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Hepatic resections for primary liver cancer

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Abstract. The medical records of 399 patients who underwent hepatic resection between January 1981 and December 1990 were reviewed. Information regarding the results of the hepatic resection in terms of the operative indication, operative procedure, operative morbidity, and mortality was abstracted. As of the end of 1990, a total of 402 hepatic resections had been completed, including those of 319 primary malignancies, 4 secondary malignancies, 2 gallbladder carcinomas, 42 cases of intrahepatic cholelithiasis, and 35 benign masses. Major hepatic resections were performed on 117 patients (29%), of whom 60 (51%) had histologically proven liver cirrhosis. Minor hepatic resections were performed on the remaining 285 patients (71%). Sepsis was the most frequent complication, which manifested primarily as wound infection (71 cases) or intra-abdominal infection (25 cases). Nonfatal hepatic failure occurred in nine patients with cirrhosis and one patient without cirrhosis. There were 38 operative deaths among the 402 hepatic resections, for an overall operative mortality of 9.4%; 25 of those deaths were due to hepatic failure after the operation, accounting for 66% of the total operative mortality. There was an increasing frequency of hepatic resection during the last 5 years. The indication for resection due to hepatocellular carcinoma increased from 87 to 195 cases. The cumulative data show a decrease in the incidence of complications and the operative mortality rate. In the most recent period, nonlethal postoperative complications occurred in 135 of 286 patients (47%). The overall 1-, 3-, and 5-year survival rates for 172 patients, excluding cases of operative mortality, palliative resection, and re-resection, were 71.0%, 39.8%, and 28.3%, respectively.

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Introduction

In Korea, the major indication for hepatic resection is hepatocellular carcinoma, and the incidence of concomitant cirrhosis is extremely high. Resecting a cirrhotic liver can involve several difficult problems. A poor functional reserve and the technical difficulty have restricted hepatic resection and increased the operative morbidity and mortality. This study was carried out using data on 402 hepatic resections in Korea for which follow-up was complete. These were performed during a 10-year period ranging from January 1981 to December 1990. We analyzed the results of hepatic resection in terms of the operative indication, operative morbidity and mortality, and long-term survival.

Patients and methods

The medical records of 399 patients who underwent hepatic resection at Seoul National University Hospital between January 1981 and December 1990 were reviewed. There were 402 hepatic resections in 399 patients because 2 patients had undergone repeated hepatic resections due to recurrence of hepatocellular carcinoma, including 1 patient who had undergone a third hepatic resection. Information regarding the patient population, diagnosis, pathology, operative procedure, and outcome was summarized. The indications for hepatic resections were classified into groups of primary malignancy, secondary malignancy, gallbladder carcinoma, intrahepatic cholelithiasis, and benign mass. The primary malignancy group included hepatocellular carcinoma (HC), cholangiocellular carcinoma (CC), mixed carcinoma, and other malignancies.

The operative procedures were divided into the following two categories: major hepatic resections, which include massive hepatic resections such as lobectomy and trisegmentectomy, and minor hepatic resections, which include sublobectomies such as segmentectomy and wedge resection. Postoperative complications were carefully monitored. All deaths occurring within 30 days after hepatic resection as well as during the initial hospitalization for hepatic resection, regardless of the time, were counted as operative mortality cases. The survival rates after hepatic resection were determined using the life-table method. Cases of operative mortality and palliative resections and re-resections were excluded.

Table 1: Annual trends in the number of hepatic resections

Diagnosis	Year										
	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	Totals
Hepatocellular carcinoma	9	12	13	26	27	25	29	50	46	45	282
Cholangiocarcinoma					5	3	6	7	5	3	29
Mixed carcinoma						1	1	1			3
Hepatoblastoma and others						1	3		1		5
Metastatic carcinoma		1				1		1	1		4
Gallbladder cancer							1		1		2
Hepatolithiasis		2	2	1	7	8	2	11	3	6	42
Benign mass	2	1	3		5	4	8	3	4	5	35
Totals	11	16	18	27	44	43	50	73	61	59	402

Results

The mean age of the patients was 52 years and the age range was 16–75 years. There were 312 men (78%) and 87 women (22%). This male predominance was attributable to the high incidence of HC in this sex.

Indications

Through the end of 1990, a total of 402 hepatic resections were completed, including those of 319 primary malignancies, 4 secondary malignancies, 2 gallbladder carcinomas, 42 cases of intrahepatic cholelithiasis, and 35 benign masses. The annual number and indications of hepatic resections are shown in Table 1.

Of the 399 patients, 322 had malignant disease, including 316 cases of primary liver cancer, which was the most frequent disease encountered in this series. There were 279 cases of HC, with a male-to-female ratio of 5.8:1; 29 cases of CC, with a male-to-female ratio of 3.1:1; 3 cases of mixed carcinoma; and 5 cases of other primary malignancies. The other primary malignancies included hepatoblastoma, malignant lymphoma, biliary cystadenocarcinoma, undifferentiated embryonal sarcoma, and leiomyosarcoma. Histological examination of resected specimens showed that 242 of the 399 patients also had liver cirrhosis. In the present study, cirrhosis includes not only true cirrhosis but also chronic active hepatitis. The details of each disease type are given below.

Hepatocellular carcinoma

The mean age of 279 patients with HC was 53 years and the age range was 16–75 years. Most cases were in the fifth and sixth decades of life. There were 238 men (85%) and 41 women (15%). There were 282 hepatic resections in 279 patients because 2 patients underwent a second resection at a later date, including 1 patient who underwent a third resection. The preoperative serum level of AFP was measured by radioimmunoassay. It was higher than 20 ng/ml in 187 patients (67%) and higher than 200 ng/ml in 106 patients (38%). HBs antigen was positive in 72% of cases; HBs antibody, in 19% of cases; and HBc antibody, in 75% of the patients. Liver cirrhosis was hdiagnosed in 221 patients (79%).

Cholangiocellular carcinoma

Hepatic resection was performed on 29 cases of histologically proven intrahepatic peripheral cholangiocarcinoma, of which 5 cases were associated with *Clonorchis sinensis* infection. The mean age was 56 years and the age range was 37–68 years. In all, 22 patients were men (76%) and 7 were women (24%). The AFP level was elevated in four cases. The serum carcinoembryonic antigen (CEA) level was elevated above 5 ng/ml in 18 cases. HBs antigen was positive in 14% of cases; HBs antibody, in 28% of cases; and HBc antibody, in 31% of the patients. Seven patients (24%) had liver cirrhosis.

Gallbladder carcinoma

The two patients with this disease were men aged 38 and 84 years. Neither patient had associated gallstones.

Metastatic carcinoma

The primary disease of all four patients with metastatic liver cancer was colorectal cancer. Hepatic resections performed on patients with direct invasion of gastric malignancies were excluded from this study. One patient had metachronous colorectal liver metastasis. In three patients, hepatic resection was performed synchronously with the colorectal primary procedure. The mean age was 48 years and the age range was 39–56 years. Three of the patients were men and one was a women. CEA was elevated in all four of these patients.

Intrahepatic cholelithiasis

Because most of the benign lesions were intrahepatic duct stones (42 cases), these cases were separated from the benign masses. Intrahepatic cholelithiasis is defined as a stone involving the right or left hepatic duct, or their branches, peripheral to their junction at the hepatic hilum. The mean age was 43 years and the age range was 22–69 years. In all, 19 patients were men (45%) and 23 were women (55%).

Table 2: Details of 402 hepatic resections classified by diagnosis, operative procedure, and operative death

Diagnosis	Operative procedure[a]								
	RTS	LTS	RL	LL	CBS	RS	LS	SP	Totals
Hepatocellular carcinoma	4[1][b]	1[1]	53[7]	20[0]	2[0]	49[9]	15[1]	138[13]	282[32]
Cholangiocarcinoma			6[2]	8[0]	1[1]		11[0]	3[1]	29[4]
Mixed carcinoma			1[0]	2[0]					3[0]
Hepatoblastoma and others			3[0]					2[0]	5[0]
Metastatic carcinoma			2[0]				2[0]		4[0]
Gallbladder cancer							1[0]	1[0]	2[0]
Hepatolithiasis			1[0]	2[0]			39[1]		42[1]
Benign mass			7[0]	4[0]			4[0]	20[1]	35[1]
Totals	4[1]	1[1]	73[9]	36[0]	3[0]	49[9]	72[2]	164[15]	402[38]

[a] RTS, Right trisegmentectomy; LTS, left trisegmentectomy; RL, right lobectomy; LL, left lobectomy; CBS, central bisegmentectomy; RS, right segmentectomy; LS, left segmentectomy; SP, subsegmentectomy or partial resection

[b] [], Number of cases of operative deaths

Table 3. Nonfatal complications of hepatic resection

Complication	No. of cases		
	Cirrhosis	No cirrhosis	Totals
Wound infection	44	27	71
Intra-abdominal infection	17	8	25
Other sepsis	1	1	2
Hepatic failure	9	1	10
Pneumonia	11	6	17
Atelectasis	9	7	16
Pleural effusion	37	24	61
Bile fistula	3	5	8
Coagulopathy	9	1	10
Postoperative bleeding	4	2	6
Renal failure	9	2	11
Esophageal varix bleeding	4	0	4
Totals	157	84	241

Benign mass

Hepatic resection was carried out on 35 patients with a variety of benign masses. The mean age was 51 years and the age range was 34–69 years. In all, 20 patients were men (60%) and 14 were women (40%). These disorders included hemangioma (12 cases), abscess (8 cases), cyst (7 cases), adenomatous hyperplasia (3 cases), hamartoma (2 cases), adenoma (1 case), cystadenoma (1 case), and pseudolymphoma (1 case). Classification of the seven cyst cases showed a congenital nonparasitic cyst (four cases), an ecchinococcal cyst (two cases), and adult polycystic disease (one case).

Operative procedures

Table 2 shows the details of the 402 operative procedures performed on the 399 patients. Major hepatic resection was performed on 117 patients (29%), of whom 60 (51%) had histologically proven liver cirrhosis. Minor hepatic resection was perfomed on 285 patients (71%), 182 (64%) of whom had liver cirrhosis. In the case of HC, the ratio of major hepatic resection and minor hepatic resection was 1:2.5. In the cirrhotic patients with considerable liver function, extensive resection was performed, whereas in the patients with a small HC and poor reserve function, subsegmental or partial resection was performed with the aid of intraoperative ultrasonography.

In the case of HC, 85 patients were considered to have undergone palliative resection, 19 due to adjacent organ invasion, 26 due to gross angioinvasion, and 16 due to a residual tumor. Postoperative pathological examination revealed a positive resection margin in 24 patients. The remaining 194 patients underwent a curative resection. In the case of CC, three patients were considered to have undergone palliative resections since histology revealed a positive resection margin. The remaining 26 patients underwent a curative resection. In the four cases of metastatic carcinoma, pathological examination did not reveal any tumor in the margins.

Postoperative complications

In the 214 patients surviving the operations, there were 241 nonlethal complications. Complications were frequently seen in 142 patients with liver cirrhosis (58.6%) (Table 3), corresponding to 157 of the 241 complications. Sepsis was the most frequent complication, which manifested primarily as wound infection (71 cases) or intra-abdominal infection (25 cases). Nonfatal hepatic failure occurred in nine patients with cirrhosis and one patient without cirrhosis. Other complications included pleural effusion (61 cases), pneumonia (17 cases), atelectasis (16 cases), biliary fistula (8 cases), coagulopathy (10 cases), postoperative bleeding (6 cases), renal failure (11 cases), esophageal varix bleeding (4 cases), and other sepsis (2 cases).

Operative mortality

There were 38 operative deaths among the 402 hepatic resection cases, for an overall operative mortality rate of 9.4%. Table 4 shows the causes of death of the 38 patients. In all, 25 of these patients died of hepatic failure after the operation, accounting for 66% of the total operative mortality. Hemorrhage from the liver was the primary cause of

Table 4. Causes of death after hepatic resection for various diagnoses

Cause of death	Diagnosis				
	Hepatocellular carcinoma	Cholangio-carcinoma	Hepato-lithiasis	Benign mass	Total
Hepatic failure	22 (19)[a]	2 (1)		1 (1)	25 (21)
Hemorrhage from liver	2 (2)	1 (0)			3 (2)
Intra-abdominal sepsis	4 (3)	1 (1)			5 (4)
Renal failure			1 (0)		1 (0)
Chest infection	1 (0)				1 (0)
Varix bleeding	3 (1)				3 (1)
Totals	32 (25)	4 (2)	1 (0)	1 (1)	38 (28)

[a] (), number of cases of liver cirrhosis

Table 5. Mortality rates in patients with hepatocellular carcinoma

	Numer of patients	Operative deaths
Operative procedure:		
Major resection	80	9
Minor resection	202	23
Presence of cirrhosis:		
With cirrhosis	221	25
Without cirrhosis	61	7
Totals	282	32

Table 6. Comparison of diagnosis and operative procedure by year of operation

	Period of study	
	1981–1985 (n = 116)	1986–1990 (n = 286)
Diagnosis:		
Hepatocellular	87	195
Cholangiocarcinoma	5	24
Mixed carcinoma		3
Hepatoblastoma and others		5
Metastatic carcinoma	1	3
Gallbladder cancer		2
Hepatolithiasis	12	30
Benign mass	11	24
Operative procedure:		
Major resection	41	76
Minor resection	75	210

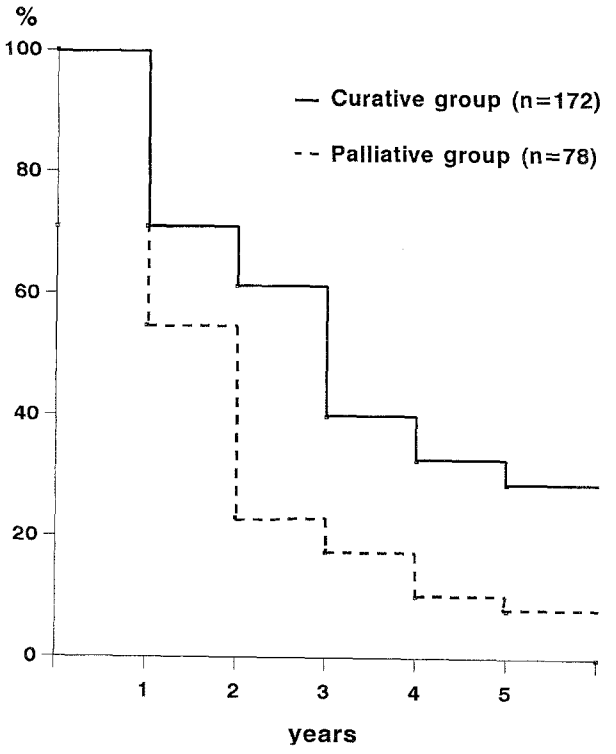

Fig. 1. Survival rates obtained for patients with hepatocellular carcinoma undergoing curative resection and patients with hepatocellular carcinoma undergoing palliative resection

death in three patients, and intra-abdominal sepsis was a major contributory cause in five patients. Other factors contributing to the death of patients were esophageal varix bleeding (three cases), renal failure (one case), and severe chest infection (one case). In all, 28 of the patients who died had preexisting cirrhosis.

The mortality rate varied with the magnitude of the operative procedure. Table 2 presents the details of mortality after the various kinds of resection, i.e., RTS, 1/4; LTS, 1/1; RL, 9/73; LL, 0/36; CBS, 0/3; RS, 9/49; LS, 2/72; and SP, 15/164. The mortality rates after resection for HC, CC, intrahepatic cholelithiasis, and benign mass, respectively, were 11.3%, 13.8%, 2.4%, and 2.9% (Table 2). There were 36 operative deaths in the primary malignancy group of 319 patients. These deaths were due predominantly to hepatic failure after resection. In all, 24 patients (67%) died of this disorder, with 12 having undergone SP, 6 having undergone RL, 5 having undergone RS, and 1 having undergone RTS. Two patients died of postoperative bleeding. One other patient died of varix bleeding and one died of sepsis.

There were 32 operative deaths (11.3%) in 282 patients with HC. The mortality rates for HC with and without cirrhosis were 11.3% and 11.5%, respectively. The mortality rate was 11.2% in major hepatic resections for HC and 11.4% in minor hepatic resections (Table 5). There was no operative death among the patients who underwent resection for mixed carcinoma, another primary malignancy, metastatic carcinoma, or gallbladder carcinoma.

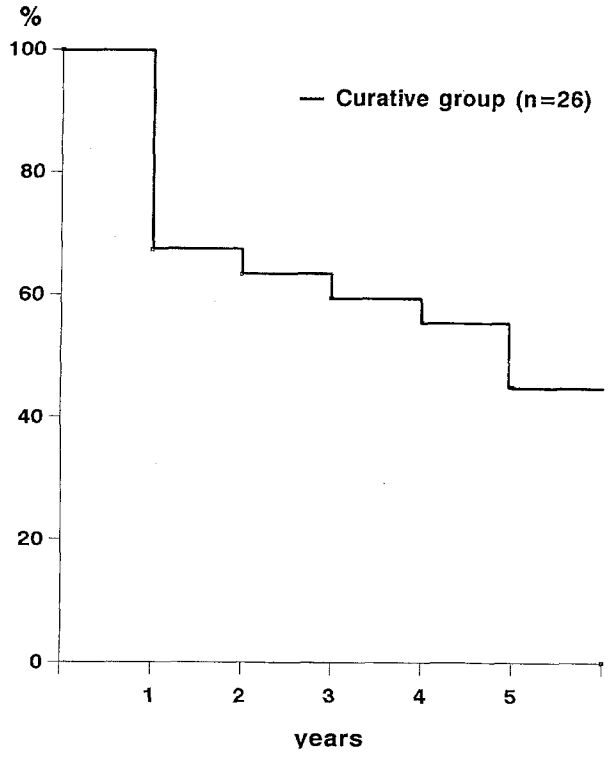

Fig. 2. Survival rates obtained for patients with cholangiocarcinoma undergoing curative resection

Comparison of indication, operative procedure, complication, and operative mortality by year of operation

Table 6 summarizes the differences in indication, operative procedure, complication, and operative mortality between the patients operated on from January 1981 to December 1985 (n = 116) and those operated on from January 1986 to December 1990 (n = 286). There was an increased frequency of hepatic resection during the last 5 years. The increased number of hepatic resections was mainly due to resection for HC. The cumulative data show a decrease in the rates of complications and operative mortality.

Long-term survival

The 1-, 3-, and 5-year survival rates for 172 patients with HC, excluding cases of operative mortality, palliative resection, and re-resection, were 71.0%, 39.8%, and 28.3%, respectively. The 1-, 3-, and 5-year survival rates of palliatively resected patients with HC who survived the operation were 54.7%, 17.3%, and 7.8%, respectively (Fig. 1). The 1-, 3-, and 5-year survival rates for the 26 patients who had undergone curative resection with CC were 67.2%, 59.5%, and 45.0%, respectively (Fig. 2).

Discussion

In Korea, primary liver cancer is the second leading cause of death by cancer in men and the fifth in women. Recently its incidence has been increasing and, especially in men, it ranks second only to stomach cancer. Our data strongly suggest that mot cases of HC in Korea are related to hepatitis B virus and usually complicated by cirrhosis. Frequent monitoring of serum AFP levels and/or ultrasonographic examination should be performed in patients with chronic liver disease.

Hepatic resection for HC represents the main reason for the increased frequency of hepatic resection in our hospital over the last 5 years. The result of such resections was often palliation with extended survival rather than a complete cure. Reoperations for recurrent tumors were performed on three patients, and those resections were successful. One patient who underwent three hepatic resections has survived for over 6 years from the time of the first operation. He underwent a right inferior segmentectomy for a 10-cm-sized mass, followed 2 years later by a right lobectomy for 6- and 4-cm-sized recurrent masses and, 2 years thereafter, by a left lateral segmentectomy for 8- and 4-cm-sized recurrent masses.

The true mortality for hepatic resectional therapy of HC is difficult to assay. One of the main determinants of mortality is the incidence of cirrhosis in patients undergoing resection. Another factor that makes it difficult to assay the mortality after hepatic resection for HC is differences in the methods of reporting mortality. Some authors exclude operative deaths, whereas others report the 30-day mortality versus hospital mortality. Some reports do not separate the results obtained for primary HC and other liver tumors, and others do not differentiate between palliative and curative resections [4]. Regarding the operative mortality after resection of HC, the rates reported for most series range from 10% to 20% [6, 11, 15]. The range is related to the number of patients with cirrhosis included in the different series. Mortality rates of 10%–15% have been reported by authors who use a more conservative segmental resection in cirrhotic patients [7, 10, 13]. The operative mortality in our series of patients with HC was 11.3%, which is comparable with the rates reported in other studies. Although a direct comparison is difficult since different studies use different methods for presenting the results [6, 17], the survival rate obtained in our study is encouraging because our series included patients who had advanced cirrhosis.

CC is a type of carcinoma arising from any portion of the intrahepatic bile duct epithelium, and it accounts for about 6.4%–25% of primary carcinomas of the liver [3, 11]. Of the 29 cases of cholangiocarcinomas resected at our institution, 5 were associated with clonorchiasis. The general gross pathological findings of *clonorchis sinensis*-associated CC in Korea, Hong Kong, and China, where *C. sinensis* infection is endemic, basically do not differ from those of the usual peripheral cholangiocarcinomas. Regardless of *C. sinensis* infection, the usual peripheral CCs grow similarly in a nodular infiltrative pattern and show no intraductal tumor growth [8]. There have been few reports of significant survival following resection for CC and mixed carcinomas. These tumors are often included with HC in reports of survival following resection for primary carcinomas of the liver. If curative resection is performed, the prognosis of peripheral CC will be better than that of HC because of the less frequent association of the former

with cirrhosis. Hepatoblastoma is a rare malignancy in children, and early surgical resection combined with chemotherapy and radiation, or both, has improved the prognosis. Our experience with hepatic resection for hepatoblastoma is insufficient for a meaningful comparison of our results with the data reported for other series.

The survival after the discovery of liver metastases from colorectal cancer varies from 6 to 10 months, depending on the extent of hepatic involvement. Survival after resection has been reported to range from 25% to 52% at 5 years [12]. Three patients in our study who underwent resection for metastatic carcinoma have survived for more than 5 years.

Gallbladder carcinomas are poorly diagnosed and, when found, are very often untreatable for cure. The overall 5-year survival rate of patients whose tumors are resectable yet extend microscopically outside the wall is 10%–15% [12]. The median survival in our series was 8 months.

Hepatolithiasis presents serious health problems in East Asian countries because recurrent or residual stones are common and patients frequently succumb to hepatic damage caused by long-standing intermittent obstructive jaundice, cholangitis, liver abscess, and septicemia. Hepatic resection is indicated when substantial liver parenchyme has been destroyed and the ducts are fibrous sacs containing numerous pigmented stones. In most cases (39/42), left-lateral segmental resections were carried out. However, a left lobectomy in two cases and a right lobectomy in one case were required when the medial segment was also affected or the right lobe was the affected portion.

As the morbidity and mortality of hepatic resection have decreased, there has been a more liberal use of resection of benign masses of the liver [4]. In this study, hemangioma was the most common benign primary lesion that required resection for pain or a mass. Mortality rates are low and the long-term follow-up is excellent after resection of benign masses.

In our patients, the complications occurring after hepatic resection compared favorably with those noted in other large series [5, 14]. The most frequent complication encountered after hepatic resection was sepsis, which manifested as wound infection or intra-abdominal infection. This finding is in accordance with those reported by other investigators [16]. With the objective of decreasing the mortality and morbidity rates associated with hepatic resection, some clinicians have applied objective methods to assess the predictability of morbidity and death [2, 9]. The overall mortality rate in our patients was similar to the rates reported for other major series [1, 6, 13]. The majority of postoperative deaths occurred in patients who underwent resection of two or more segments of a cirrhotic liver. Selection of patients by assessment of the hepatic function and reserve is necessary before any attempt at extensive resection.

We have recently seen a major change in the number of hepatic resections, with a sharp increase in the number of resections for HC. There has also been a shift to a greater number of resections for benign and other malignant conditions. Our results demonstrate that hepatic resection can be successfully performed to treat a variety of hepatic lesions. Hepatic resection is now associated with an acceptably low operative risk and enhanced survival. However, the operative risk in hepatic resection remains higher than that in other surgical procedures, and advanced cirrhosis generally precludes a major hepatic resection.

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