Hepatic resection for primary liver cancer at a private community hospital: retrospective study of 61 patients

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Objective. To review the outcome after surgical resection for primary liver cancer.
Design. Retrospective study.
Setting. Private community hospital, Hong Kong.
Patients. Sixty-one consecutive patients who underwent liver resection for primary cancer from 1992 through 1997.
Main outcome measures. Clinicopathological features, type of resection, duration of hospital stay, and actuarial overall and disease-free 5-year survival rates.
Results. Cirrhosis was present in 46 (75%) of the patients, and 42 (69%) were positive for hepatitis B surface antigen. The median tumour diameter was 8 cm (range, 1-16 cm). Liver resections consisted of hemihepatectomy (n=37), trisegmentectomy (n=4), segmentectomy (n= 11), and wedge resection (n=9). Postoperative death and major morbidity occurred in 0% and 36% of patients, respectively; ascites was the most common complication. The median hospital stay was 11 days. The actuarial overall and disease-free 5-year survival rates were 36.0% and 22.8%, respectively. These results are similar to or better than those recently reported from local or overseas centres. Multivariate analysis showed that the Child-Pugh class significantly influenced the development of complications and the length of hospital stay, whereas a well-circumscribed tumour margin, the tumour-node-metastasis stage of the tumour, and the Child-Pugh class were independent predictors of survival.
Conclusion. Surgical resection for primary liver cancer can be performed with acceptable safety and efficacy in a suitably staffed and equipped private community hospital.

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Key words: Carcinoma, hepatocellular/surgery; Hepatectomy; Liver neoplasms/surgery; Postoperative complications

Introduction

Primary liver cancer is the second most common malignant neoplasm in Hong Kong.[1] Surgical resection is the only effective treatment. Unfortunately, most patients present at an advanced stage of disease, when surgical resection is not an appropriate mode of treatment. The surveillance of hepatitis B carriers using hepatic ultrasonography and serum α-fetoprotein (AFP) tests has resulted in an earlier diagnosis of liver cancer.[2,3]

Liver resection is a major surgical undertaking. It has been associated with very high rates of postoperative mortality and morbidity, and more than 10% of patients may die of the operation even in experienced centres.[4-6] For patients who have coexisting cirrhosis of the liver, as is the case with a majority of patients in Hong Kong, the risk of requiring surgery is even higher. In the past, many patients died of bleeding during hepatectomy, or of sepsis and liver failure in the postoperative period. Recent major advances in surgical technique and physiological support have increased the safety of liver resection. Questions have been raised as to whether private community hospitals in Hong Kong have sufficient support facilities and technical expertise to perform liver resection—in particular, major liver resection, which is often needed to treat primary liver cancer.

This study reviewed the outcome after surgical resection for primary liver cancer in 61 consecutively treated patients at the Hong Kong Sanatorium and Hospital form 1992 through 1997. All the patients underwent hepatic resection performed by the first author.

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Methods

Patient criteria

Sixty-one patients were admitted to the Hong Kong Sanatorium and Hospital during the 6-year study period for liver resection, after computed tomography (CT) or magnetic resonance imaging (MRI) studies, complete blood count (including platelet count and prothrombin time), and liver function tests had been performed. A preoperative clinical diagnosis of primary liver cancer was made on the basis of an elevated serum AFP level and characteristic features of the disease that were visible in the CT or MRI scans. Biopsy of the lesion was avoided, unless there was strong suspicion of a condition for which resection would not be necessary, such as an abscess or a regenerative liver nodule.

To minimise the risk of adverse effects of surgery, all patients needed to fulfil a set of criteria of patient fitness, as formulated by the surgeon and the attending hepatologist or internal medicine specialist. These criteria for resection were as follows: (1) the patient would need to be fit to undergo major abdominal surgery and be in a 'good' risk-category based on the Child-Pugh classification of liver function[7]—that is, Child-Pugh class A or B, and not C; (2) the tumour(s) could be resected completely and without damage to the blood supply or bile ducts of the remaining liver segments; and (3) the remaining liver segments would be sufficiently large and functional to permit recovery, taking into consideration the presence of cirrhosis, chronic hepatitis, or fatty change. In the Child-Pugh classification system, the degree of increase in the serum bilirubin and decrease in albumin levels, and the extent of the prolonged prothrombin time determine the classification of a given patient. Class A denotes minimal abnormality of liver function, while class C denotes severe functional derangement. Any patient with medically uncontrolled ascites or encephalopathy is graded as being in class C.

To judge whether the remaining liver segments would be large enough to provide adequate function after operation, a discount of the hepatic preoperative functional status was estimated after performing a detailed anatomical study of the CT or MRI scans. The discount was based on the percentage volume of non-tumour liver tissue to be removed. For example, a right hemihepatectomy would be considered safe even for a patient in Child-Pugh class B, provided that the right hemiliver had been mostly replaced by a large tumour and the left hemiliver segments were enlarged; the functional discount would thus be relatively small. This anatomical assessment was as important as and complementary to the functional assessment by the Child-Pugh classification. Quantitative assessments of liver function such as the bromsulphthalein retention and indocyanin green excretion tests were not conducted.

Liver resection

The surgical operation was performed while the patient was receiving endotracheal general anaesthesia. Ceftriaxone 1g was given prophylactically by intravenous injection before the operation. A bilateral subcostal incision was made in 55 patients. Six patients underwent right thoracotomy to provide access to the superior or posterior parts of the right lobe of the liver, which allowed the wedge or segmental resection of the tumour to be performed. Intra-operative ultrasonography of the liver was used to assist the resection procedure and to look for foci of the tumour that had not been detected in the preoperative scans. Blood transfusion was given as needed and at the instruction of the attending anaesthetist. Except for a second injection of ceftriaxone given postoperatively in cases of a prolonged operation, postoperative antibiotics were used to treat only suspected or proven infection. The aim of the operation was curative so as to leave no detectable tumour. Whenever the margin of resection was judged to be close or inadequate, frozen-section microscopic examination was performed. Pathological examination, however, showed that the margin of resection was free of tumour in all cases.

Postoperative care

The endotracheal tube was removed at the end of the operation in all of the patients except two, who required ventilatory support. The patients were either returned to their ward for nursing care or transferred to the intensive care unit. An overnight postanaesthetic recovery room was not available at the Hong Kong Sanatorium and Hospital. Postoperative care was given by the surgeon and the attending hepatologist or internist. Oral feeding was started usually by the first or second day after the surgery. Patients who had undergone major resection were given an intravenous infusion of potassium hydrogenphosphate to prevent the development of hypophosphataemia.[8] After the sutures had been removed, patients were discharged home if they could feed normally, and were without fever, severe pain, or other discomfort.

Statistical analysis

Postoperative death was defined as death that occurred within 30 days of the operation, or within the same period of hospitalisation if the survival time was

longer than 30 days. Patient survival rates after resection were calculated from the Kaplan-Meier survival curve. Analysis of the univariate association of clinicopathological factors with survival endpoints was performed with the logrank test. The Cox regression model (proportional hazards regression analysis) was used to identify independent factors that affected survival. Multivariate regression analysis was performed to search for predictors of major complications, the need for blood transfusion, and the length of hospital stay. The cut-off level for statistical significance was taken as P=0.05.

Results

Patient and operation characteristics

Table 1 lists the clinicopathological features of the 61 patients in this series. The male to female ratio was 3.7:1. The median age was 54 years (range, 23-81 years); four patients were older than 70 years and three were older than 80 years. Hepatocellular carcinoma (HCC) had been diagnosed in 56 patients, and primary cholangiocarcinoma (CCA) or mixed HCC and CCA had been diagnosed in five patients. Hepatitis B surface antigen was present in 42 (69%) patients; one patient was infected with the hepatitis C virus and one had primary biliary cirrhosis. Histopathological changes of cirrhosis were confirmed in 46 (75%) patients. According to the Child-Pugh classification, there were 54 (88%) patients in class A, 7 (12%) in class B, and none in class C. The median tumour diameter was 8 cm (range of maximal diameter, 1-16 cm). The tumour-node-metastasis (TNM) staging of the tumours was assigned postoperatively according to established criteria.[9] Among the patients who had HCC, the serum AFP level was within the normal range in 18 patients and elevated in 38 patients. The median level of AFP in these 56 patients was 40 ng/mL, the highest level being 296 180 ng/mL.

Table 1. Demographic and clinicopathological features of patients with liver cancer

Feature	Patients, n=61 No. (%)
Sex	
Male	45 (74)
Female	16 (26)
Age	
<45 years	18 (30)
45-59 years	20 (33)
60-81 years	23 (38)
Hepatitis carrier state	
HBsAg*-positive	42 (69)
HBsAg-negative	18 (30)
Anti–hepatitis C virus antibodies	1 (2)
Cirrhosis	
Present	46 (75)
Absent	15 (25)
Child-Pugh class	
Class A	54 (88)
Class B	7 (12)
Class C	0
Tumour diameter	
0.0-3.0 cm	4 (7)
3.1-4.9 cm	10 (16)
5.0-9.9 cm	23 (38)
≥10 cm	24 (39)
Tumour-node-metastasis stage†	
Stage I (T1, N0, M0)	3 (5)
II (T2, N0, M0)	41 (67)
III (T3, N0, M0)	2 (3)
IV (T4, N0, M0)	15 (25)
Tumour margins	
Well circumscribed	18 (30)
Not well circumscribed	43 (70)
Portal vein invasion by tumour	
Invasion present‡	15 (25)
No invasion	46 (75)

* HBsAg hepatitis B surface antigen
† T1: tumour ≤2 cm in diameter without vascular invasion; T2: tumour <2 cm with vascular invasion, or multiple tumours <2 cm in one lobe without vascular invasion, or tumours >2 cm without vascular invasion; T3: tumour ≥2 cm with vascular invasion, or multiple tumours >2 cm in one lobe; T4: multiple tumours in more than one lobe, or tumour with vascular invasion
‡ Includes four patients who had tumour thrombus in the portal vein

Of the 61 patients, 52 (85%) underwent major resections involving right or left hemihepatectomy or hepatic segmentectomy, and nine underwent wedge resections (Table 2). Temporary clamping of the hepatic artery and the portal vein was applied in 10 patients to reduce blood loss. The median duration of the surgery was 5.0 hours (range, 1.5 to 8.5 hours). Twelve (20%) patients did not receive blood transfusion, 14 (23%) received one or two units of packed cells, and 35 (57%) received three to 13 units. Six or more units of packed cells were given to eight patients who had undergone right hemihepatectomy or right trisegmentectomy. Three of these eight patients were in Child-Pugh class B, and two had preoperative thrombocytopenia (platelet count, $\leq 30 \times 10^9$ g/L [normal range, $150\text{-}450 \times 10^9$ g/L]) due to hypersplenism. Two of the eight patients had a segment of diaphragm or the right kidney removed, one had an additional 'middle lobectomy' (segment IV), one had an additional caudate lobectomy, and one received a portal vein thrombectomy. Multivariate analysis of the clinicopathological factors and the extent of liver resection showed that only the Child-Pugh class and the size of the tumour were independently associated with blood transfusion.

On the day following the liver resection, all the patients received intercostal nerve block and other

Table 2. Anatomical classification of the liver resections performed

Type of resection	Patients, n=61 No. (%)
Hemihepatectomy*	
right	27 (44)
left	10 (16)
Trisegmentectomy†	4 (7)
Segmentectomy	
I (caudate lobe)	1 (2)
II + III (left lateral segment)	4 (7)
IV	1 (2)
V + VIII (right anterior segment)	2 (2)
VI + VII (right posterior segment)	3 (5)
Wedge resection	9 (15)

* Part of the adjacent segment was also removed in six patients
† Right hemihepatectomy and removal of segment III or segment I

analgesics to relieve pain; all patients were ambulatory. Thirty-nine (64%) of the patients were returned to their ward, while the remainder were transferred to the intensive care unit for a median of 1 day (range, 1-5 days). None of the patients were discharged to a nursing home or similar institution. The median hospital stay was 11 days (range, 7-39 days). Multivariate analysis showed that the Child-Pugh class was the only independently significant factor that affected the length of hospital stay.

Operative mortality and morbidity

The operative mortality rate was 0%; none of the patients died during the operation, and none died within 30 days of surgery or before being discharged home. The only major intra-operative complication was bleeding associated with thrombocytopenia and a coagulation defect in one patient, who needed the insertion of abdominal packing to achieve haemostasis; the packing was removed 3 days later without further bleeding.

Major postoperative complications occurred in 22 (36%) patients, the most common being postoperative ascites, which occurred to a significant degree in 12 (20%) patients and which was managed by giving diuretic therapy. Significant pleural effusion developed in three patients, and subphrenic fluid collected in another three patients, who needed catheter or needle drainage. There were no cares of true subphrenic abscess, although culture of the fluid yielded pathogenic organisms in one patient. Serious postoperative pulmonary atelectasis occurred in three patients: two responded to chest physiotherapy and analgesics, and basal pneumonitis in the third patient subsided when antibiotic treatment was given. Mild hepatic encephalopathy occurred after a right hemihepatectomy in one patient who had pre-existing cirrhosis and diabetes mellitus. The encephalopathy resolved following the administration of lactulose and the control of the diabetes.

The serum transaminase levels rose in all patients immediately after the operation. In those patients who had undergone the resection of major liver lobes or segments, the serum bilirubin level increased while the serum albumin level decreased. The levels returned to normal or near their preoperative levels within several weeks (or longer after major resections). The jaundice in one patient who had biliary cirrhosis worsened as the serum bilirubin level increased, but the jaundice subsided several weeks later as dietary intake and liver function improved. The duration of hospital stay exceeded 14 days in 16 (26%) of the 61 patients, mainly because of intractable ascites; other causes included the need to control diabetes mellitus in three patients, unstable anxiety state in one patient, and the development of cavitating pulmonary tuberculosis in another. Except for the patient who required the removal of the haemostatic abdominal packing, no patient needed a reoperation before being discharged home. Multivariate analysis showed that the Child-Pugh class was the only statistically significant factor that was independently associated with the development of major complications. Old age was not a predictor of postoperative morbidity.

Minor postoperative complications such as nausea and vomiting were uncommon. Two patients had fluid collection in their wounds, but no patient had wound disruption or purulent wound infection.

Survival rates

The actuarial overall and disease-free 5-year survival rates after resection were 36.0% (standard error of the mean, 8.2%) and 22.8% (6.6%), respectively (Fig). Of the 61 patients, 31 (51%) were alive, 29 (48%) had died of liver cancer, and one (2%) patient had been lost to follow-up at the time of writing. None of the patients died of liver failure alone without evidence of gross tumour recurrence in the liver. Of the 31 surviving patients, 21 (68%) had been free of known residual liver cancer for a median duration of 24 months after the resection (range, 5-78 months). Five have survived for 5 years or more. Liver cancer recurred in 10 of the 31 survivors, and these patients have been receiving treatment for 4 to 44 months after surgery. Twenty-nine patients died 3 to 41 months after the resection (median survival time, 4.8 months). Six (40%) of the 15 patients who died within 4.8 months had a stage IV tumour; two of these six patients had presented with intraperitoneal tumour rupture.

Prognostic factors that affected survival

Univariate analysis of the clinicopathological details and the treatment given showed that the gender, age, hepatitis B surface antigen or hepatitis C antibody status, presence or absence of liver cirrhosis, Child-Pugh class, extent of liver resection, tumour invasion of the portal vein, and the number of blood transfusions had no significant correlation with the overall survival or disease-free survival rates. An AFP level of more than 10 000 ng/mL (P=0.006), a tumour diameter of more than 5 cm (P=0.047), a lack of circumscribed tumour margins (P=0.023), and the TNM staging (stages III and IV versus I and II; P=0.003) showed a significantly adverse effect on the survival rate by univariate analysis.

Multivariate analysis using the Cox regression model identified three factors as independent predictors of survival: the presence or absence of well-circumscribed tumour margins, the TNM staging, and the Child-Pugh class.

Discussion

Despite the high frequency of primary liver cancer in Hong Kong and South-East Asia, expertise in the surgical treatment of this disease has been limited mostly to academic institutions. Our experience from the 61 consecutive liver resections for primary liver cancer reported here affirms the safety of such surgical treatment in a private community hospital in Hong Kong. The absence of postoperative death, the length of hospital stay, and the acceptable though frequent occurrence of major complications are similar to the results that have been reported recently from a local university teaching hospital,[10] and similar to or better than some of the internationally reported findings.[11-14] It is difficult to make a direct comparison of the characteristics of the patients, the nature of their tumours, and the extent of the resections of this study with those reported from other institutions. However, the median tumour diameter of 8.3 cm, frequency of coexisting cirrhosis (75%), percentage of Child-Pugh class B patients (12%), and proportion (67%) of patients receiving major resection in the form of hemihepatectomy or trisegmentectomy (Tables 1 and 2) are similar to the figures from recently reported series.[10,15]

While the zero operative mortality rate of this study is encouraging, we do not feel complacent about the high frequency of major complications, use of blood transfusion, and the associated long duration of hospital stay. Multivariate analysis showed that these factors are strongly correlated with liver resection in patients of Child-Pugh class B. The high risk of morbidity in these patients can be minimised by giving more vigorous perioperative medical treatment

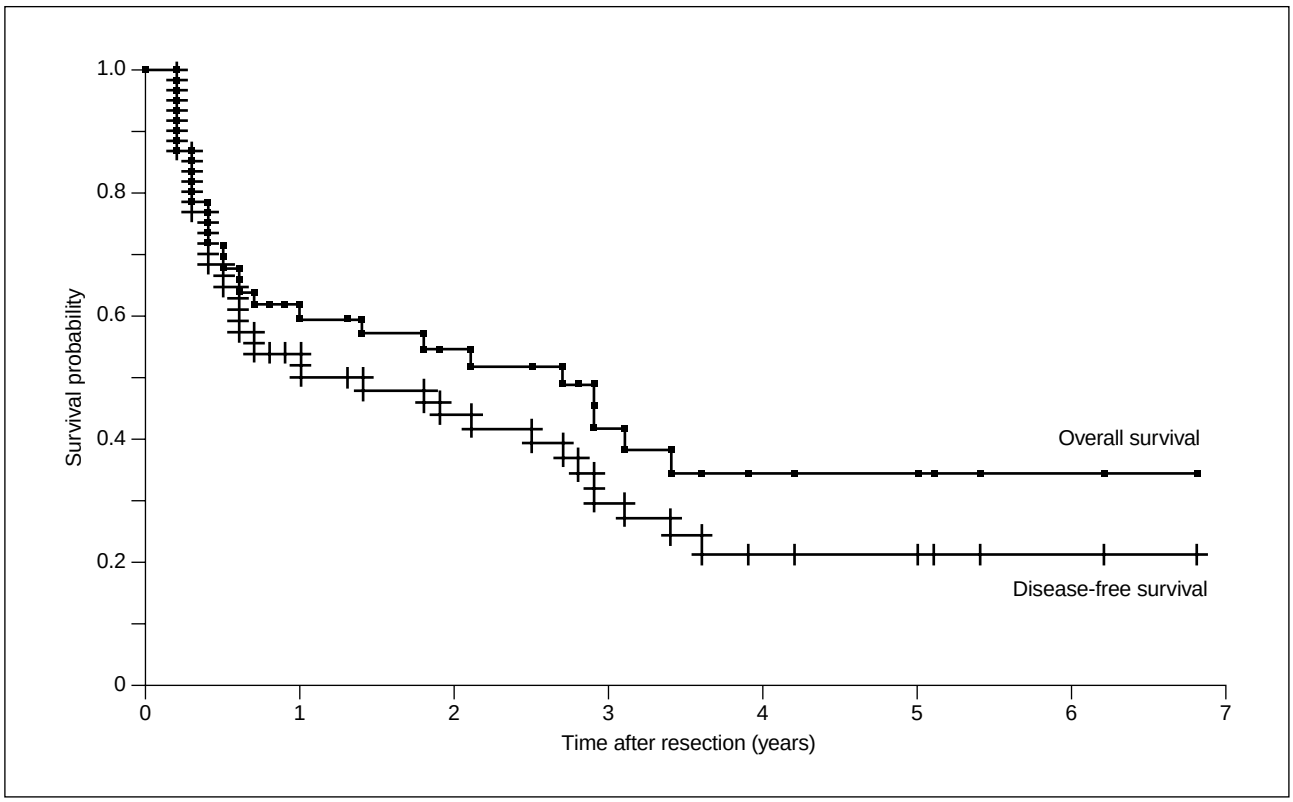

Fig. Actuarial overall and disease-free survival curves after liver resection

that aims at improving hepatic function and by giving perioperative nutritional support.[14] In addition, suppressing hepatitis B virus replication by giving antiviral drug treatment (which is done for patients with advanced liver disease and for liver transplant recipients) can minimise morbidity.[16,17]

Minimising the use of blood transfusion would also be desirable. Multivariate analysis did not show any adverse influence of blood transfusion on the survival rate in this series; others, however, have suggested such an influence.[18] Many factors dictate the use of blood transfusion during hepatectomy and include the size and location of the tumour, the functional status of the liver (ie the Child-Pugh class, as shown in this study), the technique of dissection, and the clinical judgement of the attending anaesthetist. By improving the preoperative preparation of the Child-Pugh class B patient, refining surgical technique, and ensuring coordination between the surgeon and the anaesthetist, major liver resection even in the cirrhotic patient can probably be performed without blood transfusion in most if not all cases.

The relatively low 5-year survival rates found in this study (36.0% overall and 22.8% disease-free) reflect the high percentage of advanced-stage tumours and are similar to the rates reported (35.0% overall and 22.8% disease-free) during 1987 to 1994 by a teaching institution in Hong Kong.[19] Nevertheless, the figures represent a substantial improvement compared with the reported local survival rate of only 15% about 10 years ago.[6] Studies have shown that factors such as the AFP level, tumour diameter, portal or hepatic vein invasion, and the margin of resection independently influence survival.[15,20,21] This study showed similar trends, but statistical significance was not demonstrated, possibly owing to the relatively small number of subjects.

The main site of tumour recurrence after resection is the remaining portion of the liver; a small proportion of patients may also develop lung, bone, brain, or disseminated metastases. The rather short median time to tumour recurrence of 4.8 months in this series, mostly within the liver, is disconcerting. Poon et al[22] have recently reported the median interval to recurrence to be only 6.0 months. More sensitive preoperative imaging studies, such as lipiodol-arteriography combined with CT, CT of the lungs, and possibly positron emission tomography are thus needed to identify all foci of the tumour before resection is performed. In the future, adjuvant therapy may significantly improve the survival rate; a prospective randomised study from Hong Kong has shown that internal radiotherapy of the liver by the intra-arterial injection of iodinated I 131 lipiodol can prolong survival.[23] Surgical treatment of liver cancer will be further improved by the early detection and diagnosis of small tumours, especially if more resources can be provided to target screening[2,3] of high-risk groups of the population.

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