Resection of Hepatocellular Carcinoma : Personal Experience with 67 Patients and Long-Term Results

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Abstract

Hepatocellular carcinoma (HCC) is the most common cancer in Thailand. Hepatic resection has been accepted as the only chance for cure. However; very limited information about the operative treatment and survival of HCC in Thailand has been documented.

The author reviewed the experiences of surgical treatment of HCC at the National Cancer Institute, Bangkok and reports herein the long term outcome.

From January 1986 to January 1996 a total of 884 primary liver cancers admitted in our institute were reviewed. 112 consecutive hepatic resections were performed by the author. 67 of 112 patients were HCC of which clinical features, survival rate and recurrence were studied.

Liver cirrhosis was associated in 49 patients (73.1%). HBsAg was positive in 58 patients (86.6%). Preoperative AFP level was more than 400 ng/ml in 35 patients. The resectability for HCC was 11.0 per cent. In 50 of 67 hepatic resection, major hepatic resection were carried out. Postoperative major complications were found in 14 patients (20.9%). Postoperative mortality rate of 5 patients was 7.5 per cent. Survival curve was calculated by Kaplan-Meier with the overall survival rate at 1, 2, 3, 4, 5 years was 63.2 per cent, 28.6 per cent, 21.1 per cent, 14.5 per cent and 11.5 per cent respectively. 1, 3, 5 years survival rate for a tumor less than 5 cm was 91.0 per cent, 57.0 per cent, 49.4 per cent, tumor size of 5-10 cm was 57.5 per cent, 16.0 per cent, 9.0 per cent and tumor size more than 10 cm was 52.2 per cent, 0 per cent, 0 per cent. A significant difference in survival rate was observed by size. Postoperative recurrences were observed in 45 patients (67.2%) and 82.8 per cent of the patients had intrahepatic recurrence within 2 years.

Hepatic resection is an appropriate treatment for a tumor less than 10 cm. However, a tumor larger than 10 cm should be considered for multimodality approaches. Intrahepatic recurrence is high and similar to the reports from the Orient. Close follow-up with prompt treatment for recurrence is the important factor to obtain better results.

Key word : Hepatocellular Carcinoma, Hepatic Resection, Long-Term Result

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Liver cancer has been considered to be a highly malignant and is a major problem in South-East Asia. It has been estimated that liver cancer in this region is responsible for 16.5 per cent of new cancers in males and 4.5 per cent in females[1]. In Thailand, liver cancer is the most frequent malignant neoplasm of males and third in females. It is responsible for 16.3 per cent of all new cancers in males and 5.5 per cent in females[2]. Except in the Northeastern part of Thailand which is an endemic area of Cholangiocarcinoma (CCC), Hepatocellular carcinoma (HCC) is the most-frequent histological type of primary liver cancer nationwide[3].

Among the various treatment modalities for HCC, it has been generally accepted that hepatic resection is the best chance for cure. However, most patients have underlyng liver cirrhosis, and because of the malignant nature of this disease, the resectability rate is very low.

With remarkable advances in non surgical treatment of HCC such as transcatheter chemoembolization (TAE), percutaneous ethanol injection, the survival of unresectable HCC has improved. On the other hand, with recent improvement of liver surgical techniques and greater knowledge of liver anatomy, the survival rate of surgical treatment for HCC has also increased. However, very limited information about the operative treatment and survival of HCC has been documented in Thailand.

The purpose of this paper was to summarize and review a single surgeon's experience and results in hepatic resection for HCC in Thailand.

PATIENTS AND METHOD

From January 1986 to January 1996, a total of 884 patients with primary liver cancer were admitted to the National Cancer Institute Hospital, Bangkok, Thailand. Of these patients, 609 patients were Hepatocellular carcinoma (HCC) and 275 were Cholangiocarcinoma (CCC). 112 consecutive hepatic resections for primary liver cancer were performed by the author during this period. 67 of these 112 hepatic resections were HCC of which clinical features, survival rate and recurrence were studied in this report. Of the 67 hepatic resections, 30 were performed during the period of January 1986 and December 1989, and the other 37 cases were from January 1990 to January 1996.

There were 55 male and 12 female patients. The male and female ratio was 4.6 : 1. The age of patients ranged from 17 years to 73 years, with a mean age of 47.1 years. Liver function was assessed by Child-Pugh's classification[4] 60 patients had child's class A, and 7 patients had Child's class B.

Operative procedures

Operative precedures used were classified in accordance with the anatomical extent of resection. Major hepatic resection was defined as 2 or more than 2 segments resected, i.e. lobectomy, extended lobectomy. Minor hepatic resection was defined as resection of one or less than one segment, i.e., lateral segmentectomy, subsegmentectomy of Couinaud's segment, wedge resection.

Surgical technique

Most of the major hepatic resections were carried out with extrahepatic control of the arterial and portal inflow of the part of the liver that was to be resected. Hepatic vein dissection was mainly approached by the intrahepatic method. Various methods of parenchymal transection were used, such as ultrasonic dissector, microwave coagulator but recently using a Kelly clamp instead of finger fracture method was the main parenchymal transection technique. Furthermore, total vascular exclusion technique was applied in some cases where the tumor was close to major vessels and without cirrhosis.

Follow-up

The patients were followed-up and assessed every 3 months by clinical examination, hepatic profile, alpha fetoprotein (AFP) and ultrasonogram, follow-up was possible for all but 4 patients were lost to follow-up.

Statistics

Operative mortality means that the patient died within 30 days after the operation. Postoperative survival was analyzed according to the Kaplan-Meier survival method, comparison between groups was done by the Chi-Square test.

RESULTS

Clinical features

Liver cirrhosis was the associated disease in 49 patients (73.1%). The maximal diameter of the tumor was less than 5 cm in 10 patients (14.9%), between 5 and 10 cm in 34 (50.8%) and more than 10 cm in 23 patients (34.3%). Tumor size less than 5 cm, 5-10 cm, more than 10 cm had associated liver

Table 1. Operative procedures in 67 hepatic resections.

Major resection (≥2 segments)		Minor resection (≤ 1 segment)	
Right trisegmentectomy	9	Lateral segmentectomy	3
Extended right lobectomy	6	Medial segmentectomy	1
Right lobectomy	21	Right posterior segmentectomy	2
Extended left lobectomy	1	S4b+S5+S6	1
Left lobectomy	10	S4b+S5	5
Central bisegmentectomy	3	S5+S6	1
		S1	1
		Partial resection	3
Total	50 (74.6%)	Total	17 (25.4%)

Table 2. Postoperative complications.

Rupture of esophageal varices	1
Massive ascites	2
Biloma (Bile leakage)	3
Massive pleural effusion	2
Intraabdominal bleeding	1
Intestinal obstruction	1
Subphrenic collection	1
Renal failure	1
Pneumonia	1
Total	14/67 (20.9%)

cirrhosis in 5 patients (50%), 24 patients (70.6%) and 20 patients (87.0%) respectively. HBsAg was found to be positive in 58 patients (86.6%). Anti-HCV was measured in 20 cases and was found to be positive in only one case. Preoperative serum level of alpha-fetoprotein(AFP) was lower than 10 ng/ml, 10-400 ng/ml and more than 400 ng/ml in 16 patients (23.9%), and 35 patients (52.2%) respectively,

The resectability rate for total primary cancer in this study was 12.7 per cent and for HCC was 11.0 per cent, for CCC was 16.4 per cent respectively.

Table 1 shows the details of operations done on 67 patients.

Mortality and Morbidity

Postoperative complications were observed in 20.9 per cent of the 67 patients and summarized in Table 2. Three patients had biloma and needed nonsurgical drainage, and all of these patients received preoperative transcatheter chemoembolization, 5 patients died within 30 days post operative period, yielding an operative mortality rate of 7.5 per cent. Hepatic failure was the main cause of death in 4 patients and another one was ARDS. These four patients were found to under right trisegmentomy and all of them were Child-Pugh Class B liver cirrhosis.

Survival

There were 13 patients and 5 patients who survived more than 3 years and 5 years respectively in this series. Of those patients who survived more than 5 years, 80 per cent had no cirrhosis, and 4 of 5 patients had tumor size 5-10 cm; another one had tumor size less than 5 cm.

Overall survival and survival for different subsets of patients are presented in Fig. 1 and 2. The overall 1, 2, 3, 4 and 5 year survival rates of all patients were 63.2 per cent, 28.6 per cent, 21.1 per cent, 14.5 per cent, and 11.5 per cent, respectively. The 1, 2, 3, 4, 5 year survival rates of the patients with a tumor less than 5 cm were 91 per cent, 75 per cent, 57 per cent, 49.4 per cent and 49.4 per cent, Those patients with a tumor 5 to10 cm were 57 per cent, 18.8 per cent, 16.0 per cent, 12.5 per cent and 9 per cent. Those with a tumor larger than 10 cm, 1 and 2 years survival rates were 52.2 per cent, and 12 per cent but there was no 3 year- survival in this group. There was significant difference in survival rates according to tumor size, ($p < 0.05$).

Recurrence

During surveillance, postoperative recurrence was observed in 45 patients (67.2%) of 67 patients. Table 3 shows the details of the 45 patients with recurrence. Intrahepatic recurrence was found

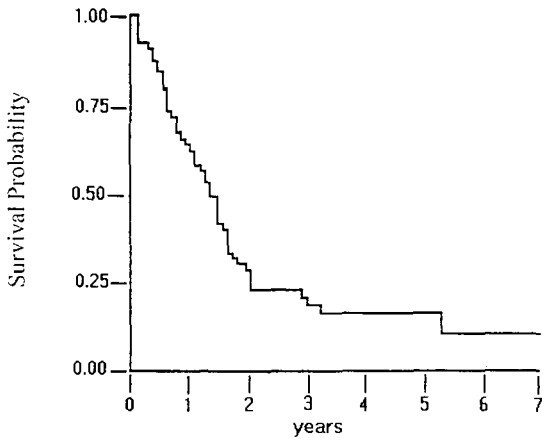

Fig. 1. Cumulative survival rate after hepatic resection for hepatocellular carcinoma in all patients (n = 67).

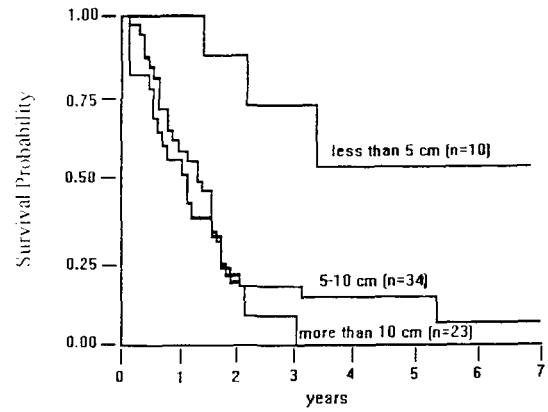

Fig. 2. Cumulative survival rate after hepatic resection for hepatocellular carcinoma by tumor size. Survival curves were significantly different ($p<0.05$) amongst the three groups.

Table 3. Sites of recurrence after liver resection.

Liver	37
Liver & Lung	1
Liver & Skin	1
Lung	3
Lymph node	1
Atrium	1
Bone	1
Total	45 (67.2%)

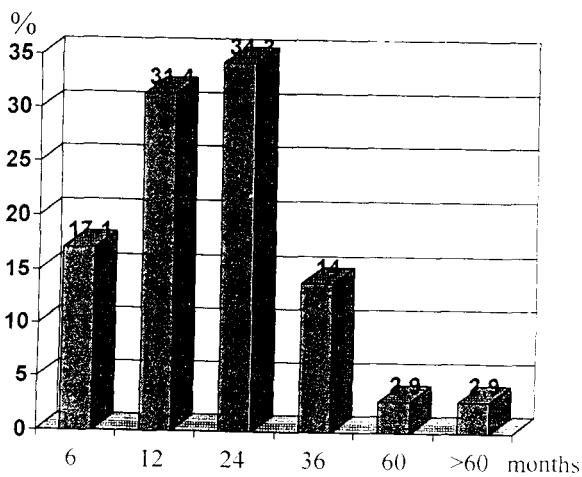

Fig. 3. Time of intrahepatic recurrence (available in 35 cases) after resection of tumor.

in 37 (55.2%) patients. Most of the patients (82.8%) had intrahepatic recurrence within 2 years. (Fig. 3)

DISCUSSION

The incidence of HCC in Thailand is rather high. Chronic carriers of the hepatitis B have been shown to be at high risk in many studies[5]. The prevalence of chronic carriers of HBsAg amongst healthy adult Thais has been found to range 8-14 per cent[6].

HBsAg was found to be positive in 86.6 per cent in this report.

In the East, HCC is associated with cirrhosis in about 80 per cent of patients and in 70 per cent of patients who have surgery[7]. Liver cirrhosis was present in 73.1 per cent in our series.

The survival of untreated HCC is generally not more than 3 years even in minute cancer. In Thailand the average mean survival of HCC who present with symptoms is about 4.1 months[8].

Numerous treatment options are available for patients with HCC. Although liver resection gives the best chance of cure the percentage of patients suitable for resection remains low. The resectability rate for HCC was 11.0 per cent in this report. Other treatment modalities are requested for unresectable HCC, chemotherapy, intratumoral injection of alcohol, intraarterial chemotherapy, emboli-

zation, internal radiotherapy using radiolabelled particles have been developed recently.

Hepatic resection for HCC is usually followed by a high morbidity and mortality due to cirrhosis of the liver. But well selection of cirrhosis and refinements in surgical technique and better knowlege of the physiology of the resected liver, operative mortality and postoperative complications for liver resection in cirrhosis are low reported by the current literature[10].

In general, patients with cirrhosis and portal hypertension have an operative mortality as high as 30 per cent, the operative mortality is only 10 per cent when the remainig liver is normal. In this series, operative mortality rate was 7 per cent.

Technical progress in liver resection over the last 10 years has been associated with a large experience in newer techiques aimed at safe resection, such as ultrasonic aspirator, microwave coagulator[11]. Intraoperative ultrasound examination is also an important part of liver resection[12]. Control of the hepatic veins is the most dangerous step of the resection, some surgeons[12] advocate an extrahepatic method for this step, but we performed hepatic vein division *via* intrahapic approach which seems to be much safer.

Starzl et al[13] recognized four practical resections : right lobectomy, left lobectomy, trisegmentectomy (right trisegmentectomy or extended right lobectomy) and lateral segmentectomy, but most surgeons recently use planning of hepatic resection based on the more detailed division into eight subsegments as described by Couinaud[14]. Most of our patients were operated with Major hepatic resection (74.6%). This is due to 65.7 per cent of our tumors being more than 5 cm. Takenaka et al[15] have also reported that more than 40 per cent of patients with stage I and II disease under went a partial liver resection with complete extirpation of the tumor, but 50 per cent of this with stage III and IV were operated with more than a bisegmentectomy.

Overall survival of our patients at 5 years was 11.5 per cent similar to that observed in most other Asian studies except Japan[16] and similar to some Western experience[10,18]. However, various new strategies for liver resection have proved successful and the survival rates of recent reports have improved in which the 5 year survival rate was 26.4 - 58.8 per cent[19,20].

A significant difference in the survival rate was observed by size in this study, it has been suggested that cancer recurrence and survival were related to the size of the tumor. Tang et al[21] reported the survival rate of tumors of 2 cm or less in diameter was 85 per cent, as opposed to 60 per cent for those whose tumors had a diameter between 4 and 5 cm.

The prognostic factors contribute to the high rate of recurrence were the portal invasion of the tumor, the presence of intrahepatic metastasis, the abscence of fibrous tumor capsule, tumor infiltration and poor differentiation of cancer cells. The incidence of intrahepatic recurrence is estimated to be 22 per cent to 56 per cent[22,23] Belghiti et al[24] noted an extremely high cumulative intrahepatic recurrence rate at 5 years fellowing hepatectomy for HCC in 100 per cent of patients. In our study the intrahepatic recurrent rate of 55.2 per cent is similar to that reported by other authors.

It was reported that the median interval between hepatic resection and recurrence was 10 to 17 months and most occured within 2 years postoperatively[25,27] In our series, the recurrence rate within 2 years after the first hepatic resection was 82.8 per cent.

There are several modes of treatment for recurrent HCC, such as TACE, Ethanol injection, surgical resection. However, surgical resection if possible remains one of the most effective modalities. Zhou et al[28] reported the 5 years survival rates after the second hepatic resection was as high as 41.8 per cent which was significantly better than those who were treated by other palliative methods. Hu et al[29] also did a comparative study between those patients with resectable recurrent HCC treated with hepatectomy and who received TACE, the results of 5 years survival rate in the resection group was significantly better than that in the TACE group.

To achieve successful longterm survival and increase the chance for rehepatectomy, it is necessary to detect the intrahepatic recurrence earlier. Serial monitoring of serum AFP and Ultrasound examination of the remnant liver are useful in recognizing recurrence[24].

To improve the survival rate of patients with HCC by prevention of a recurrence, some investigators advocated that adjuvant repeated hepatic

arterial chemotherapy may be effective for decreasing the rate of recurrence in the remnant liver in patients bearing risk factors for recurrence(30,31).

SUMMARY

In summary, the present data suggest that hepatic resection is an appropriate treatment for HCC less than 10 cm. But HCC which is larger than 10 cm multimodality approach should be considered for improvement of the survival.

Intrahepatic recurrence is as high as other reports from the Orient. Close follow-up is mandated for early detection of the recurrence, and if recurrence occurs prompt treatment with the multimodality approach is the key to obtain longterm survival.

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ประสบการณ์และผลการรักษาระยะยาว การผ่าตัดมะเร็งตับชนิดเซลล์ตับ 67 ราย

*ธีรวุฒิ คูหะเปรมะ, พ.บ.**

มะเร็งตับชนิดเซลล์ตับ Hepatocellular Carcinoma เป็นมะเร็งที่พบบ่อยในประเทศไทย การผ่าตัดมะเร็งตับยังเป็นวิธีการรักษาที่ดีที่สุด แต่ผลการรักษามะเร็งชนิดนี้ยังมีรายงานน้อยมากในประเทศไทย รายงานนี้เป็นการศึกษาประสบการณ์ และผลการรักษาระยะยาวของผู้ป่วยมะเร็งตับชนิดเซลล์ตับที่ได้รับการผ่าตัดที่สถาบันมะเร็งแห่งชาติ ตั้งแต่ มกราคม 2529 ถึง มกราคม 2539 มีผู้ป่วยมะเร็งตับชนิดปฐมภูมิ จำนวน 884 ราย เข้ารับการรักษาที่สถาบันมะเร็งแห่งชาติ กรุงเทพ ฯ ในจำนวนนี้เป็นผู้ป่วยมะเร็งตับชนิดเซลล์ตับ (HCC) 609 ราย คิดเป็นร้อยละ 68.9 ในช่วงระยะเวลาดังกล่าวนี้มีผู้ป่วยมะเร็งตับปฐมภูมิได้รับการผ่าตัดโดยผู้รายงานจำนวน 112 ราย ซึ่งใน 112 รายนี้ประกอบด้วยมะเร็งตับชนิดเซลล์ตับ (HCC) 67 ราย (59.8%) ผู้ป่วยมะเร็งตับชนิดเซลล์ตับจำนวน 67 รายนี้ ได้ถูกนำมาศึกษา และรายงาน ณ ที่นี้ โดยพบว่าใน 67 ราย มีโรคตับแข็งร่วมด้วย 49 ราย (73.1%) ผลการตรวจ HBsAg พบว่าเป็นผลบวก 58 ราย (86.6%) ผลการตรวจเลือดหาแอลฟาฟีโตโปรตีน (AFP) ก่อนผ่าตัดพบว่า และมีค่าสูงกว่า 400 ng/ml 35 ราย (52.2%) อัตราการผ่าตัด (Resectability) ในผู้ป่วย 67 ราย เท่ากับร้อยละ 11.0 ของมะเร็งตับชนิดเซลล์ตับทั้งหมด การผ่าตัดที่ใช้เป็นการผ่าตัดใหญ่ 50 ราย (74.6%) โรคแทรกซ้อนหลังการผ่าตัดพบใน 14 ราย (20.9%) มีผู้ป่วย 5 รายเสียชีวิตหลังผ่าตัด เท่ากับร้อยละ 7.5 อัตราอยู่รอดหลังผ่าตัดโดยวิธี Kaplan–Meier พบว่าอัตราอยู่รอด 1, 2, 3, 4, 5 ปี โดยทั่วไปเท่ากับ 63.2%, 28.6%, 21.1%, 14.5% และ 11.5% ตามลำดับ แต่เมื่อดูอัตราอยู่รอดโดยแบ่งตามขนาดของก้อนมะเร็งพบว่า อัตราอยู่รอด 1, 3, 5 ปี สำหรับมะเร็งที่ก้อนเล็กกว่า 5 ซม. มีอัตราอยู่รอดเท่ากับ 91.1%, 57%, 49.4% และสำหรับมะเร็งที่ก้อนอยู่ระหว่าง 5–10 ซม. พบว่ามีอัตราอยู่รอดเท่ากับ 57.5%, 16% และ 9% ตามลำดับ ส่วนมะเร็งที่มีขนาดก้อนใหญ่กว่า 10 ซม. พบอัตราอยู่รอด 1 และ 2 ปีเท่ากับ 52% และ 12% แต่ไม่พบว่ามีอัตราอยู่รอด 3 ปี จากการศึกษานี้พบว่า อัตราการอยู่รอดหลังผ่าตัดมีความแตกต่างกัน ตามขนาดของก้อนมะเร็งอย่างมีนัยสำคัญ การคืนกลับของโรคหลังการผ่าตัดพบว่ามี 45 ราย (67.2%) ซึ่งผู้ป่วยส่วนใหญ่ ร้อย 82.8 จะมีมะเร็งเกิดขึ้นใหม่ในตับภายใน 2 ปี หลังผ่าตัด

จากการศึกษานี้สรุปได้ว่าการผ่าตัดมะเร็งตับในผู้ป่วยที่มีก้อนมะเร็งเล็กกว่า 10 ซม. ได้ผลดีและเป็นวิธีที่เหมาะสม แต่ในมะเร็งที่มีขนาดใหญ่กว่า 10 ซม. การใช้วิธีผสมผสานกันมารักษา น่าจะเป็นวิธีช่วยเพิ่มประสิทธิภาพการรักษาที่ดีกว่า และอัตราการคืนกลับของมะเร็งที่เกิดขึ้นในตับที่เหลือหลังผ่าตัด มีอัตราที่สูงเช่นเดียวกันในรายงานอื่น ๆ ดังนั้นการติดตามผู้ป่วยหลังผ่าตัดอย่างใกล้ชิด เพื่อให้พบมะเร็งที่เกิดขึ้นใหม่เร็วที่สุด จึงเป็นวิธีที่ดีที่สุดในการทำให้ผลการรักษามะเร็งชนิดนี้ดีขึ้น

คำสำคัญ : มะเร็งตับชนิดเซลล์ตับ, การผ่าตัดตับ, ผลการรักษาระยะยาว

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