

OPEN

The Preference for Anterior Approach Major Hepatectomy: Experience Over 3 Decades and a Propensity Score-Matching Analysis in Right Hepatectomy for Hepatocellular Carcinoma

Kun-Ming Chan, MD, Yu-Chao Wang, MD, Tsung-Han Wu, MD, Chen-Fang Lee, MD, Ting-Jung Wu, MD, Hong-Shiue Chou, MD, Ming-Chin Yu, MD, and Wei-Chen Lee, MD

Abstract: Surgical treatment for primary hepatocellular carcinoma (HCC) has progressed enormously over time. The aim of this study was to analyze the evolution of surgical techniques and outcomes of patients undergoing major right hepatectomy (RH) over the last few decades.

A retrospective review of 557 consecutive patients who had undergone RH for HCC between January 1982 and December 2011 was performed. Patients were categorized into subgroups and analyzed according to period and surgical approach to hepatectomy. Based on a propensity score-matching model, the surgical approach in patients in the second period was also analyzed in terms of anterior approach (AA) and conventional approach (CA)-RH.

Tumor factors remained the most important prognostic factors related to postoperative HCC recurrence throughout the 2 periods examined in this study. Comparison of patients selected by a propensity score-matching model showed that AA-RH led to significantly better outcomes including recurrence-free survival (RFS) ($P = 0.011$) and overall survival (OS) ($P = 0.012$) in patients with HCC as compared with CA-RH. The 5-year RFS and OS were 33.4% and 52.2% after AA-RH, and 21.0% and 36.5% after CA-RH.

Major hepatectomy has evolved into a safe procedure that can be performed with confidence. RH by an AA has shown several advantages over CA-RH, and can thus be recommended as the standard procedure for liver resection in patients who require right hepatectomy.

(*Medicine* 94(34):e1385)

Abbreviations: AA = anterior approach, AA-RH = anterior approach right hepatectomy, AFP = α -fetoprotein, CA = conventional approach, CA-RH = conventional approach right hepatectomy, CT = computed tomography, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HR = hazard ratio, ICG = indocyanine green, IVC = inferior vena cava, MRI = magnetic

Editor: Shefali Agrawal.

Received: May 8, 2015; revised: June 17, 2015; accepted: July 23, 2015. From the Division of Liver and Transplantation Surgery, Department of General Surgery, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan.

Correspondence: Kun-Ming Chan, Division of Liver and Transplantation Surgery, Department of General Surgery, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan, 5, Fu-Hsing Street, Kwei-Shan District, Taoyuan City 33305, Taiwan (e-mail: chankunming@adm.cgmh.org.tw).

The authors have no funding and conflicts of interest to disclose. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved. This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001385

resonance imaging, OS = overall survival, RFS = recurrence-free survival, RH = right hepatectomy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a common malignancy as well as a leading cause of cancer mortality worldwide. Since the liver is a silent organ, patients with HCC are mostly asymptomatic. As a result, the majority of patients are diagnosed at an advanced stage, making surgical resection unfeasible. It is estimated that fewer than 20% of HCC patients are eligible for liver resection at the time of diagnosis.^{1,2} Among those patients eligible for liver resection, a proportion of patients with huge liver tumors or tumors near major vascular structures require major liver resection such as right hepatectomy (RH) or even extended-RH.³⁻⁵

Along with the advancement of diagnostic tools and methods of anesthesia, the surgical approach used for major hepatectomy has shown much progress during the last 3 decades.⁶ Numerous surgical approaches for RH have been reported in the literature, the most common of which are the conventional approach (CA) and the anterior approach (AA) with or without the hanging maneuver. Traditionally, CA for RH required complete mobilization of the right liver before parenchymal transection. This was considered a standard procedure and was widely utilized for major right hepatic resection in numerous centers worldwide. Subsequently, AA with or without the liver hanging maneuver that transected the liver parenchyma before mobilization of the right liver was introduced by many experienced surgeons.^{7,8} Although the theoretical advantages of the AA over the CA are well established, RH using AA remains a technically demanding method, making numerous surgeons reluctant to perform this approach.^{9,10} As such, the pros and cons of the surgical approach for RH remain debatable. In this study, we gathered data and retrospectively reviewed our experience of HCC patients who had undergone major RH over a 3-decade period. Additionally, since the treatment of HCC has changed greatly over the last few decades, the patient cohort was grouped according to the timeframe to evaluate the evolution of outcome over the years. Subsequently, the outcome based on surgical approach and the potential benefit of each surgical technique was also evaluated.

MATERIALS AND METHODS

Patients

A total of 2608 patients who had undergone curative hepatic resection for HCC from January 1982 to December 2011 at the Department of General Surgery, Chang Gung

Memorial Hospital at Linkou Medical Center, were retrospectively reviewed. All patients were pathologically confirmed HCC. Based on the Brisbane terminology of hepatic resection,¹¹ patients who had undergone RH by resection of Caunaud's segments 5 to 8 or extended-RH by resection of segment 5 to 8 plus segment 1 and/or 4 were enrolled for this study under the approval of the Institutional Review Board. Of these, 557 patients (455 men and 102 women) with ages ranging from 8 to 89 years (median age 56 years) were analyzed.

A standard data collection through reviewing medical records was completed for all cases in this study. It included comprehensive information including clinical characteristics of patients, laboratory tests, radiological imaging, operative findings, histological examination of liver specimens, and postoperative follow-up in terms of cancerous status and patient's outcome.

Preoperative Assessment

Patients were assessed clinically by history and physical examination, followed by investigations including serum laboratory tests, measurement of α -fetoprotein (AFP), abdominal ultrasonography, dynamic computed tomography (CT), and hepatic angiography as appropriate. The assessment of liver functional reserve to determine eligibility for hepatic resection was mainly based on the Child-Pugh score before introduction of the indocyanine green (ICG) test. Thereafter, Makuuchi algorithm using the ICG retention rate at 15 minutes was employed to determine eligibility for as well as the extent of hepatic resection.¹²

Hepatic Resection

During hepatic resection, a right subcostal or bilateral subcostal abdominal incision with an upward midline extension was made to expose the liver. Hilar dissection was performed to divide the right hepatic artery and portal vein. For CA-RH, the right liver was then completely mobilized away from the diaphragm and retrohepatic space step-by-step until sufficient exposure of the inferior vena cava (IVC). Additionally, all small venous branches communicating with the right liver and IVC were individually ligated to facilitate isolation of the right hepatic vein. The vascular inflow and outflow of the right liver was effectively controlled either by ligation or suture before performing transection of the hepatic parenchyma.

For AA-RH, the right liver was not mobilized nor was there any need for IVC or right hepatic vein exposure. After hilar dissection, transection of the hepatic parenchyma was carried out following control of vascular inflow into the right liver. The vascular inflows were selectively controlled by tourniquet clamping for the right portal vein and Bulldog hemo-clamp for the right hepatic artery. In the AA using the liver hanging maneuver, a tunnel was created between the liver and IVC to enable passage of a 12-Fr Silastic Penrose tube (Cow Doring, Midland, MI) for liver hanging, as previously described.¹³ The parenchymal transection was started from the anterior surface of the liver to the hepatic hilum and down to the anterior surface of the IVC. The IVC was clearly exposed after complete parenchymal transection, and all small veins between the IVC and the right liver were divided and ligated. The right hepatic bile duct and vascular structure including the right hepatic vein, right portal vein, and right hepatic artery were subsequently transected and sutured one by one. Finally, the right liver was taken out of the abdominal cavity after being separated from the surrounding ligaments and retrohepatic space.

Hepatic parenchymal transection was performed using either the Kelly clamp crush technique or an ultrasonic dissector

(Cavitron Ultrasonic Surgical Aspirator, CUSA; Valleylab, Inc., Boulder, CO). Hepatic resection was mostly performed by CUSA transection after it was introduced into our institute in the year 2002.

Patient's Follow-Up

After hepatic resection, all patients were followed-up at regular intervals until death or the end of the present study. Clinical assessments including physical examination, serum laboratory tests, AFP measurement, and abdominal ultrasonography were performed at monthly intervals in the initial 3 months and at 3-month intervals thereafter. CT and/or magnetic resonance imaging (MRI) were arranged on an annual basis or when suspicious of HCC recurrence.

Statistical Analysis

Outcome measures included recurrence-free survival (RFS) and overall survival (OS). RFS was defined as the time between the dates of hepatectomy to the date of detection of HCC recurrence. OS was measured from the date of hepatectomy to the date of death or the end of this study. Survival curves were constructed using the Kaplan–Meier method and analyzed by means of the log rank test; patients with hospital mortality were excluded from the RFS and OS analysis. The categorical variables were assessed using the χ^2 or Fisher exact test as appropriate, and the independent-samples *t* test was used for continuous data. Univariate analyses of the variables were conducted using Kaplan–Meier method and compared by the log rank test to identify potential prognostic factors of RFS. All the potential prognostic factors with a *P*-value of <0.1 from univariate analyses were then selected for multivariate analyses using the Cox proportional hazards regression model. All statistical analyses were performed using SPSS statistical software version 19.0 (SPSS, Inc., Chicago, IL) for Windows. A *P*-value of less than 0.05 was considered to be statistically significant.

RESULTS

Clinicopathological Characteristics of Patients

Of the patients who underwent RH or extended-RH, 278 cases were performed during the initial 2 decades from 1982 to 2001 (period I), and the remaining 279 hepatectomies were performed between 2002 and 2011 (period II). All surviving patients were regularly followed-up at the institute for at least 10 years or until the end of this study. The clinicopathological features of patients in the 2 periods are compared in Table 1. Patient age, severity of underlying liver disease in terms of liver cirrhosis, maximum tumor size, hepatectomy type, and hospital stay differed significantly between the 2 periods. The tumor size and proportion of patients undergoing major operation with extended-RH were significantly higher in the second period. Additionally, patients in the second period were significantly older but had a shorter hospital stay. In this study, the distribution of viral hepatitis in the 2 periods was similar, with hepatitis B virus (HBV) accounting for more than 60% of patients.

Variance of Prognostic Factors Affecting HCC Recurrence

The clinicopathological factors affecting cancer recurrence in patients who underwent hepatectomy for HCC were analyzed according to period. Table 2 shows the univariate and

TABLE 1. Clinicopathological Characteristics of Patients Undergoing Right Hepatectomy for Primary Hepatocellular Carcinoma

| Characteristics | Period I, n = 278 (%) | Period II, n = 279 (%) | P-Value |
|-----------------------------|-----------------------|------------------------|---------|
| Age (years), median (range) | 55 (8–84) | 57 (17–89) | <0.0001 |
| Sex (male/female) | 229:49 | 226:53 | |
| Hepatitis status | | | 0.426 |
| Hepatitis B positive | 179 (64.4) | 169 (60.6%) | |
| Hepatitis C positive | 42 (15.1) | 40 (14.3%) | |
| Hepatitis B and C positive | 16 (5.8) | 14 (5.0%) | |
| None | 41 (14.7) | 56 (20.1%) | |
| Liver cirrhosis | | | <0.0001 |
| Child-Pugh class A | 102 (36.7) | 156 (55.9) | |
| No | 176 (63.3) | 123 (44.1) | |
| Maximum tumor size (cm) | | | |
| Median, range | 8.0 (1.0–26.0) | 9.3 (1.0–23.0) | 0.014 |
| Hepatectomy type | | | <0.0001 |
| Right hepatectomy | 258 (92.8) | 218 (78.1) | |
| Extended right hepatectomy | 20 (7.2) | 61 (21.9) | |
| Hospital stay (days) | | | |
| Median, range | 21 (3–123) | 18 (5–107) | 0.008 |
| Hospital mortality | 19 (6.8) | 25 (9.0) | 0.352 |

multivariate analysis of prognostic factors in period I. Univariate analysis showed that HBV positivity, tumor size ≥ 10 cm, presence of vascular invasion and satellite nodules, and extended-RH were significant prognostic factors. Subsequently, multivariate regression analysis of these factors identified 2 risk factors; tumor size ≥ 10 cm ($P < 0.001$, hazard ratio [HR] = 1.80) and the presence of satellite nodules ($P = 0.003$, HR = 1.61), affecting HCC recurrence in period I.

Table 3 presents the risk factors affecting HCC recurrence among patients in period II. Positivity for HBV, tumor size ≥ 10 cm, the presence of vascular invasion and satellite nodules, and extended-RH were significant prognostic factors in the univariate analysis. Moreover, multivariate regression analysis showed that the presence of vascular invasion ($P = 0.006$, HR = 1.56) and satellite nodules ($P = 0.001$, HR = 1.70) were independent prognostic risk factors affecting HCC recurrence in period II. The presence of satellite nodules was the only prognostic factor in both study periods.

Postoperative Outcome

The RFS curves of patients in the 2 periods are illustrated in Figure 1A. In the first period, the RFS for 1, 3, and 5 years was 46.7%, 30.8%, and 25.2%, respectively. In the second period, the RFS for 1, 3, and 5 years was 53.7%, 34.8%, and 26.2%, respectively. However, there was no significant difference in RFS curves between the 2 periods ($P = 0.45$).

The cumulative OS for 1, 3, and 5 years in the first period was 72.3%, 49.0%, and 36.6%, respectively. Period II had significantly better survival curves than that of period I ($P = 0.04$), with a 1-, 3-, and 5-year OS of 81.8%, 58.3%, and 46.2%, respectively (Figure 1B).

Conventional Versus Anterior Approach Right Hepatectomy

Among patients who underwent major liver resection in the second period, clinical features and outcomes were compared according to the different approaches of hepatectomy. Of

these, CA-RH was performed in 169 patients, and 110 patients received AA-RH. Table 4 summarizes the clinicopathological features of these 2 subgroups; patients' age, percentage of underlying liver cirrhosis, maximum tumor size, and ratio of early HCC recurrence (≤ 2 years) differed significantly between the 2 approaches. The comparison showed that a significant proportion of older patients, and those with underlying liver cirrhosis and larger tumors with a median maximum tumor size of 11.4 cm, had undergone major RH using the AA method.

The postoperative outcome in terms of early HCC recurrence was significantly better in the AA group than the CA group. Fifty-six percent of patients had HCC recurrence within 2 years after AA-RH, and 61.7% of patients encountered HCC recurrence within 2 years following CA-RH ($P = 0.04$). However, the RFS and OS curves did not differ significantly between these 2 approaches (Figure 2). The 1-, 3-, and 5-year RFS in patients undergoing CA was 48.7%, 32.0%, and 24.0%, respectively, and in patients undergoing AA the equivalent values were 61.5%, 39.2%, and 28.5%, respectively ($P = 0.148$). The cumulative 1-, 3-, and 5-year OS of CA and AA was 81.2%, 55.2%, and 44.1% versus 82.7%, 63.2%, and 48.9%, respectively ($P = 0.311$).

Comparison of Approaches Via Propensity Score Matching

Among 279 patients who had major liver resection in the second period, 78 pairs of patients were selected from the 2 approach groups after matching on the basis of the propensity score model. According to the matching model, there were no significant differences between these 2 groups for the following patient characteristics: age, gender, viral hepatitis, underlying liver cirrhosis, preoperative ICG test, hepatectomy type in terms of RH and extended-RH, tumor number, and maximum tumor size. Analysis of outcomes revealed that patients in the AA group enjoyed not only significantly better RFS but also better OS than those in the CA group. The 1-, 3-, and 5-year RFS was 44.3%, 25.4%, and 21.0% for patients in the CA group

TABLE 2. Univariate and Multivariate Analyses of Clinicopathological Factors Affecting HCC Recurrence in Patients After Right Hepatectomy During Period I (1982~2001)

| Factors | Univariate Analysis | | Multivariate Analysis | |
|-------------------------|----------------------------|---------|-----------------------|---------|
| | Median Months, (95% of CI) | P-Value | HR (95% CI) | P-Value |
| Age (years) | | | | |
| ≥60 | 23.6 (13.7–33.5) | 0.003 | 1 | 0.211 |
| <60 | 8.1 (5.8–10.5) | | 1.24 (0.88–1.74) | |
| Gender | | | | |
| Male | 10.1 (7.5–12.6) | 0.029 | 1.31 (0.88–1.97) | 0.181 |
| Female | 31.6 (3.3–59.9) | | 1 | |
| Hepatitis B virus | | | | |
| Positive | 9.8 (7.1–12.6) | 0.326 | — | |
| Negative | 14.1 (5.8–22.9) | | | |
| Hepatitis C virus | | | | |
| Positive | 29.5 (14.2–44.7) | 0.021 | 1 | 0.515 |
| Negative | 10.1 (7.4–12.7) | | 1.14 (0.75–1.73) | |
| Liver cirrhosis | | | | |
| Child-Pugh class A | 14.4 (7.4–21.3) | 0.956 | — | |
| No | 10.1 (7.7–12.5) | | | |
| AFP (ng/ml) | | | | |
| ≥400 | 6.7 (3.5–9.9) | 0.046 | 1.31 (0.98–1.75) | 0.061 |
| <400 | 13.7 (7.6–19.8) | | 1 | |
| Tumor number | | | | |
| Multiple | 11.8 (4.9–18.8) | 0.934 | — | |
| Solitary | 11.0 (8.2–13.7) | | | |
| Maximum tumor size (cm) | | | | |
| ≥10 | 5.8 (4.0–7.6) | <0.0001 | 1.80 (1.31–2.45) | <0.001 |
| <10 | 21.4 (9.5–33.4) | | 1 | |
| Tumor capsule | | | | |
| Presence | 12.4 (6.5–18.3) | 0.019 | 1 | 0.109 |
| Absence | 7.8 (4.3–11.2) | | 1.27 (0.94–1.71) | |
| Vascular invasion | | | | |
| Presence | 7.5 (3.7–11.3) | 0.045 | 1.03 (0.75–1.42) | 0.841 |
| Absence | 13.4 (6.9–20.0) | | 1 | |
| Satellite nodule | | | | |
| Presence | 5.4 (4.0–6.9) | <0.0001 | 1.61 (1.17–2.21) | 0.003 |
| Absence | 16.9 (9.9–23.9) | | 1 | |
| Resection margin | | | | |
| ≤0.5 cm | 14.5 (4.9–24.1) | 0.470 | — | |
| >0.5 cm | 11.7 (9.3–14.0) | | | |
| Hepatectomy type | | | | |
| RH | 11.7 (8.6–14.7) | 0.283 | — | |
| Extended-RH | 4.5 (2.7–6.3) | | | |

AFP = alpha-fetoprotein, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, RH = right hepatectomy.

TABLE 3. Univariate and Multivariate Analyses of Clinicopathological Factors Affecting HCC Recurrence in Patients After Right Hepatectomy During Period II (2002–2011)

| Factors | Univariate Analysis | | Multivariate Analysis | |
|-------------------------|----------------------------|---------|-----------------------|---------|
| | Median Months, (95% of CI) | P-Value | HR (95% CI) | P-Value |
| Age (years) | | | | |
| ≥60 | 21.9 (11.1–32.8) | 0.237 | — | |
| <60 | 11.7 (6.5–16.9) | | | |
| Gender | | | | |
| Male | 13.8 (7.6–20.0) | 0.922 | — | |
| Female | 14.5 (2.7–26.3) | | | |
| Hepatitis B virus | | | | |
| Positive | 12.1 (7.5–16.7) | 0.050 | 1.37 (0.99–1.88) | 0.052 |
| Negative | 23.8 (8.5–39.0) | | 1 | |
| Hepatitis C virus | | | | |
| Positive | 21.0 (10.7–21.3) | 0.648 | — | |
| Negative | 13.3 (6.5–20.0) | | | |
| Liver cirrhosis | | | | |
| Child-Pugh class A | 14.7 (7.9–21.5) | 0.230 | — | |
| No | 15.5 (6.0–24.9) | | | |
| ICG 15 minutes (%) | | | | |
| <10 | 15.5 (9.3–21.6) | 0.311 | — | |
| ≥10 | 9.9 (5.2–14.5) | | | |
| AFP (ng/ml) | | | | |
| ≥400 | 8.1 (3.4–12.8) | 0.067 | 1.10 (0.81–1.50) | 0.510 |
| <400 | 20.9 (14.5–27.3) | | 1 | |
| Tumor number | | | | |
| Multiple | 19.2 (7.4–31.0) | 0.841 | — | |
| Solitary | 13.8 (7.1–20.6) | | | |
| Maximum tumor size (cm) | | | | |
| ≥10 | 8.2 (3.9–12.4) | 0.013 | 1.10 (0.80–1.52) | 0.524 |
| <10 | 21.6 (12.1–31.1) | | 1 | |
| Tumor capsule | | | | |
| Presence | 19.1 (13.4–24.8) | 0.083 | — | |
| Absence | 8.2 (3.1–13.4) | | | |
| Vascular invasion | | | | |
| Presence | 8.0 (3.9–12.1) | <0.0001 | 1.56 (1.13–2.15) | 0.006 |
| Absence | 35.9 (20.0–51.8) | | 1 | |
| Satellite nodule | | | | |
| Presence | 9.8 (4.7–14.9) | <0.0001 | 1.70 (1.25–2.30) | 0.001 |
| Absence | 21.9 (10.6–32.3) | | 1 | |
| Resection margin | | | | |
| ≤0.5 cm | 11.7 (6.7–16.7) | 0.062 | 1.26 (0.93–1.72) | 0.133 |
| >0.5 cm | 21.9 (10.6–33.2) | | 1 | |
| Hepatectomy type | | | | |
| RH | 19.2 (12.6–25.7) | 0.046 | 1 | 0.253 |
| Extended-RH | 8.8 (0.01–18.6) | | 1.22 (0.86–1.74) | |
| Hepatectomy approach | | | | |
| CA | 11.3 (7.1–15.6) | 0.148 | — | |
| AA | 21.1 (14.0–28.2) | | | |

AA = anterior approach, AFP = alpha-fetoprotein, CA = conventional approach, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, RH = right hepatectomy.

respectively, and 63.3%, 45.5%, and 33.4%, respectively in patients in the AA group (Figure 3A, $P = 0.011$). The 1-, 3-, and 5-year OS in the AA group was 89.7%, 67.1%, and 52.2%, respectively, which was significantly better than that in the CA group, with 75.7%, 48.5%, and 36.5% for 1-, 3-, and 5-year OS, respectively (Figure 3B, $P = 0.012$).

DISCUSSION

Liver resection remains the gold standard for HCC treatment because it offers the most favorable outcome, particularly for large tumors that involve almost an entire lobe of liver and for small HCC in awkward positions that are located deep in the center of the liver, which are not suitable for any of the other

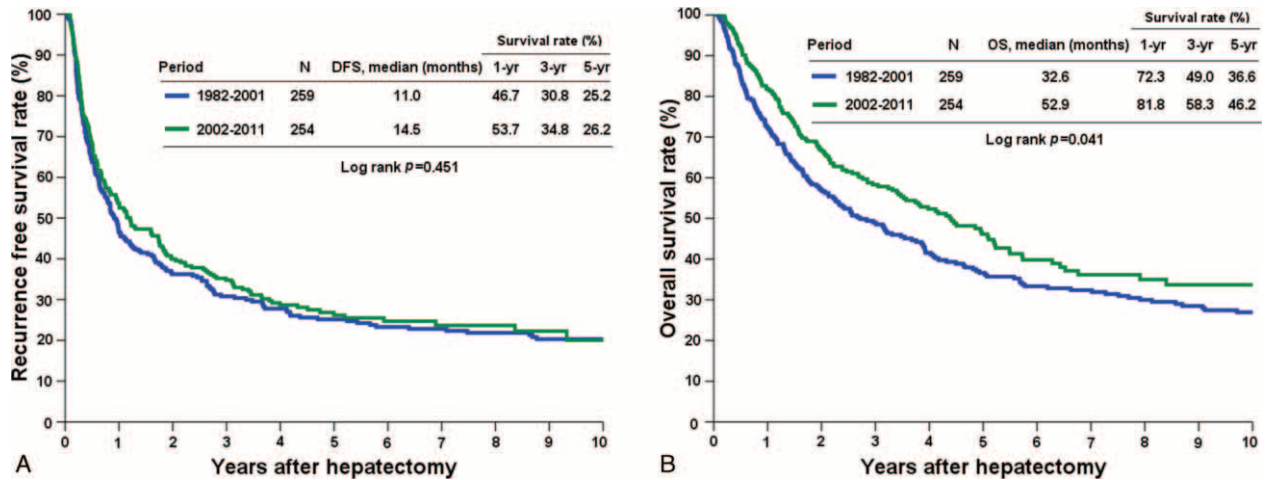


FIGURE 1. Kaplan–Meier survival curves of patients who underwent right hepatectomy, according to the period of treatment. (A) The recurrence-free survival did not differ significantly between the 2 periods. (B) Patients in the recent period demonstrated significantly better overall survival than those in the first period ($P=0.041$).

TABLE 4. Comparison of Clinical Characteristics According to Hepatectomy Approach for Patients With HCC

| Characteristics | Conventional Approach, n = 169 (%) | Anterior Approach, n = 110 (%) | P-Value |
|-----------------------------|------------------------------------|--------------------------------|---------|
| Age (years), median (range) | 56 (22–89) | 62 (17–86) | 0.009 |
| Sex (male/female) | 135:34 | 91:19 | 0.554 |
| Hepatitis status | | | 0.236 |
| Hepatitis B positive | 110 (65.2) | 59 (53.6) | |
| Hepatitis C positive | 20 (11.8) | 20 (18.2) | |
| Hepatitis B and C positive | 7 (4.1) | 7 (6.4) | |
| None | 32 (18.9) | 24 (21.8) | |
| Liver cirrhosis | | | 0.023 |
| Child-Pugh class A | 85 (50.0) | 62 (64.6) | |
| No | 84 (50.0) | 48 (35.4) | |
| ICG 15 minutes (%) | | | 0.469 |
| <10 | 116 (72.5) | 69 (68.3) | |
| ≥10 | 44 (27.5) | 32 (31.7) | |
| Hepatectomy type | | | 0.563 |
| RH | 134 (79.3) | 84 (76.4) | |
| Extended-RH | 35 (20.7) | 26 (23.6) | |
| Maximum tumor size (cm) | | | <0.0001 |
| Median, range | 8.0 (1.0–23.0) | 11.5 (2.3–22.6) | |
| Blood loss (ml) | | | 0.457 |
| Median, range | 600 (50–4000) | 500 (50–5000) | |
| Operative time (minutes) | | | 0.058 |
| Median, range | 316 (170–658) | 350 (161–652) | |
| Hospital stay (days) | | | 0.058 |
| Median, range | 18 (5–107) | 17 (8–106) | |
| Hospital mortality | 15 (8.9) | 10 (9.1) | 0.951 |
| HCC recurrence* | | | 0.040 |
| ≤2 years | 95 (61.7) | 56 (56.0) | |
| >2 years | 25 (16.2) | 9 (9.0) | |
| None | 34 (22.1) | 35 (35.0) | |

HCC = hepatocellular carcinoma, ICG = indocyanine green test, RH = right hepatectomy.

*Hospital mortality excluded (n = 25).

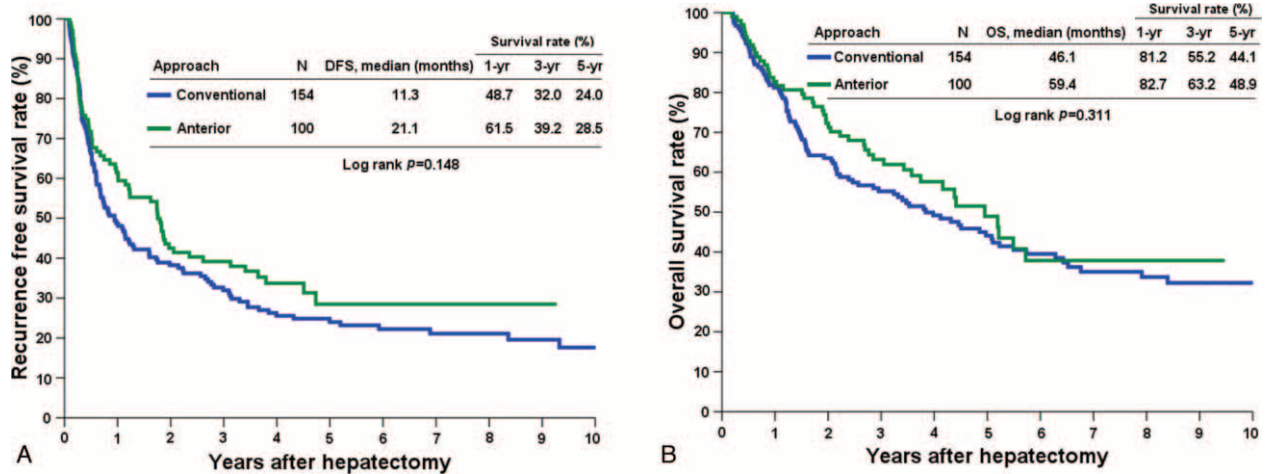


FIGURE 2. Comparison of survival curves of patients who underwent major right hepatectomy between 2002 and 2011. Neither the recurrence-free survival (A) or overall survival (B) differed significantly between the 2 approaches.

current treatments, including locoregional therapy, radiotherapy, and liver transplantation. Accordingly, major liver resection in terms of RH or extended-RH is mandatory.^{3–5} We therefore collected our experience, and analyzed differences between timeframes and the outcomes according to surgical approaches of major hepatectomy for HCC. To our knowledge, the study presents the largest series of major hepatectomy for HCC reported to date.

The advancement of anesthesia and surgical techniques, and a thorough understanding of hepatic anatomy as well as better perioperative patient care, has dramatically contributed to the effectiveness and safety of hepatectomy for HCC during the last few years. As a result, major hepatectomy specifically for huge HCC has been increasingly performed and is accepted as a safe procedure.¹⁴ As shown in this study, more patients have undergone major RH in the last decade than in the previous 2 decades in our institute. Additionally, the severity of the patient in terms of age, underlying cirrhotic liver, and tumor size appeared to be more serious in the second period. The hospital

stay was shorter in the second period, and hospital mortality showed no significant increase over the first period. These results explain why the current management of patients with major RH for HCC is considered safe.

Numerous previous studies have reported several important prognostic factors capable of predicting the outcome of HCC patients undergoing liver resection, and similar factors were also noted in this study.^{15–17} However, the present study only analyzed certain groups of patients undergoing major hepatectomy, and the prognostic factors shown here might not be representative of all HCC patients. Generally, the prognostic factors affecting tumor recurrence can be categorized into 3 core groups, related to host factors, surgical factors, and tumor factors.¹⁸ Compared with the other 2 groups of factors, tumor factors had a greater impact on HCC recurrence after major hepatectomy in this study. The presence of satellite nodules accounts for the multiplicity of HCC characteristics, and thus was a significant prognostic factor of HCC recurrence after liver

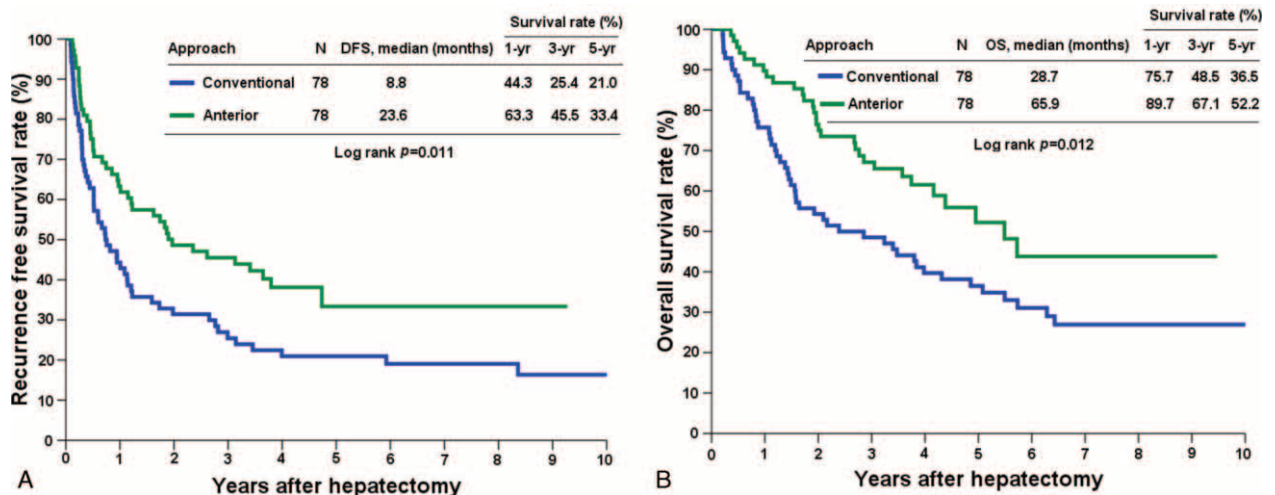


FIGURE 3. Kaplan–Meier survival curves in patients undergoing right hepatectomy after propensity score-matching. Right hepatectomy by an anterior approach showed a significantly better outcome over the conventional approach in terms of recurrence-free survival (A) and overall survival (B).

resection. Additionally, the presence of vascular invasion is not only a risk factor affecting HCC recurrence after liver resection but has also recently been identified as an important factor in the outcome of patients undergoing liver transplantation for primary HCC.^{19,20}

After the initial introduction of AA-RH,²¹ AA with or without the modified hanging maneuver has shown several advantages over CA, especially for large HCC occupying the entire right liver.^{7,13,22,23} RH for patients with a large HCC and underlying cirrhosis remains a great challenge in liver surgery. From the surgical perspective, AA is able to prevent complications related to mobilization of the right liver before parenchymal transection. Specifically, mobilization of the right liver in patients with a large HCC might be difficult due to limited space, and the surgeon is likely to encounter excessive bleeding or iatrogenic tumor rupture as well as risk of squeezing cancer cells into the systemic circulation.

AA also has the advantage of minimizing tumor cell dissemination,⁹ which could greatly reduce the chance of postoperative HCC recurrence. Earlier reports also demonstrated that patients who underwent AA had a better outcome than those who underwent CA.^{13,22,23} As shown in this study, patients who underwent AA had a significantly better outcome in terms of postoperative early HCC recurrence (≤ 2 years). Moreover, the propensity score-matching study also showed that both RFS and OS were significantly superior in the AA group compared with the CA group. The results further confirm the advantages of AA for major RH in HCC. However, the study was limited by its retrospective nature, and further prospective research in terms of patient selection, feasibility of liver resection, surgical techniques, and outcomes based on this AA might be required. Apart from that, the advantages of the AA-RH could be explored for patients with other malignancies such as colorectal cancer hepatic metastasis as well.

CONCLUSION

The advancement of surgical techniques and perioperative patient care have led to great progress in major liver resection for HCC in terms of effectiveness and safety during the last decade. Although the RFS did not differ between the 2 periods, the OS has significantly improved in recent years. The results indicate that recent efforts regarding regular postoperative follow-up as well as multimodality treatments for postoperative HCC recurrence have dramatically contributed to the improvement in overall outcome of patients undergoing liver resection. Despite being technically demanding, AA has demonstrated several advantages over CA-RH. Therefore, right hepatectomy via the AA could be recommended as the preferred technique or even as a standard procedure for liver resection in patients with HCC.

REFERENCES

1. Forner A, Reig ME, de Lope CR, et al. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis.* 2010;30:61–74.
2. El-Serag HB, Marrero JA, Rudolph L, et al. Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology.* 2008;134:1752–1763.
3. Huang JF, Wu SM, Wu TH, et al. Liver resection for complicated hepatocellular carcinoma: challenges but opportunity for long-term survivals. *J Surg Oncol.* 2012;106:959–965.
4. Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. *J Am Coll Surg.* 2002;194:592–602.
5. Yeh CN, Lee WC, Chen MF. Hepatic resection and prognosis for patients with hepatocellular carcinoma larger than 10 cm: two decades of experience at Chang Gung memorial hospital. *Ann Surg Oncol.* 2003;10:1070–1076.
6. Rahbari NN, Mehrabi A, Mollberg NM, et al. Hepatocellular carcinoma: current management and perspectives for the future. *Ann Surg.* 2011;253:453–469.
7. Belghiti J, Guevara OA, Noun R, et al. Liver hanging maneuver: a safe approach to right hepatectomy without liver mobilization. *J Am Coll Surg.* 2001;193:109–111.
8. Lai EC, Fan ST, Lo CM, et al. Anterior approach for difficult major right hepatectomy. *World J Surg.* 1996;20:314–317.
9. Liu CL, Fan ST, Cheung ST, et al. Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: a prospective randomized controlled study. *Ann Surg.* 2006;244:194–203.
10. Meng WC, Shao CX, Mak KL, et al. Anatomical justification of Belghiti's 'liver hanging manoeuvre' in right hepatectomy with anterior approach. *ANZ J Surg.* 2003;73:407–409.
11. Bismuth H. Revisiting liver anatomy and terminology of hepatectomies. *Ann Surg.* 2013;257:383–386.
12. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. *Semin Surg Oncol.* 1993;9:298–304.
13. Wu TJ, Wang F, Lin YS, et al. Right hepatectomy by the anterior method with liver hanging versus conventional approach for large hepatocellular carcinomas. *Br J Surg.* 2010;97:1070–1078.
14. Zhou YM, Li B, Xu DH, et al. Safety and efficacy of partial hepatectomy for huge (≥ 10 cm) hepatocellular carcinoma: a systematic review. *Med Sci Monit.* 2011;17:RA76–RA83.
15. Lee WC, Jeng LB, Chen MF. Estimation of prognosis after hepatectomy for hepatocellular carcinoma. *Br J Surg.* 2002;89:311–316.
16. Poon RT, Fan ST, Ng IO, et al. Different risk factors and prognosis for early and late intrahepatic recurrence after resection of hepatocellular carcinoma. *Cancer.* 2000;89:500–507.
17. Yeh CN, Chen MF, Lee WC, et al. Prognostic factors of hepatic resection for hepatocellular carcinoma with cirrhosis: univariate and multivariate analysis. *J Surg Oncol.* 2002;81:195–202.
18. Tung-Ping PR, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. *Ann Surg.* 2000;232:10–24.
19. Chan KM, Chou HS, Wu TJ, et al. Characterization of hepatocellular carcinoma recurrence after liver transplantation: perioperative prognostic factors, patterns, and outcome. *Asian J Surg.* 2011;34:128–134.
20. Shin WY, Suh KS, Lee HW, et al. Prognostic factors affecting survival after recurrence in adult living donor liver transplantation for hepatocellular carcinoma. *Liver Transpl.* 2010;16:678–684.
21. Ozawa K. Hepatic function and liver resection. *J Gastroenterol Hepatol.* 1990;5:296–309.
22. Liu CL, Fan ST, Lo CM, et al. Anterior approach for major right hepatic resection for large hepatocellular carcinoma. *Ann Surg.* 2000;232:25–31.
23. Li L, Wang HQ, Wang Q, et al. Anterior vs conventional approach hepatectomy for large liver cancer: a meta-analysis. *World J Gastroenterol.* 2014;20:17235–17243.