	431	292	183	93	14	0	

Patients at risk												
Period 1	563	390	314	273	242	213	165	129	98	59	46	
Period 2	532	412	344	303	360	214	187	175	165	146	109	
Period 3	683	560	495	450	416	304	192	111	51	8	0	

Fig. 1. OS (A) and DFS (B) according to three periods (period 1: 1996–2007; period 2: 2008–2012; and period 3: 2013–2017). Compared to the previous 10 years, the most recent 5-year OS and DFS improved significantly (5-year OS: 68.1% vs. 80.7% vs. 90.5%, $p<0.001$; 5-year DFS: 41.4% vs. 50.7% vs. 61.1%, $p<0.001$). OS, overall survival; DFS, disease-free survival.

the most recent 5-year period (2013–2017) increased from 68.1% to 90.5%. Similarly, 5-year DFS significantly improved from 41.4% to 61.1% compared with earlier periods. Early recurrence rate within 2 years was also significantly reduced to 25.8% in the recent 5-year period. These findings are significant, as they indicate an improved long-term survival rate after curative LR for HCC. Other studies have also reported significant improvements in survival. In a study conducted by Ariizumi, et al.[5] in Japan, involving 460 patients with HCC who underwent anatomic LR using the Glissonian pedicle approach over 30 years, an improvement in OS of up to 75% was demonstrated during the last 5-year period (2010–2014). Yamashita, et al.,[6] also from Japan, conducted a study involving 1000 patients with HCC who underwent LR over 20 years. They reported a consistent improvement in OS up to 78%, specifically during the period 2005–2011. However, recurrence-free survival (RFS) did not show a significant improvement and remained at 34%. In a study conducted by Goh, et al.[4] in Singapore over 18 years, an improvement in OS was demonstrated, increasing from 45.8% to 66.9%.

In our study, tumor size >5 cm, the presence of cirrhosis, MVI, intraoperative transfusion, and major complications were identified as poor prognostic factors for OS and DFS in patients who underwent primary curative LR for HCC. In contrast, the more recent period was associated with improved OS and DFS, suggesting that the prognosis of HCC improved over time. The favorable outcomes in the recent period could be attributed to several factors. One potential reason is the trend toward diagnosing smaller tumors or reduced prevalence over time, which may have positively influenced survival rates. Additionally, improved surgical techniques may have played a significant role in reducing intraoperative transfusions and major complications, leading to improved survival rates. Similar results have been reported previously. Chok, et al.[20] demonstrated that postoperative complications were a poor prognostic factor for OS and RFS (HR: 1.37; $p<0.001$). Yang, et al.[21] reported that infective postoperative complications significantly decreased OS and RFS. Moreover, regarding resection margins, the proportion of wide margins over 1 cm decreased from period 1 to 3, and the proportion of very close resection margins under 1 mm also declined. Previous studies have demonstrated that narrow margins are associated with higher recurrence rates and poorer survival outcomes.[22,23] In our findings, the decrease in wide resection margins may have been influenced by the increased use of parenchyma-preserving LR and minimally invasive approaches for early-stage tumors. In contrast, the decline in very close resection margins, such as tumors adjacent to the resection line, likely reflects advancements in intraoperative ultrasound guidance and surgical precision.

In addition, subgroup analysis of long-term survival based on AJCC staging revealed improvements in OS and DFS from period 1 to 3 for both stage I and II. However, no significant improvement in OS and DFS was observed for patients with advanced stage III HCC. Although the small number of HCC patients in stage III may have limited the statistical power of

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our analysis, the results suggested that tumor characteristics of advanced HCC exert a stronger influence on survival than surgical advancements.

The main limitation of our study is that it was a retrospective study conducted at a single institution, which rendered it susceptible to selection bias. Due to the extended study period, there were instances of incomplete EMRs before 2005, which led to missing data.

In conclusion, our study demonstrated a significant improvement in the long-term survival rates of patients with HCC who underwent primary curative LR based on 22 years of experience, including a previous study conducted at our institution a decade ago. Over this period, the actual 5-year OS rate increased from 68.1% a decade ago to 90.5% in the most recent 5-year period (Fig. 1A). Notably, the DFS rate also showed substantial improvement, increasing from 41.4% to 61.1% (Fig. 1B). A favorable short-term surgical outcome was achieved, with 90-day mortality decreasing from 2.3% to 0.3% (Table 2). These remarkable outcomes are likely attributable to early detection, appropriate patient selection for surgical resection, and advancements in surgical technique.

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AUTHOR CONTRIBUTIONS

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