Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience

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Sheung Tat FAN	MS, MD, PhD, DSc, FRCS (Glasg & Edin), FACS
Chung Mau LO	MS, FRCS (Edin), FACS
Ronnie T.P. POON	MS, PhD, FRCS (Edin), FACS
Chun YEUNG	MBBS, FRCS (Glasg), FACS
Chi Leung LIU	MBBS, MS, MD, FRCS (Edin), FACS
Wai Key YUEN	MBBS, FRCS (Glasg), FRACS (Gen Surg), FACS
Chi Ming LAM	MBBS, MS, PhD, FRCS (Edin)
Kelvin K.C. NG	MS, PhD, FRCSEd (Gen)
See Ching CHAN	MS, FRCS (Edin)

Department of Surgery, The University of Hong Kong,
Queen Mary Hospital, Pok Fu Lam Road, Hong Kong

Correspondence to:

Professor Sheung Tat FAN
Department of Surgery
The University of Hong Kong
Queen Mary Hospital
102 Pok Fu Lam Road
Hong Kong
Tel: (852) 2255 4703
Fax: (852) 2986 5262
Email: stfan@hku.hk

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Mini-Abstract

A continuous improvement of the survival results of hepatectomy for hepatocellular carcinoma was observed in the past 20 years. The improvement was seen in patients with cirrhosis, those undergoing major hepatectomy, and those with liver tumors of TNM stages II, IIIA and IVA.

Structured Abstract

Objective: To investigate the trend of the post-hepatectomy survival outcomes of hepatocellular carcinoma (HCC) patients by analysis of a prospective cohort of 1198 patients over a 20-year period.

Summary Background Data: The hospital mortality rate of hepatectomy for HCC has improved but the long-term survival rate remains unsatisfactory. We reported an improvement of survival results 10 years ago. It was not known whether there has been further improvement of results in recent years.

Methods: The patients were categorized into two 10-year periods: period 1, before 1999 (group 1, n=390) and period 2, after 1999 (group 2, n=808). Patients in group 2 were managed according to a modified protocol and technique established in previous years.

Results: The patients in group 2 were older and had a higher incidence of co-morbid illness and cirrhosis. They had a lower hospital mortality rate (3.1% vs. 6.2%, $p = 0.012$) and longer 5-year overall survival (54.8% vs. 42.1%, $p < 0.001$) and disease-free survival rates (34.8% vs. 24%, $p = 0.0024$). An improvement in the overall survival rate was observed in patients with cirrhosis, those undergoing major hepatectomy, and those with tumors of TNM stages II, IIIA and IVA. A significant increase in the survival rates was also seen in patients whose tumors were considered

transplantable by the Milan criteria (72.5% vs. 62.7%, p = 0.0237). Multivariate analysis showed a significantly more favorable patient survival for hepatectomy in period 2.

Conclusions: A continuous improvement of survival outcomes after hepatectomy for HCC was achieved in the past 20 years even in patients with advanced diseases. Hepatectomy remains the treatment of choice for resectable HCC in a predominantly HBV-based Asian population.

Hepatocellular carcinoma (HCC) is one of the most lethal malignancies. Liver transplantation is the best treatment for HCC but is limited by the number of deceased organ donations. Even with the application of living donor liver transplantation, not many patients can benefit from the procedure.[1] In Asia, resection of HCC remains the treatment of choice for potentially curable diseases. Resection of HCC is not without risk, especially in the presence of cirrhosis. Nevertheless, the results of resection of HCC have been steadily improving. In 1999, we reported the first series of hepatectomy for HCC without hospital mortality.[2] In 2000, we reported an improved long-term survival rate over a 10-year period.[3] In the last 10 years, we continued to refine the surgical technique, expand the indications of hepatectomy and improve perioperative care. This study evaluated whether there was further improvement of the survival results since our last reports.

PATIENTS AND METHODS

Between 1989 and 2008, 1198 consecutive patients underwent resection of HCC at the Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China. The patients were managed and operated according to a protocol previously established.[2] Further modifications have been made in recent years (Table 1). All data were collected prospectively by a single research assistant. The patients were categorized into two 10-year periods: before December 1998 (period 1, patients designated as group 1, n=390) and after January 1999 (period 2, patients designated as group 2, n=808).

Preoperative Management

The patients were selected for resection based on assessments of the general condition, tumor status, liver function and remnant liver volume. The criteria for resectability on imaging were: absence of extrahepatic metastasis, anatomically suitable and technically feasible disease, and

absence of main portal vein or inferior vena cava (IVC) tumor thrombus. Involvement of the first-ordered branch of the portal vein to the junction with the contralateral branch and common hepatic duct and bilobed involvement did not preclude resection. Partial resection of the IVC was performed if the IVC was invaded by the tumor. A tumor near to the main drainage vein of the remnant liver was accepted for major hepatectomy if reconstruction of the hepatic vein was technically feasible. Computed tomography (CT) volumetry was performed if the remnant liver volume was estimated insufficient for postoperative recovery. Patients with remnant liver volume less than 30% underwent portal vein embolization of the ipsilateral lobe to induce contralateral lobe hypertrophy.[4] Liver function assessment was based largely on the results of the indocyanine green (ICG) clearance test. An ICG retention rate of 14% at 15 minutes after intravenous injection was acceptable for major hepatectomy. For minor hepatectomy, the cut-off value was 22%.[5]

On the day before surgery, the patient was given a light meal. In the evening, the bowel was washed out with Phospho-soda buffered oral saline laxative (Fleet; CB Fleet Co., Inc. Lynchburg, VA). Bowel washout was performed in case en bloc resection of the HCC with the colon was required and it could also reduce the discomfort arising from poor bowel movement in the immediate postoperative period. Antibiotic and a proton pump inhibitor were given at the time of induction of general anesthesia.

Surgical Techniques

Surgery was performed through a bilateral subcostal incision with an upward midline incision in most of the patients. Intraoperative ultrasonography was performed routinely as in the previous protocol to detect additional tumors in the liver, to define the topographic relationship of the tumor with major vascular pedicles and its possible invasion, and to determine the plane of liver transection and the width of the tumor-free resection margin.[2]

Liver transection was performed mainly with the ultrasonic dissector. In period 2, a new model of ultrasonic dissector was used. The change included an incorporation of electrocautery into the tip of the instrument and reduction in the lumen size of the ultrasonic dissector tip from 2 mm to 1 mm, which allowed precise dissection of intrahepatic structures and immediate coagulation of fine branches exposed by the ultrasonic dissector. The use of the ultrasonic dissector allowed exposure of major intrahepatic portal pedicles and hepatic vein that served as an important anatomic landmark for a precise hepatectomy.[6] During the operation, meticulous attention was paid to protect the liver remnant by avoiding prolonged liver rotation and liver compression by the retractor and inflow vascular occlusion. Preservation or reconstruction of the major hepatic vein was also required to avoid liver congestion.[7] Liver rotation from the right side to the left side for exposure of the IVC and resection of a tumor in the segment 6 or 7 was intermittent, similar to the Pringle maneuver. During liver transection, the central venous pressure was maintained at a low level (< 5 mm Hg) by restricting intravenous fluid administration to reduce bleeding.[8] Fluid replacement was performed once the liver transection was completed. Intermittent Pringle maneuver was not employed routinely in period 2 unless the liver transection was difficult due to venous congestion and inability to reduce the central venous pressure (in the situation of concomitant cardiac valvular disease or elderly patients). Hemostasis was achieved by electrocautery, argon beam coagulation and suturing. Argon beam coagulation was avoided at the site of suturing to reduce the chance of dislodgment of ligature. Large bite suturing was avoided to reduce the errors of occluding the major hepatic vein or its branches. Bile leakage from the transection surface, hilar plate and portal pedicle was checked by dilute methylene blue instillation into the bile duct via a cystic duct cannula (without common bile duct occlusion) or by compression onto the transection surface by a piece of clean gauze. Thorough irrigation was made to remove debris and clots. The wound was not closed until a pool of irrigant at the site of transection was totally clear. Abdominal drain was not deployed unless there was

doubt about bile leakage.[9] Before wound closure, local anesthetic (bupivacaine, 3 mg/kg) was used to infiltrate the wound at the plane between the peritoneum and abdominal muscle.

Postoperative Care

After surgery, the patients, particularly those with cirrhosis and major hepatectomy, were monitored in the intensive care unit (ICU) with attention to the fluid balance, oxygenation and tissue perfusion. Patients with evidence of fluid retention, low urine outputs and low blood pressure were treated with low-dose noradrenaline rather than further fluid administration. Mechanical ventilation was given to patients after a prolonged operation, marginal liver function and unstable hemodynamics. All patients were given albumin and antibiotic for about 3 days. More potent antibiotic was given promptly once a sign of sepsis was detected. Incentive spirometry was performed in all patients to prevent atelectasis and pneumonia. Parenteral nutrition consisting of branched-chained amino acid-enriched solution, low-dose dextrose, medium- and long-chain triglycerides and phosphate was started immediately after hepatectomy in all patients with cirrhosis or major hepatectomy and was continued for 5 to 7 days by means of a central venous catheter inserted aseptically.[10] Once parenteral nutrition was started, no other intravenous fluid was given so as to avoid liver congestion. For patients with diabetes mellitus and receiving parenteral nutrition, tight blood sugar control was achieved to reduce infection.[11]

Adjuvant Therapy

Postoperative adjuvant treatment for HCC was normally not given except in special circumstances. In group 1, 14 patients received chemoembolization for histologic margin involvement by the tumor and 30 patients were enrolled in a randomized trial of systemic epirubicin and chemoembolization.[12] In group 2, 40 patients received interferon in a randomized trial and 4 patients received chemoembolization for involvement of resection

margin by the tumor.[13]

Follow Up and Management of Recurrence

All patients were followed up by the surgical team monthly in the first year and quarterly thereafter if no recurrence was detected. Only 25 patients defaulted the follow up. The first CT or magnetic resonance imaging (MRI) was performed about 1 month after hepatectomy and repeated about every 3 to 4 months in the first year and every 6 months in subsequent years. The diagnosis of recurrence was based on typical imaging findings on CT or MRI, and if necessary, percutaneous fine-needle aspiration cytology. Recurrences were treated aggressively using the multi-modality approach. Patients with anatomically resectable tumors and preserved liver function would be considered for re-resection. Otherwise, the tumors were treated by chemoembolization, alcohol injection, radiofrequency ablation, high intensity focused ultrasound[14] or liver transplantation, depending on the location of the tumor and the liver function of the patient. Patients with extrahepatic recurrence were treated by resection if the lesion was solitary and anatomically feasible. For patients with multiple tumors, systemic chemotherapy was given only if the general condition of the patient was satisfactory.

Statistical Analysis

In this study, major hepatectomy was defined as resection of 3 or more liver segments according to the Couinaud nomenclature.[15] Minor hepatectomy was defined as resection of 2 or fewer liver segments. Hospital mortality was defined as death during the period while the patient was in the hospital for the hepatectomy. All complications were prospectively recorded and the severity was graded by the Clavien-Dindo classification.[16] All HCCs were confirmed by histologic examinations. A positive resection margin was defined as the presence of tumor cells at the line of transection due to microscopic involvement by the main tumor, venous permeation or microsatellite nodules. A survival analysis was performed using

the time of hepatectomy to the date of death or last follow up. The end point of disease-free survival was recurrence of tumor or death (excluding hospital mortality). Seventeen patients in period 1 and 11 patients in period 2 had residual diseases at the time of hepatectomy. They were excluded in the disease-free survival analysis. The last censored date was 31 December 2009. Continuous variables were expressed as median (range) and compared between groups by the Mann-Whitney *U* test. Discrete variables were compared by the χ^2 test. Survival curves were computed using the Kaplan-Meier method and compared between groups by the log-rank test. The logistic regression analysis was performed to define factors that affected hospital mortality. Cox proportional hazard models were performed to define factors that determined the overall and disease-free survival rates. All statistical analyses were made using the statistical software (SPSS 16 for Windows, SPSS Inc, Chicago, IL). Statistical significance was defined as $p < 0.05$.

RESULTS

Comparison of the two groups of patients showed that patients in the period 2 were older and had a higher incidence of co-morbid illness, but more patients in this group had asymptomatic tumors or tumors detected by screening (Table 2). The liver function in terms of Child-Pugh classification, ICG retention rate and international normalized ratio was similar between the two groups. The preoperative serum albumin and creatinine levels were lower and the serum bilirubin level was higher among the patients in group 2.

In period 2, there were fewer patients with thoracic extension of skin incision. The incidence of tumor rupture, either spontaneous or iatrogenic, was lower among the patients in group 2. The need for major hepatectomy was also lower. For patients having right hepatectomy, the anterior approach was used predominantly in period 2 (28.6% vs. 62%, $p < 0.001$). The

ultrasonic dissector was used in almost all patients and the use of Pringle maneuver was limited to 16% of the patients in the second period (Table 3). The blood loss volume, transfusion volume and the percentage of patients having blood transfusion were significantly lower in the patients in group 2 whether it was major or minor hepatectomy. Abdominal drain was deployed in 20.9% of the patients in group 2.

For the pathological status, while the tumor-node-metastasis (TNM) staging[17] of the tumors of the two groups were similar, the patients in group 2 had smaller tumors (Table 4). The incidence of microvascular invasion was similar. The incidence of a tumor involving the resection margin was lower in group 2. More patients in group 2 had underlying cirrhosis.

In the postoperative period, fewer patients in period 2 required mechanical ventilation. The complication rate was lower, especially for Clavien-Dindo grades IIIA and V severity. The hospital mortality rate of the patients in group 2 was significantly lower than that of the patients in group 1 (6.2% vs. 3.1%, p = 0.012). The reduction in the hospital mortality rate was seen mostly in cirrhotic patients (7.8% vs. 3.1%, p = 0.007). Both the ICU and hospital stay durations were shorter in group 2 (Table 5).

By the logistic regression analysis, blood loss volume and preoperative serum creatinine level were the significant factors affecting the hospital mortality in group 1, whereas the need for blood transfusion, preoperative serum creatinine level, age and major hepatectomy were the significant factors for patients in group 2. For the entire group of patients, age (relative risk 1.047, 95% coincidence interval 1.018–1.076, p = 0.001), blood loss (relative risk 1.185, 95% coincidence interval 1.07–1.31, p = 0.001), the need for blood transfusion (relative risk 2.055, 95% coincidence interval 1.01–4.18, p = 0.047), preoperative serum creatinine level (relative risk 1.008, 95% coincidence interval 1.002–1.013, p = 0.007), and major hepatectomy

(relative risk 2.26, 95% coincidence interval 1.023–4.992, p = 0.044) were the significant factors predicting hospital mortality.

Recurrence of tumors occurred in 78.2% of patients in group 1 and 60.2% of patients in group 2 ($p < 0.001$) after a median follow-up duration of 47.3 months and 35.4 months, respectively. The incidence of recurrence within the first year of hepatectomy and the pattern of recurrence were similar between the two groups (Table 6). For the treatment of intrahepatic recurrence, many more patients in group 2 had re-resection of tumors. Chemoembolization was the main treatment method in the patients in group 1. Radiofrequency ablation replaced alcohol injection almost totally as the major ablation method in group 2. For the treatment of extrahepatic recurrence, the incidence of resection was the same and fewer patients in group 2 had systemic chemotherapy.

The 1-, 3- and 5-year overall survival rates of the patients in group 1 were 74.8%, 54.2% and 42.1%, respectively and those of the patients in group 2 were 83.3%, 64.9% and 54.8%, respectively ($p < 0.001$; Figure 1A). The 1-, 3- and 5-year disease-free survival rates of the patients in group 1 were 53.1%, 33.2% and 24%, respectively, and those of the patients in group 2 were 59.4%, 41.4% and 34.8%, respectively ($p=0.0024$; Figure 1B). In terms of TNM staging, higher overall survivals rates were observed in the patients with stages II, IIIA and IVA diseases in group 2 (Figure 2A). The disease-free survival rates were also significantly higher in the patients with TNM stages II and IIIA in group 2 (Figure 2B).

The survival analysis was performed with regard to the tumor status that was considered transplantable based on pathology findings. There was a significantly increased 5-year survival rate in the HCC patients with tumor status within the Milan criteria[18] from 62.7% in period 1 to 72.5% in period 2 (Figure 3A). A similar increase in the disease-free survival rate

was seen (40.2% in group 1 and 49.2% in group 2; Figure 3B), although the difference did not reach statistical significance.

The survival analysis was performed with respect to the extent of hepatectomy. The median survival duration of the patients in group 2 having major hepatectomy was longer than that of the patients in group 1 (52.5 months vs. 37.9 months, $p = 0.0054$; Figure 4A). A similar phenomenon was seen in patients having minor hepatectomy (100.3 months vs. 56.83 months, $p = 0.0002$; Figure 4B). For disease-free survival, however, a significant increase was seen in patients having minor hepatectomy only (32 months vs. 20 months, $p = 0.0028$; Figures 4C and 4D).

Major hepatectomy was performed mostly in patients with TNM stage III and IV tumors (69.4% of group 1 and 70.5% of group 2). The overall 5-year survival rates of TNM stage III and IV patients having major hepatectomy of group 1 and 2 patients were 25.4% and 36.6%, respectively ($p = 0.0034$). The 5-year disease-free survival rate was also higher, in period 2 though the difference did not reach statistical significance (11.0% vs. 19.5%, $p = 0.0675$).

The survival analysis was also performed in groups of patients with different underlying diseases. An improved overall survival rate was seen in the patients in group 2 who had underlying cirrhosis or normal liver (Figure 5).

For patients receiving treatments for their recurrences, the patients in group 2 had longer post-treatment survival, though the difference was not significant (Table 6).

Further survival analysis was performed by grouping the patients into four 5-year sequential periods. A steady and significant improvement in the overall and disease-free survival rates

was seen (Figure 6).

By univariate and multivariate analyses, blood loss volume (> 2 liters), tumor nodule number (> 1), cirrhosis, venous invasion and TNM stage were the significant factors influencing the disease-free survival of the patients in group 1. For the patients in group 2, significant factors identified were symptomatic presentation, number of tumor nodule (> 1), microvascular invasion, positive resection margin and TNM stage. For the entire group, symptomatic presentation, blood loss (> 2 liters), number of tumor nodule (> 1), positive resection margin, microvascular invasion and TNM stage were the significant factors influencing the disease-free survival (Tables 7 and 8).

Significant factors identified for predicting overall survival were similar to those for predicting disease-free survival except that the ICG retention rate (> 14%) and development of postoperative complications were additional factors for groups 1 and 2, respectively. For the entire group, symptomatic presentation, blood loss volume (> 2 liters), postoperative complication, number of tumor nodule (> 1), positive resection margin, venous invasion and TNM stage were the significant factors (Tables 8 and 9). In addition, the period in which the patients were operated was one of the determinants of survival. Patients operated in the second period had 61.5% longer median survival duration than that of the patients in the first period.

DISCUSSION

In this study, we demonstrated an improvement of the results of hepatectomy for HCC despite an older patient population, a higher incidence of co-morbid illness, a higher incidence of cirrhosis, and worse liver function in patients operated in the second 10-year.

The reduction in the hospital mortality rate was particularly obvious in cirrhotic patients. It was associated with less intraoperative bleeding and blood transfusion irrespective of the extent of hepatectomy, shorter intensive care unit and hospital stays, and a lower complication rate. The improvement in the long-term survival was also observed in patients with underlying cirrhosis and even in patients with advanced TNM stages who underwent major hepatectomy. Since the operations were performed by the same team of surgeons, the accumulated experience was definitely a contributory factor but constant attention to refinement of the surgical technique and perioperative care were important reasons.

With strict selection of HCC patients for hepatectomy basing on their liver function, preoperative renal function became an important factor influencing hospital mortality. Careful scrutiny of patients' renal function was therefore mandatory. Patients with impaired renal function should be cared in the ICU for fluid balance control and considered for perioperative hemodialysis. Blood loss was also identified consistently to be an important factor predisposing to hospital mortality. Bleeding usually occurred during liver transection. Thus, the Pringle maneuver was a routine procedure in our early series and is currently used in many centers.[19-21] However, in our recent practice, the Pringle maneuver has not been used routinely during liver transection because we found that without the time constraint of the Pringle maneuver, liver transection is unhurried and precise. Without the Pringle maneuver, a lower bleeding and transfusion volume can actually be achieved even in patients undergoing major hepatectomy. The reduction in bleeding volume is accomplished by the cautious and slow application of the ultrasonic dissector and the restriction of intravenous fluid infusion to reduce the central venous pressure. However, older patients are at a higher risk of having more bleeding during liver transection because it is difficult to maintain normal blood pressure with a low central venous pressure. Patients with renal impairment have a higher risk of postoperative renal failure if fluid infusion is restricted. We have also observed that a

low central venous pressure is ineffective because tumor compression on the hepatic veins or iatrogenic and premature division of the outflow tract are responsible for liver congestion. In such situations, Pringle maneuver is employed to achieve rapid liver transection and minimum blood loss.

The incidence of postoperative complication remained high, even though it was lower in the second period. Considering the nature of the operation, postoperative complications seemed inevitable. However, with careful postoperative management and possibly improved technique, the incidence of complications, particularly Clavien-Dindo grades IIIa and V severity, were reduced in period 2. Infection remained an important cause of rapid deterioration of liver function of HCC patients after hepatectomy. In our current protocol, systemic antibiotic is normally given for 3 to 5 days despite the sterile nature of the operation because contamination may occur during the operation and presence of a thin layer of ischemic liver at the transection site, though minimal, may be the source of occult infection. Pneumonia is the most common infection and should be prevented at all costs. Once a sign of infection appeared, we modified the antibiotic protocol promptly and looked for the source of infection. If hyperglycemia was noted, tight blood sugar control was considered mandatory.[11] With early intervention, further deterioration could be withheld. However, control of infection is possible only if the liver function is preserved. That attests the need for preservation and protection of the liver remnant during the operation.[5,7]

Pathologic characteristics of the tumor such as microvascular invasion, multiplicity and TNM stage remain the major determinants of long-term survival. In this study, solitary tumor was associated with favorable prognosis but tumor size was not a significant factor. Thus, the higher incidence of smaller tumors in the patients in group 2 could not account for better survival rates. A further implication is that hepatectomy for a solitary tumor irrespective of

the tumor size is a worthwhile procedure.[22,23] Large tumors, however, frequently impinge on the major hepatic veins or the liver hilum. Resection of a large tumor yet preserving blood supply and venous drainage of the remnant liver is feasible as long as high quality CT or MRI is available for careful planning of the operation. Restoration of the portal vein and hepatic vein is possible nowadays with conduits such as the cryopreserved vein or ringed Gor-Tex graft.

In the second period of the study, more patients presented with asymptomatic tumors that were detected by screening. They had higher survival rates. On the contrary, patients with symptomatic presentation had less favorable survival outcomes. In these patients, symptoms were produced because of the rapidly increasing tumor size related to fast tumor growth or intra-tumoral bleeding, both indicative of aggressive biological behaviors. Fortunately, the incidence of ruptured HCC being associated with even worse prognosis was lower in period 2. To offer the patients the maximum survival benefits, we operated on symptomatic patients early and avoided intraoperative tumor rupture.[24] Thus, the overall survival duration of symptomatic patients was longer in the second period (Table 9). A similar increase in the survival rate was also observed in asymptomatic patients (Table 9). Hence, a higher incidence of asymptomatic patients in the second period may not be an important reason for the improvement of the results.

Blood loss volume was consistently found to influence the long-term survival in the first period, but with meticulous efforts to reduce bleeding, blood loss volume was not a significant factor in the second period. Blood transfusion, however, is still needed in some patients with difficult hepatectomy. Unlike the pathological factors, bleeding and transfusion are surrogate markers of technical factors that can be modified.[25] Another technical factor is the tumor-free resection margin. Positive resection margin, though lower in incidence in

period 2 of the current study, has a profound influence on the long-term survival. The width of the macroscopic tumor-free resection margin needed to avoid microscopic positive resection margin and local recurrence is controversial. There are suggestions that the width of the tumor-free resection margin is irrelevant because HCC is potentially multifocal and microscopic involvement of the margins is related to the aggressive behaviors of the tumor.[26-28] Moreover, tumors encroaching the major hepatic vein or the portal pedicle may not have sufficient tumor-free resection margins if preservation of the remnant liver volume is needed. Yet, meticulous attention to achieve tumor free resection margin in situations other than those involving the liver hilum seems warranted.

Postoperative complications did influence the overall long-term survival rate. The exact reason is not known. It is not impossible that complications such as bleeding and infection are frequently associated with systemic inflammatory response. The latter phenomenon may produce a favorable microenvironment in the liver remnant and extrahepatic organs for circulating cancer cells to deposit and grow.[29] Septic complications, therefore, must be prevented at all costs. To prevent cancer cell disseminating into the systemic circulation, the "no touch" technique such as the anterior approach right hepatectomy is preferred.[23] The anterior approach is also applicable to left liver resection.[30]

Both the disease-free and overall survival rates have improved but the overall survival rate was much higher than the disease-free survival rate in the second period even for late TNM stage diseases. This was due to our aggressive treatment for both intra- and extra-hepatic recurrences. Treatment of recurrence is more likely to be associated with better outcomes if the recurrence is small and few and treatment is prompt. Only a close follow up and surveillance imaging can detect early recurrence. However, the median survival duration of patients treated for their recurrence was not significantly longer than patients in group 1. This

implies that the current liver tumor ablation treatment (including radiofrequency ablation and chemoembolization) cannot not completely control all tumor growth or prevent further recurrences and their efficacy has not changed over the years. Further studies to refine local ablation treatments and design of strategies to eradicate microscopic tumor foci are needed.

In this study, hepatitis B is the predominant cause of HCC, whereas hepatitis C and alcoholism are rare etiologies. Thus, it is impossible to demonstrate whether improvement of results occurred in patients with etiologies other than hepatitis B. Nevertheless, compared with the reported series with hepatitis C as the predominant etiology, the results of the current series appeared more favorable.[31] Availability of effective treatments of hepatitis B may account for the difference.[32] The other deficiencies of this study is the possibility of lead-time bias and inability to classify patients preoperatively into the Milan criteria accurately. With improved imaging modalities, accurate classification of tumor staging is anticipated.[33]

In summary, a continuous improvement of hospital mortality and long-term survival results was observed in the past 20 years in HCC patients having hepatectomy. The improvement is in pace with that of liver transplantation for HCC.[34] The overall survival rate of patients with tumor status that is considered transplantable after hepatectomy is comparable with that accomplished by liver transplantation.[35] Although the disease-free survival rate of such patients is far below that of the transplant patients, prompt treatment of recurrence detected by vigorous postoperative surveillance did result in long-term survival. Thus, hepatectomy should remain the treatment of choice for resectable HCC and preserved liver function in regions with deceased organ scarcity. Improvement of survival was also observed in patients with advanced diseases. The 5-year overall survival rates of 81.7%, 77.2%, 44%, and 28.2% for TNM stages I, II, IIIA, and IVA patients after hepatectomy, respectively, may become the current standard. Further improvement of results depend on technical refinement to reduce

blood loss to the minimum, avoid blood transfusion, preserve liver remnant function, secure tumor-free resection margins, and meticulous perioperative care to reduce complications. Life-long surveillance for recurrence and prompt treatment are mandatory but development of more effective local ablation methods are needed to lengthen post-recurrence survival.

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FIGURE LEGENDS

Figure 1. Comparison of A, overall survival rates and B, disease-free survival rates of HCC patients after hepatectomy between patients in group 1 (1989–1998) and group 2 (1999–2008).

Figure 2. Comparison of A, the overall survival rates and B, the disease-free survival rates of HCC patients after hepatectomy by TNM stage.

Figure 3. Comparison of A, the overall survival rates and B, the disease-free survival rates of HCC patients whose tumors were within the Milan criteria after hepatectomy.

Figure 4. Comparison of A, B, the overall survival rates and C, D, the disease-free survival rates of HCC patients having major or minor hepatectomy between patients in group 1 and group 2.

Figure 5. Comparison of the overall survival rates of HCC patients after hepatectomy with underlying A, cirrhosis, B, chronic hepatitis and C, normal liver.

Figure 6. Comparison of A, the overall survival rates and B, the disease-free survival rates of

HCC patients operated in 4 sequential periods.

Table

Table 1. Major changes in the management protocol.

	Period 1	Period 2
Preoperative assessment	Indocyanine green clearance test	Indocyanine green clearance test
		Serum creatinine < 150 μmol/l
Intraoperative procedure	Pringle maneuver	No Pringle maneuver except in difficult liver transection
	Thoraco-abdominal incision	Avoidance of unnecessary thoraco-abdominal incision
	Ultrasonic dissector	Reduction in lumen size of the tip and incorporation of electrocautery
	Middle hepatic vein not exposed to avoid bleeding	Exposure of the middle hepatic vein as a guide to precise right or left hepatectomy
	Abdominal drainage	Abdominal drainage only if bile leakage is anticipated
	--	Infiltration of wound by local anesthetic before closure
Postoperative care	--	Low dose inotrope if blood pressure is low (after excluding bleeding)
		Tight control of blood sugar level (< 8 mmol/l
		Incentive spirometry

Table 2. Comparison of preoperative data.

	Group 1 (n=390)	**Group 2 (n=808)**	**P value**
Age (year)	54 (5–82)	56 (13–86)	0.003
Male : Female	325 : 65	648 : 160	0.193
Presence of co-morbid illness	108 (27.7%)	318 (39.4%)	< 0.001
Asymptomatic HCC	130 (33.3%)	405 (50%)	< 0.001
HCC detected by screening	71 (18.2%)	284 (35.1%)	< 0.001
Child-Pugh class			
A	374 (95.9%)	774 (95.8%)	0.932
B	16 (4.1%)	34 (4.2%)	
MELD score			
All patients	7.61 (6–17)	7.61 (6–20)	0.21
Cirrhosis	8.08 (6–17)	7.68 (6–20)	0.003
Chronic hepatitis	7.5 (6–14)	7.69 (6–15)	0.12
Indocyanine green retention (15 min) rate (%)	11.3 (1.5–66.9)	11.4 (1.2–78)	0.914
Platelet count ($\times 10^9$/l)	174 (34–667)	179 (27–713)	0.127
Serum albumin (g/l)	41 (23–53)	40 (17–56)	< 0.001
Serum bilirubin (μmol/l)	11 (2–63)	12 (2–61)	0.003
International normalized ratio	1 (0.8–1.5)	1 (0.8–1.6)	0.92
Serum creatinine (μmol/l)	90 (34–204)	87 (35–839)	< 0.001
Serum alpha-fetoprotein (ng/ml)	230 (2–1,335,900)	82 (1–1,112,000)	< 0.001
Hepatitis B	323 (82.8%)	700 (86.6%)	0.07
Preoperative portal vein embolization	0	31 (3.8%)	< 0.001

HCC, hepatocellular carcinoma

Table 3. Comparison of operation data.

	Group 1 (n=390)	**Group 2 (n=808)**	**P value**
Incision with thoracic extension	58 (14.9%)	84 (10.4%)	0.025
Tumor rupture	38 (9.7%)	41 (5.1%)	0.002
Resection			
Major hepatectomy	268 (68.7%)	465 (57.5%)	< 0.001
Minor hepatectomy	122 (31.3%)	343 (42.5%)	
Anterior approach right hepatectomy	65 (16.7%)	222 (27.5%)	< 0.001
Pringle maneuver	205 (52.6%)	134 (16.6%)	< 0.001
Use of ultrasonic dissector	279 (71.5%)	748 (92.6%)	< 0.001
Blood loss (l)	1.5 (0.1–20)	0.7 (0.01–15)	< 0.001
Major hepatectomy	1.7 (0.2–20)	0.92 (0.1–15)	< 0.001
Minor hepatectomy	1 (0.1–7)	0.5 (0.01–5)	< 0.001
Blood transfusion (l)	0.43 (0–9.9)	0 (0–3.84)	< 0.001
Major hepatectomy	0.6 (0–9.9)	0 (0–3.84)	< 0.001
Minor hepatectomy	0 (0–9)	0 (0–2.4)	< 0.001
No. (%) of patients with blood transfusion	216 (55.4%)	110 (13.6%)	< 0.001
Major hepatectomy	163 (60.8%)	87 (18.7%)	< 0.001
Minor hepatectomy	53 (43.4%)	23 (6.7%)	< 0.001
Abdominal drain	333 (85.4%)	169 (20.9%)	< 0.001
Laparoscopic resection	0	26 (3.2%)	0.196
Resection of portal vein / thrombectomy	20 (5%)	52 (6.4%)	0.372
Resection of inferior vena cava	9 (2.3%)	12 (1.5%)	0.309

Table 4. Comparison of pathology data.

		Group 1 (n=390)	Group 2 (n=808)	P value
Cirrhosis		193 (49.5%)	488 (60.4%)	< 0.001
Chronic hepatitis		143 (36.7%)	219 (27.1%)	
Normal liver		54 (13.8%)	101 (12.5%)	
Tumor size (cm)		7.5 (0.5–25)	5.3 (0.7–28)	< 0.001
Number (%) patients with solitary tumor		270 (69.2%)	585 (72.4%)	0.255
Microvascular invasion		179 (45.9%)	396 (49%)	0.312
Resection margin involved by tumor		38 (9.7%)	30 (3.7%)	0.01
TNM stage	I	21 (5.4%)	70 (8.7%)	0.290
	II	141 (36.2%)	269 (33.3%)	
	IIIA	121 (31%)	269 (33.3%)	
	IVA	107 (27.4%)	200 (24.7%)	
No. (%) of patients with tumor status within the Milan criteria		110 (28.2%)	343 (42.4%)	< 0.001
Liver pathology of patients with tumor status within Milan criteria				
	Normal	3 (2.7%)	25 (7%)	.106
	Chronic hepatitis	26 (23.6%)	60 (17.4%)	
	Cirrhosis	81 (73.6%)	258 (75.2%)	

Table 5. Comparison of postoperative data.

	Group 1 (n=390)	Group 2 (n=808)	P value
Mechanical ventilation	208 (53%)	139 (17.2%)	< 0.001
Intensive care unit stay (days)	2 (0–128)	1 (0–49)	0.001
Overall complication rate	153 (39.2%)	200 (24.8%)	< 0.001
Severity of complications			
Clavien-Dindo grade IIIa	96 (24.6%)	124 (15.3%)	< 0.001
IIIb	13 (3.3%)	20 (2.5%)	0.395
IVa	1 (0.26%)	12 (1.5%)	0.072
IVb	0	3 (3.7%)	0.555
V	23 (5.9%)	23 (2.8%)	0.01
Hospital mortality rate	24 (6.2%)	25 (3.1%)	0.012
Major hepatectomy	20 (7.5%)	20 (4.3%)	0.070
Minor hepatectomy	4 (3.3%)	5 (1.5%)	0.250
Hospital mortality rate			
Cirrhosis	15 (7.8%)	15 (3.1%)	0.007
Chronic hepatitis	6 (4.2%)	5 (2.3%)	0.354
Normal liver	3 (5.6%)	5 (5%)	1.000
Hospital stay (days)	12 (2–130)	10 (1–198)	< 0.001
Adjuvant treatment	54 (15.5%)	90 (11.1%)	0.185

Table 6. Comparison of follow-up data of patients without hospital mortality and residual tumor at hepatectomy.

	Group 1 (n=349)	**Group 2 (n=772)**	**P value**
Median (range) follow-up duration (months)	47.3 (1.2–244)	35.4 (0.4–131.8)	< 0.001
Overall recurrence rate	273 (78.2%)	465 (60.2%)	< 0.001
Recurrence within first year (%)	44.1	39.1	0.114
Recurrence pattern			
Intrahepatic	146 (53.5%)	241 (51.8%)	0.664
Extrahepatic	44 (16.1%)	78 (6.7%)	0.817
Both	83 (30.4%)	146 (31.3%)	0.778
First treatment for intrahepatic recurrence	229	387	
Re-resection	12 (5.2%)	45 (11.6%)	0.008
Chemoembolization	136 (59.3%)	181 (46.8%)	0.002
Alcohol injection	18 (7.8%)	1 (0.26%)	< 0.001
Radiofrequency ablation	6 (2.6%)	64 (16.5%)	< 0.001
Liver transplantation	3 (1.3%)	2 (0.5%)	0.366
High Intensity Focused Ultrasound	0	4	0.302
First treatment for extrahepatic recurrence	127	224	
Resection	25 (19.7%)	51 (22.8%)	0.5
Systemic chemotherapy	34 (26.8%)	31 (13.8%)	0.003
Median (range) survival duration after treatment of recurrence (months)	29.13 (1.13–239)	33 (0.3–123)	0.1142
Median (range) post-treatment survival duration of patients with intrahepatic recurrence only	38.3 (2.8–193.2)	48.5 (0.3–111.3)	0.068
Median (range) post-treatment survival duration of patients with extrahepatic recurrence only	11 (1.23–239)	37.2 (1.3–119.3)	0.0515
Median (range) overall survival duration (months)	42.3 (0.07-244.03)	68.33 (0.03-131.8)	< 0.001
Median (range) disease-free survival (months)	14.57 (0.53-235.63)	19.23 (0.4-130.93)	0.0024
Median (range) overall survival duration (months) of patients with tumor within the Milan criteria	85.67 (0.07–241.5)	112.93 (0.03–131.8)	0.0237
Median (range) disease-free survival duration (months) of patients with tumor within the Milan criteria	33.53 (1.1–235.6)	54.3 (0.97–130.9)	0.2659

Table 7. Univariate analysis of risk factors for disease-free survival.

	Group 1 (1989–1998)		Group 2 (1999–2008)		Entire group (1989–2008)	
	Patient number	**Median survival (months)**	**Patient number**	**Median survival (months)**	**Patient number**	**Median survival (months)**
Symptomatic presentation						
Yes	227	8.93	379	11.60	606	10.27
No	122	29.27*	393	41.33*	515	36.13*
Co-morbid illness						
No	254	11.73	470	15.47	724	14.47
Yes	95	22.00	302	32.00*	397	28.00*
Alpha-fetoprotein (ng/ml)						
≤ 500	200	16.43	522	28.23	722	23.7
> 500	145	8.47	247	9.1*	392	8.83*
Blood loss						
≤ 2 liters	224	21.20	682	22.2	906	21.97
> 2 liters	120	8.70*	88	7.7*	208	8.47*
Blood transfusion						
No	168	22.67	677	22.2	845	22.27
Yes	179	10.27*	95	7.7*	274	9.13*
Postoperative complication						
No	224	14.83	600	21.93	824	19.17
Yes	125	14.10	172	13.70	297	13.93*
No. of tumor						
Solitary	250	21.83	566	35.33	816	29.97
Multiple	99	6.63*	206	6.33*	305	6.57*
Tumor size						
≤ 5cm	131	29.40	391	44.60	522	36.63
> 5cm	218	9.10*	381	9.6*	599	9.23*
Liver status						
Non-cirrhotic	178	15.87	306	19.23	484	18.27
Cirrhotic	171	12.43*	466	19.17	637	16.97
Resection margin						
Not involved	318	16.43	746	20.40	1064	19.03
Involved	31	4.53*	26	4.43*	57	4.53*
Microvascular invasion						
Absent	192	29.97	396	52.43	588	42.5
Present	157	6.23*	376	8.03*	533	7.47*
Tumor rupture						
Absent	317	16.10	737	21.73	1054	19.17
Present	32	3.63*	35	8.60*	67	7.47*
Tumor-node-metastasis stage						
I/II	154	40.20	333	75.23	487	59.13
IIIA/IVA	195	6.07*	439	8.10*	634	7.57*
Period						
1989–1998	-	-	-	-	349	14.57
1999–2008	-	-	-	-	772	19.23*

* $p < 0.05$, comparison within group 1, 2 or entire group

Table 8. Significant factors predicting survival by multivariate analysis.

		Relative risk	95% confidence interval	P value
Disease-free survival				
Group 1	Blood loss (> 2 liters)	1.103	1.039–1.170	0.001
	No. of tumor nodule (> 1)	1.059	1.012–1.108	0.014
	Cirrhosis	1.672	1.316–2.125	< 0.001
	Microvascular invasion	1.508	1.155–1.969	0.003
	Tumor-node-metastasis stage	1.394	1.201–1.618	< 0.001
Group 2	Symptomatic presentation	1.283	1.059–1.555	0.011
	No. of tumor nodule (> 1)	1.069	1.034–1.106	< 0.001
	Microvascular invasion	1.459	1.160–1.836	0.001
	Positive resection margin	1.839	1.195–2.830	0.006
	Tumor-node-metastasis stage	1.421	1.232–1.638	< 0.001
Entire group	Symptomatic presentation	1.268	1.087–1.480	0.03
	Blood loss (> 2 liters)	1.046	1.008–1.086	0.017
	No. of tumor nodule (> 1)	1.069	1.041–1.098	< 0.001
	Positive resection margin	1.372	1.017–1.849	0.038
	Microvascular invasion	1.432	1.203–1.704	< 0.001
	Tumor-node-metastasis stage	1.356	1.222–1.504	< 0.001
Overall survival				
Group 1	Blood loss (> 2 liters)	1.104	1.060–1.149	< 0.001
	Indocyanine green retention rate (> 14%)	1.017	1.005–1.030	0.007
	Cirrhosis	1.722	1.344–2.206	< 0.001
	Tumor-node-metastasis stage	1.665	1.471–1.884	< 0.001
Group 2	Symptomatic presentation	1.416	1.125–1.782	0.003
	Postoperative complication	1.590	1.271–1.990	< 0.001
	No. of tumor nodule	1.055	1.016–1.095	0.005
	Positive resection margin	3.046	1.943–4.774	< 0.001
	Microvascular invasion	1.603	1.233–2.085	< 0.001
	Tumor-node-metastasis stage	1.557	1.331–1.822	< 0.001
Entire group	Symptomatic presentation	1.316	1.105–1.569	0.002
	Blood loss (> 2 liters)	1.079	1.043–1.116	< 0.001
	Postoperative complication	1.252	1.061–1.478	0.008
	No. of tumor nodule	1.047	1.018–1.076	0.001
	Positive resection margin	1.386	1.030–1.866	0.031
	Microvascular invasion	1.379	1.148–1.656	0.001
	Tumor-node-metastasis stage	1.476	1.325–1.644	< 0.001
	Period (1989 – 1998)	1.200	1.013–1.421	0.035

Table 9. Univariate analysis of risk factors for overall survival.

	Group 1 (1989–1998)		Group 2 (1999–2008)		Entire group (1989–2008)	
	Patient number	**Median survival (months)**	**Patient number**	**Median survival (months)**	**Patient number**	**Median survival (months)**
Age						
≤ 60	261	42.80	502	79.10	763	62.80
> 60	129	41.27*	306	63.13	435	53.93*
Symptomatic presentation						
Yes	260	30.97	403	41.33**	663	37.37
No	130	69.20*	405	112.93*†	535	100.3*
Alpha-fetoprotein (ng/ml)						
≤ 500	220	45.73	548	79.10	768	65.87
> 500	166	28.33	256	39.33*	422	37.37*
Indocyanine green retention (15 min) rate						
≤ 14%	248	49.20	537	67.93	785	60.07
> 14%	127	32.87*	232	84.0	359	56.83
Blood loss						
≤ 2 liters	243	60.03	709	77.80	952	68.50
> 2 liters	141	26.00*	97	21.43*	238	25.30*
Blood transfusion						
No	174	66.03	698	82.07	872	71.67
Yes	214	29.00*	110	21.40*	324	26.13*
Postoperative complication						
No	237	43.30	608	94.90	845	65.93
Yes	153	37.90	200	43.27*	353	41.27*
No. of tumor						
Solitary	270	60.30	585	96.20	855	77.00
Multiple	120	18.57*	223	28.97*	343	25.67*
Tumor size						
≤ 5cm	143	70.83	401	106.67	544	94.90
> 5cm	247	32.80*	407	37.97*	654	34.83*
Liver status						
Non-cirrhotic	197	49.23	320	69.63	517	60.83
Cirrhotic	193	35.27*	488	65.93	681	58.57
Resection margin						
Not involved	352	47.07	778	73.13	1130	63.70
Involved	38	13.40*	30	10.93*	68	12.97*
Microvascular invasion						
Absent	211	66.03	412	> 131.80	623	104.20
Present	179	25.3*	396	34.10*	575	29.93*
Tumor rupture						
Absent	352	44.73	767	77.00	1119	63.80
Present	38	19.03*	41	19.67*	79	19.67*
Tumor-node-metastasis stage						
I/II	162	95.43	339	> 131.80	501	141.57
IIIA/IVA	228	23.00*	469	33.23*	697	29.77*
Period						
1989–1998	-	-	-	-	390	42.30
1999–2008	-	-	-	-	808	68.33*

* $p < 0.05$, comparison within group 1, 2 or entire group

** p=0.0116, comparison between groups 1 and 2

† p=0.0082, comparison between groups 1 and 2

Figure 1

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Figure 1

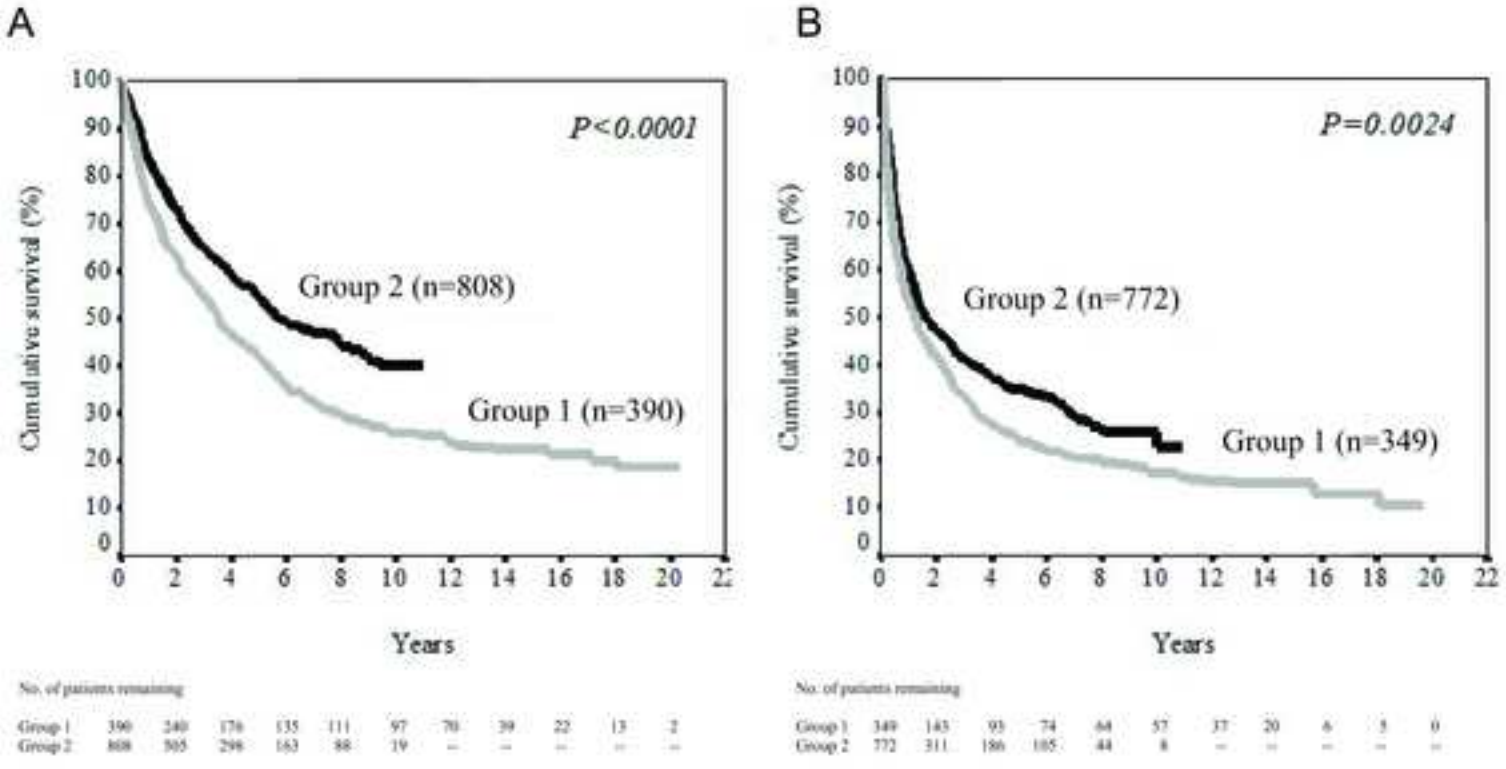

Figure 2A

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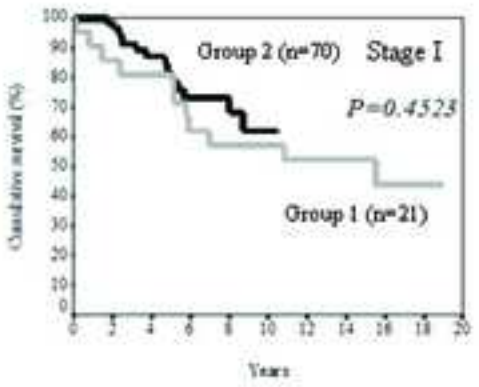
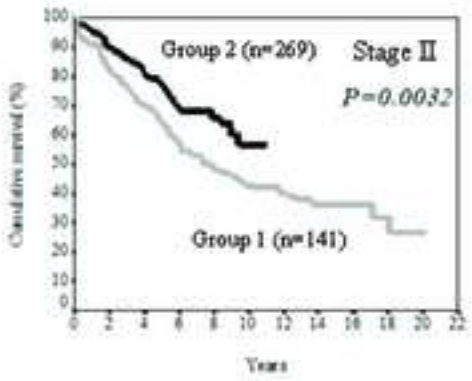
Figure 2

A



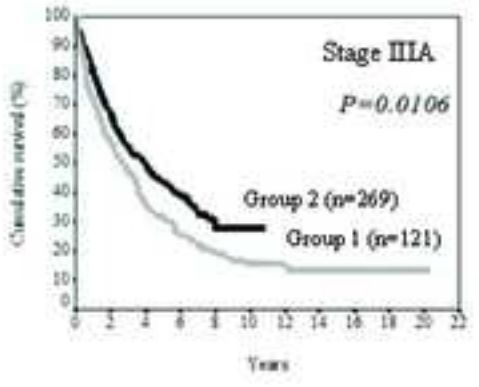
No. of patients remaining

Group 1	21	18	17	13	12	12	9	8	4	2	0
Group 2	70	56	37	24	16	3	–	–	–	–	–



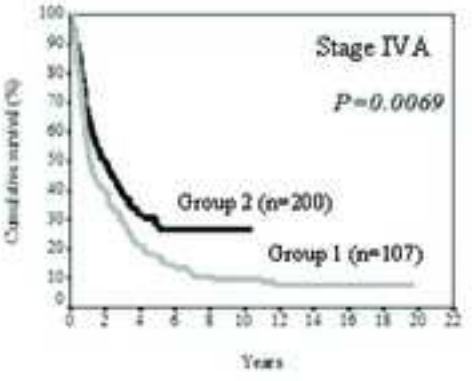
No. of patients remaining

Group 1	141	113	96	78	65	57	41	20	10	6	1
Group 2	269	214	143	83	47	7	–	–	–	–	–



No. of patients remaining

Group 1	121	68	41	29	23	18	14	9	6	4	1
Group 2	269	153	85	44	15	8	–	–	–	–	–



No. of patients remaining

Group 1	107	41	22	15	11	10	6	2	2	1	0
Group 2	200	82	33	12	10	1	–	–	–	–	–

Figure 2B

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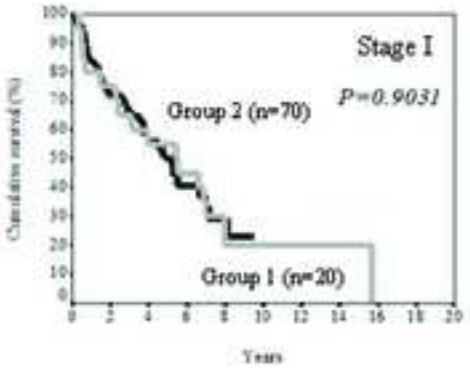
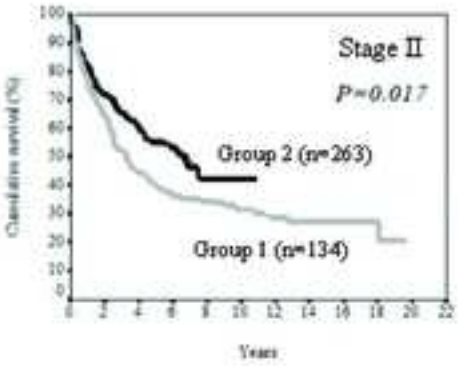
Figure 2

B



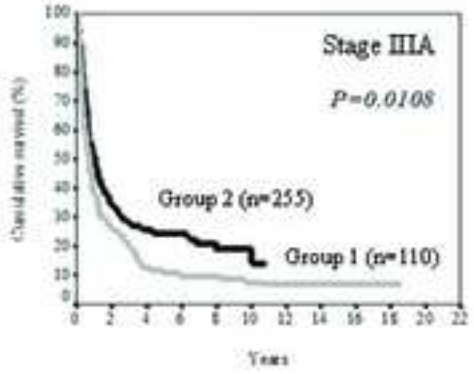


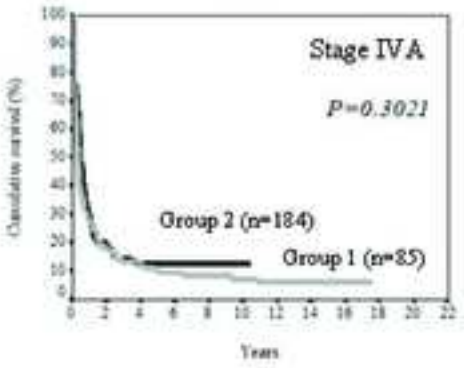
No. of patients remaining

Group 1	20	15	11	9	4	4	3	2	0	–	–
Group 2	70	41	24	12	5	0	–	–	–	–	–

No. of patients remaining

Group 1	134	85	58	47	43	39	26	14	4	4	0	
Group 2	263	167	105	60	25	4	–	–	–	–	–	





No. of patients remaining

Group 1	110	28	13	10	10	8	5	3	1	1	0	
Group 2	255	75	44	27	9	3	–	–	–	–	–	

No. of patients remaining

Group 1	85	13	11	8	7	6	3	1	1	1	0	–
Group 2	184	28	13	6	5	1	–	–	–	–	–	

Figure 3

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Figure 3

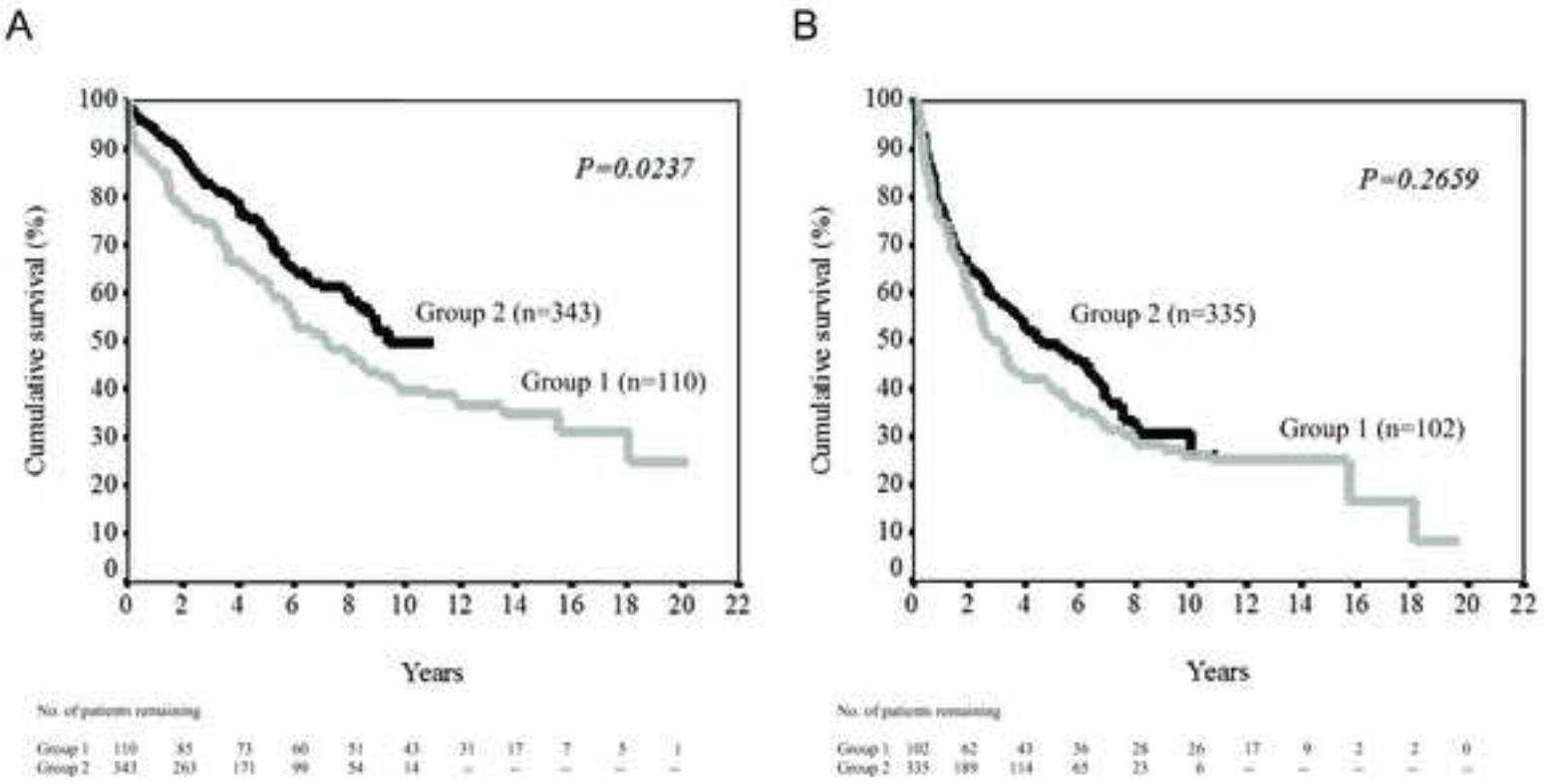

Figure 4

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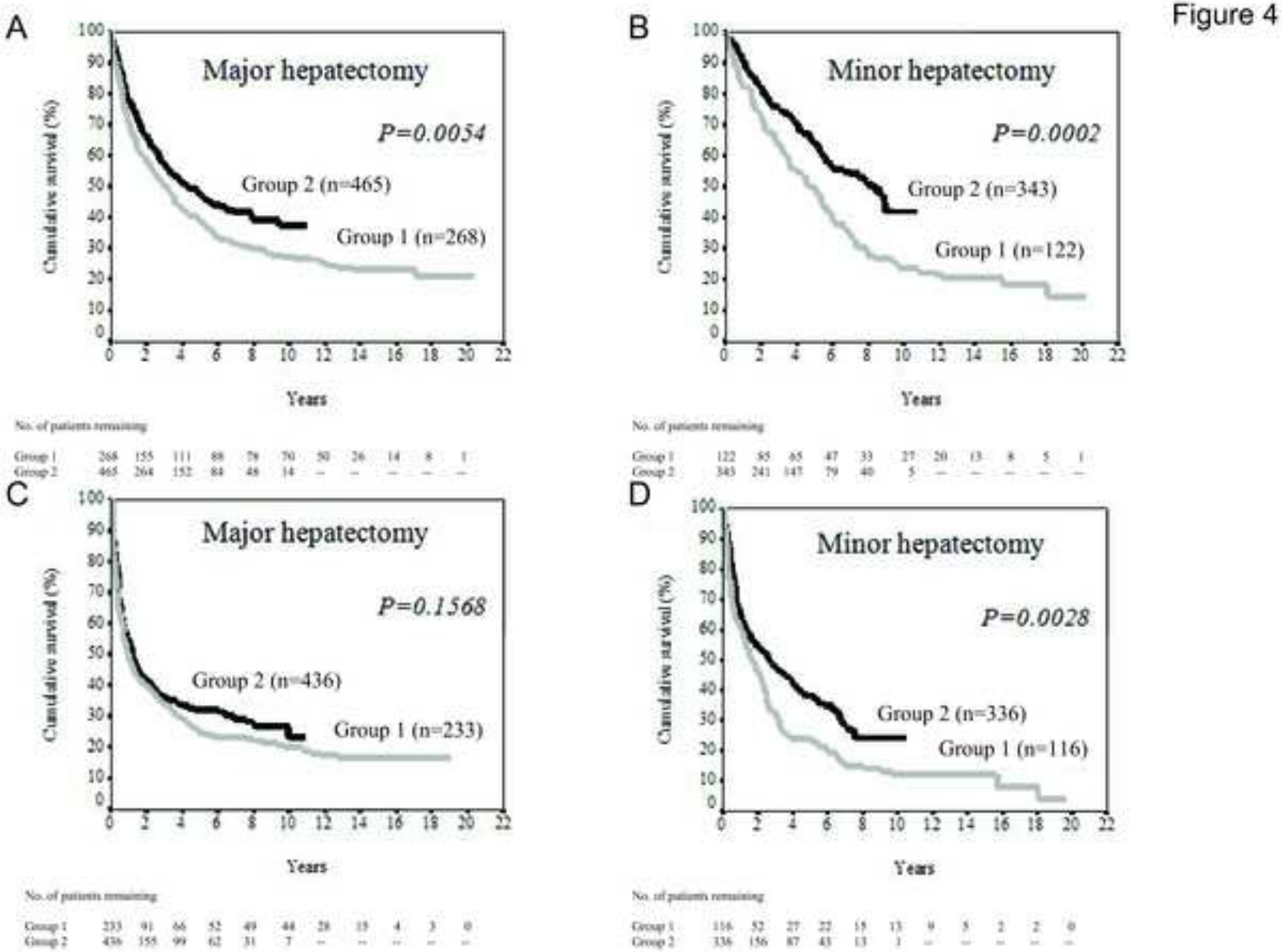

Figure 4

Figure 5
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Figure 5

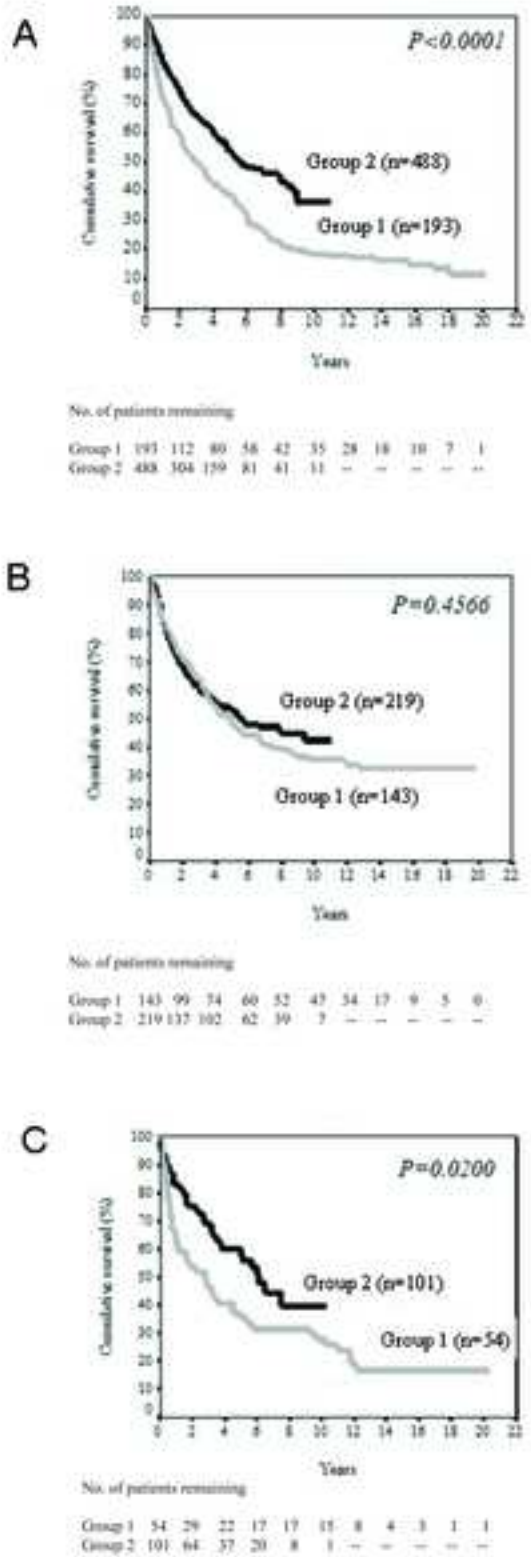

Figure 6

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Figure 6