J Hepatobiliary Pancreat Surg (2005) 12:365–370
DOI 10.1007/s00534-005-1002-3

Journal of HBP Surgery

Systematic hepatectomy for small hepatocellular carcinoma in Korea

Kyung-Suk Suh

Department of Surgery, College of Medicine, Seoul National University, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea

Abstract
Background/Purpose. Systematic hepatectomy for small hepatocellular carcinoma (HCC) is a widely preferred modality, but evidence concerning its benefits is lacking. The aim of this study was to document hepatic resection for small HCC in Korea, and to determine whether patient survival or the pattern of tumor recurrence was influenced by the methods used.
Methods. Ten major hospitals that perform hepatectomy for HCC in Korea were surveyed for surgeons' opinions concerning systematic hepatectomy and current trends in hepatic resection for small HCC. An analysis was also performed of 119 patients who underwent curative hepatectomy for small HCC (size < 5 cm) between January 2000 and December 2002 at Seoul National University Hospital. Seventy-four of these 119 patients underwent anatomical resection (AR) and 45 had a nonanatomical resection (NAR). Recurrence-free survival, recurrence pattern, overall survival rates, and the risk factors for recurrence were analyzed.
Results. In the survey, eight of ten surgeons preferred systematic hepatectomy and considered it to aid prognosis. No significant difference was found between the AR and NAR groups in terms of the clinicopathologic findings, except that the presence of underlying hepatic cirrhosis was more prevalent in the NAR group. The postoperative morbidity rate was higher in the NAR group (33.3% vs 27.0%), but this difference was not statistically significant. The respective 1- and 3-year recurrence-free survival rates were 78.1% and 49.7% in the AR group, and 68.9% and 46.5% in the NAR group ($P > 0.05$). The corresponding 1- and 3-year overall survival rates were 88.8% and 80.8% in the AR group and 91.0% and 71.4% in the NAR group ($P > 0.05$).
Conclusions. Although systematic hepatectomy seems to be superior to nonanatomical hepatectomy from the oncological and anatomical aspects, this superiority is not reflected by the recurrence patterns or the survival and recurrence rates of the two procedures. Postoperative recurrence appears, rather, to be related to the underlying liver condition.

Key words Systematic hepatectomy · Hepatocellular carcinoma · Hepatic resection · Recurrence

Introduction

Hepatic resection for liver cancer is widely accepted due to its remarkably low operative morbidity and mortality, and its proven impact on prognosis.[1,2] Improved knowledge of hepatic anatomy and advances in imaging technologies have facilitated an approach based on the resection of individual hepatic segments.[3–5] Anatomical hepatectomy is preferred for hepatocellular carcinoma (HCC) because of the tumor's tendency to invade the portal veins and spread along their intrasegmental branches.[6] Anatomical hepatectomy also has the advantage that it may reduce the ischemic area, congestion, and bleeding. But questions remain as to whether anatomical resection (AR) provides more favorable recurrence-free survival and operative morbidity rates than nonanatomical resection (NAR).

Therefore, the purpose of this study was to determine current trends of hepatic resection for small HCC and to investigate whether the hepatic resection method influenced patient survival and the pattern of tumor recurrence.

Methods

Ten major Korean hospitals performing hepatectomy for HCC were surveyed. Patient numbers, sex, age, and type of operation were investigated, and a questionnaire also ascertained surgeons' opinions concerning systematic hepatectomy.

As well as this survey, an analysis of patients with HCC who underwent curative hepatic resection at Seoul National University Hospital between January

Offprint requests to: K.-S. Suh
Received: October 18, 2004 / Accepted: June 7, 2005

2000 and December 2002 was carried out. There were 214 of these patients and 119 patients with a tumor size less than 5 cm were enrolled in this study. The anatomical definitions of segments and lobes according to Couinaud were used to describe ARs. Non anatomical resection (NAR) was defined as the resection of a lesion without regard to segmental or lobar anatomy. Anatomical resection (AR) was performed in 74 patients (AR group) and NAR in 45 (NAR group). The following parameters were compared in the two groups: patient age, sex, Child-Pugh classification, serum hepatitis B surface antigen (HBsAg), underlying hepatic cirrhosis, serum α-fetoprotein, number and size of tumors, and tumor-free resection margin. The maximum diameter of the largest tumor, if there were multiple tumors was used to describe tumor size. Postoperative analysis of variables included number and type of complications and length of hospital stay. We also examined patterns of recurrence, recurrence-free survival rates, and overall survival rates. Recurrence-free survival was defined as the time elapsed until recurrence, and overall survival time was determined from the date of hepatic resection until death. The χ^2 test, Fisher's exact test, and Student's *t*-test were used for group comparisons, as appropriate. Overall survival rates and cumulative recurrence-free survival rates were evaluated using the Kaplan-Meier method and compared using the log-rank test. For univariate analysis of the risk factors for recurrence, patients who experienced recurrence during the follow-up period were compared with those who did not, with respect to the clinicopathologic variables listed in Table 1. The Cox stepwise regression model was used for multivariate analysis. A difference of $P \leq 0.05$ was taken to be significant. Numerical data are expressed as means ± SDs unless otherwise specified. SPSS statistical software (SPSS, Chicago, IL, USA) was used for the statistical calculations.

Results

Survey

Ten major hospitals participated in the survey, and the total number of patients who underwent hepatic resection between January 2000 and December 2002 was 1107 (male/female ratio, 3.03; average age, 53.4 years; range, 10–79 years), and 592 of these involved a tumor of less than 5 cm. Either AR or NAR was performed in 879 of these 1107 patients, with 729 (82.9%) receiving an AR and 150 (17.1%) receiving an NAR. Of the 729 AR patients, major resection involving a hemiliver or more was performed in 344 patients (47.2%).

Surgeons' opinions concerning preferences and the method of systematic hepatectomy were also elicited. Eight of ten surgeons performed systematic hepatectomy whenever possible, and considered that it aided prognosis. To determine the resection boundary for systematic hepatectomy, six surgeons used the Glissonian approach, two preferred intraoperative sonography, and two used ultrasound-guided selective portal venous dye injection.

Analysis of patients at Seoul National University Hospital who received curative hepatectomy for small HCC

The clinical and pathologic features of the patient groups with AR and NAR are summarized in Table 1. No significant differences were observed in host or tumor factors, except that the frequency of underlying hepatic cirrhosis was significantly higher in the NAR group ($P < 0.05$). Operative procedures performed in the AR group are summarized in Table 2: 13 of the 74 patients had a resection involving more than two liver sections.

The lengths of hospital stay for the AR group and NAR group were 24.3 ± 12.3 days and 26.0 ± 16.1 days,

Table 1. Patient clinical and pathological data

Variables	Anatomical group ($n = 74$)	Nonanatomical group ($n = 45$)	P
Age (years), mean ± SD	57.0 ± 9.7	57.7 ± 7.9	0.675
Sex (male/female)	56/18	37/8	0.402
Child grade (A/B)	70/4	43/2	0.815
HBsAg (positive/negative)	53/21	32/13	0.952
Hepatic cirrhosis (positive/negative)	36/38	32/13	0.016
α-fetoprotein (>25 ng/≤25 ml)	25/49	22/23	0.082
Tumor number (single/multiple)	62/12	41/4	0.256
Tumor size (cm), mean ± SD	3.4 ± 1.1	3.1 ± 1.1	0.281
Resection margin (cm), mean ± SD	1.04 ± 0.88	0.98 ± 0.78	0.695

HBsAg, hepatitis B surface antigen

Table 2. Operative procedures for anatomical resection

Anatomical resection	Number of patients (%)
Monosegmentectomy	19 (25.7%)
Bisegmentectomy	40 (54.0%)
Right superior bisegmentectomy	5 (6.8%)
Right inferior bisegmentectomy	3 (4.1%)
Right anterior sectionectomy	4 (5.4%)
Right posterior sectionectomy	18 (24.3%)
Left lateral sectionectomy	10 (13.5%)
Hepatectomy	15 (20.3%)
Central hepatectomy	2 (2.7%)
Right hemihepatectomy	5 (6.8%)
Left hemihepatectomy	8 (10.8%)

Table 3. Operative mortality and morbidity

	Anatomical group ($n = 74$)	Nonanatomical group ($n = 45$)	P
Operative mortality	0	0	
Postoperative complication			
Postoperative bleeding	2	2	
Bile leakage	1	1	
Pneumonia	0	1	
Hyperbilirubinemia	2	0	
Fluid collection	8	4	
Ascites	5	2	
Pleural effusion	1	4	
Wound problem	1	1	
Total	20 (27.0%)	15 (33.3%)	NS

NS, not significantly different

respectively ($P > 0.05$). Postoperative complications after each type of hepatic resection are listed in Table 3. The complication rate was higher in the NAR group (33.3%; 15/45) than in the AR group (27.0%; 20/74), but the difference was not significant. Two cases of postoperative bleeding requiring operative intervention occurred in each group. No operation-related death occurred.

Altogether, 58 (48.7%) patients experienced tumor recurrence: 56 had an intrahepatic recurrence and 2 an extrahepatic recurrence. No significant differences were observed in the pattern of recurrence in terms of the number of recurrent tumors (Fig. 1). Table 4 shows the recurrence pattern in relation to the site of recurrent tumors. At a median follow-up of 30 months, the recurrence rates of the two groups were similar. Local recurrence at the resection margin only occurred in 5 patients (6.8%) in the AR group and in 2 (4.4%) patients in the NAR group. The frequency of recurrence in an opposite lobe was high in both groups, at 18.9% in the AR and 20.0% in the NAR group.

The 1- and 3-year recurrence-free survival rates were 78.1% and 49.7% in the AR group and 68.9% and 46.5% in the NAR group, respectively ($P = 0.80$; Fig. 2). The corresponding 1- and 3-year overall survival rates were 88.8% and 80.8% in the AR group and 91.0% and 74.1% in the NAR group ($P = 0.50$; Fig. 3). The 1- and 3-year cumulative recurrence rates of these 119 patients were 25.4% and 51.6%, respectively. According to univariate analysis of the factors listed in Table 1, two factors were significantly associated with recurrence — underlying hepatic cirrhosis ($P = 0.006$) and tumor

Table 4. Pattern of recurrence in relation to the site of recurrent tumor

Recurrence site	Anatomical group ($n = 74$)	Nonanatomical group ($n = 45$)	P
Resection margin	5 (14.3%)	2 (8.7%)	
Same lobe	7 (20.0%)	6 (26.1%)	
Opposite lobe	14 (18.9%)	9 (20%)	
Both lobes	8 (22.9%)	5 (21.7%)	
Extrahepatic	1 (2.8%)	1 (4.4%)	
Total	35 (47.3%)	23 (51.1%)	NS

NS, not significantly different

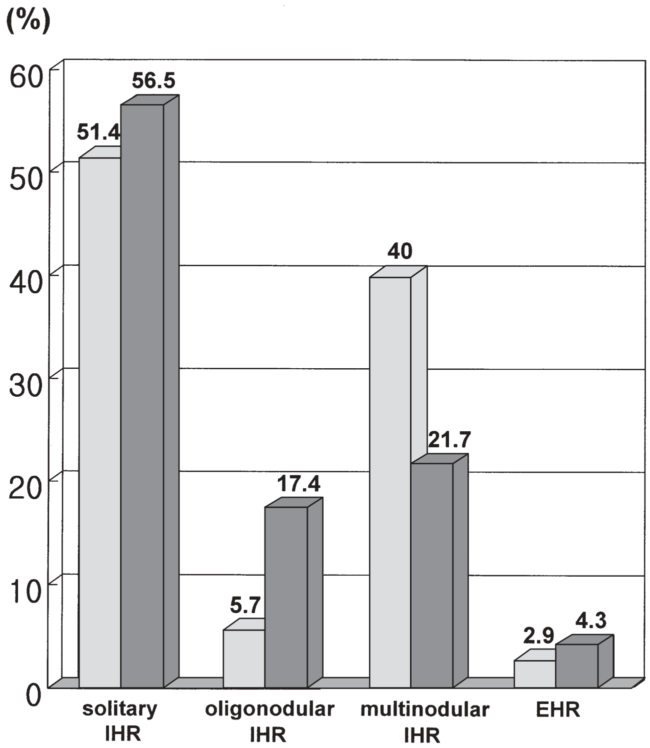

Fig. 1. Pattern of recurrence in relation to the number of recurrent tumors. No significant differences were observed between the two groups ($P > 0.05$). *Oligonodular* means two or three tumor nodules; *multinodular* means four or more tumor nodules. *IHR*, intrahepatic recurrence; *EHR*, extrahepatic recurrence. *Light bars*, anatomical resection (n = 74); *dark bars*, nonanatomical resection (n = 45)

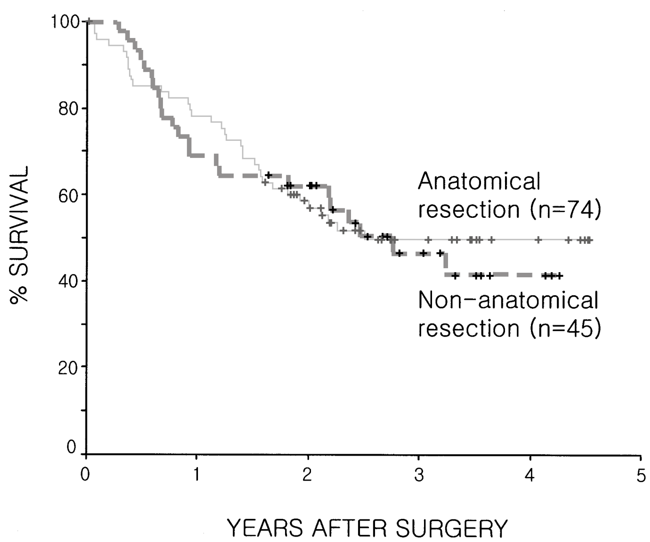

Fig. 2. Cumulative recurrence-free survival after hepatic resection in relation to the type of operation. No significant difference was observed in patient survival between the anatomical (*solid line*; $n = 74$) and the nonanatomical (*dashed line*; $n = 45$) groups ($P > 0.05$)

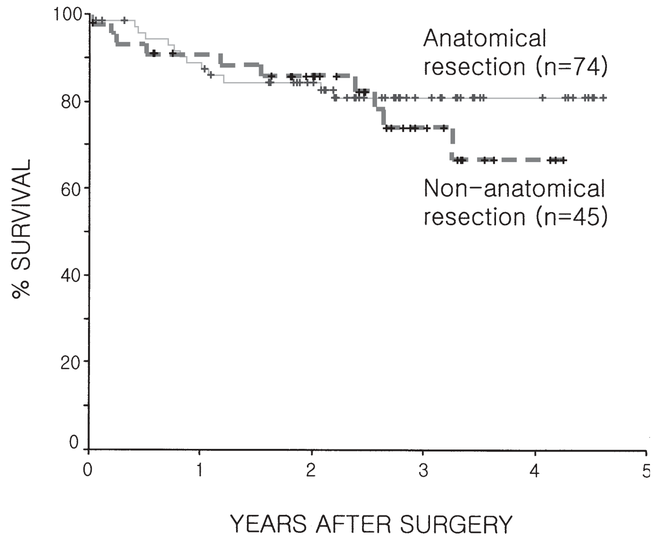

Fig. 3. A comparison of overall patient survival after anatomical (*solid line*; $n = 74$) or nonanatomical (*dashed line*; $n = 45$) resection. No significant difference was observed between the groups ($P > 0.05$)

number ($P = 0.018$). The results of multivariate analyses of these factors showed that only underlying hepatic cirrhosis was identified as an independent risk factor for recurrence.

Discussion

Two possible explanations may be tendered for the intrahepatic metastasis of HCC. First, metastasis originates from tumor invasion of the portal venous branches. With a sudden increase in intrahepatic pressure, such as that caused by a cough, tumor cells may be detached, and, as a result of the reversal of blood flow, may be carried into an adjacent portal venous branch that supplies a hepatic region proximal to the tumor.[7] Second, portal vein branches inside the liver can act as efferent vessels,[8] which may facilitate the spread of tumor cells from satellite metastases in the immediate vicinity of a large tumor (i.e., lying within the same segment) to the corresponding part of the same sector, and ultimately to the complete hemiliver (bilateral spread). With respect to the resection technique, it seems important to understand that early satellite metastases lie in the same segment as the macroscopically identifiable main tumor mass. Because satellite metastases can spread by invading portal vein branches at an early stage, to decrease the chance of leaving behind satellite metastases, an anatomical resection (AR) based on Couinaud's liver segments is preferred. From this point of view, systematic hepatectomy has an oncological rationale.

Many surgeons in Korea believe that systematic hepatectomy for small HCC is beneficial for prognosis, and therefore, they seem to choose it whenever possible. Anatomical resection is also our policy for hepatic resection in HCC, but for patients with cirrhosis and impaired liver function, we have chosen limited resection, although it is nonanatomical. As for the type of operation, the rate of AR in our survey was 73.9%, and for AR the rate of major resection was 34.4% and that of limited resection 65.6%.

In terms of the surgical treatment of HCC, the balance between surgical curability and hepatic functional preservation is of importance. The cirrhotic liver has a limited capacity to regenerate, and limited resection is an important aspect of preserving liver function, and thus reducing the possibility of hepatic failure.[9,10] The preservation of hepatic functional reserve may also enhance the long-term prognosis by allowing effective treatment options to be used if recurrence should develop.[11] Ochiai et al.[12] reported that the surgical margin had no relationship with recurrence or the recurrence pattern. Of the recurrent patterns of HCC, multiple tumors in both lobes of the remnant liver have been reported to be common.[13–15] Poon et al.[16] also reported that the width of the resection margin did not influence postoperative recurrence rates after hepatectomy for HCC. This is because intrahepatic recurrence can arise from multicentric carcinogenesis in the remnant liver, which cannot be prevented by a wide resection margin. In our study, the rate of recurrence at the resection margin or in the same lobe was 34.3% (12/35) in the AR group and 34.8% (8/23) in the NAR group. In contrast, the recurrence rate in the opposite lobe or diffuse recurrence in both lobes was 62.9% (22/35) in the AR group and 60.8% (14/23) in the NAR group. No difference in the pattern of recurrence was observed between the two groups, and in particular, anatomical resection did not decrease the ipsilateral recurrence rate. Furthermore, no significant intergroup difference was observed in recurrence-free and cumulative survival rates, given a median follow-up of 30 months. Therefore, the type of operation (i.e., AR vs NAR) was not found to be related to recurrence. Thus, NAR with an adequate resection margin may be used as an alternative in patients with impaired liver function when a tumor is located at a border between several liver segments.

The only prognostic factor associated with recurrence was underlying hepatic cirrhosis, which means that metachronous de-novo tumor recurrence is more important than intrahepatic metastasis. Poon et al.[16] reported that most recurrences occurred in a distal segment or in multiple segments, rather than at the resection line — even in patients with a positive margin. Shirabe et al.[17] showed that patients with a better liver function, as demonstrated by preoperative indocyanine green retention, were more likely to live for 10 years after surgery than patients with poor liver function. Yamanaka et al.[18] found that patients with hepatitis C-related chronic liver disease were more likely to develop HCC 3 or more years after resection. These authors concluded that the "carcinogenic potential" of the chronically damaged liver was responsible for the appearance of new lesions.

In conclusion, although systematic hepatectomy is superior to NAR from oncological and anatomical respects, it does not seem to be related to the tumor recurrence pattern, or to recurrence or survival rates. Rather, postoperative recurrence is likely to be related to the underlying liver condition.

References

1. Lai EC, Fan ST, Lo CM, Chu KM, Liu CL, Wong J. Hepatic resection for hepatocellular carcinoma. An audit of 343 patients. Ann Surg 1995;221:291–8.
2. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S. et al. Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. Ann Surg 2002;236:397–406; discussion, 406–7.
3. Billingsley KG, Jarnagin WR, Fong Y, Blumgart LH. Segment-oriented hepatic resection in the management of malignant neoplasms of the liver. J Am Coll Surg 1998;187:471–81.
4. Machi J, Oishi AJ, Furumoto NL, Oishi RH. Intraoperative ultrasound. Surg Clin North Am 2004;84:1085–111.
5. Patel NA, Roh MS. Utility of intraoperative liver ultrasound. Surg Clin North Am 2004;84:513–24.
6. Makuuchi M, Imamura H, Sugawara Y, Takayama T. Progress in surgical treatment of hepatocellular carcinoma. Oncology 2002;62(Suppl 1):74–81.
7. Scheele J, Stangl R. Segment orientated anatomical liver resection. In: Blumgart L, Fong Y, editors, Surgery of the liver and biliary tract. London: Saunders; 2000. p. 1743–63.
8. Toyosaka A, Okamoto E, Mitsunobu M, Oriyama T, Nakao N, Miura K. Intrahepatic metastases in hepatocellular carcinoma: evidence for spread via the portal vein as an efferent vessel. Am J Gastroenterol 1996;91:1610–5.
9. Kanematsu T, Takenaka K, Matsumata T, Furuta T, Sugimachi K, Inokuchi K. Limited hepatic resection effective for selected cirrhotic patients with primary liver cancer. Ann Surg 1984;199:51–6.
10. Bismuth H, Houssin D, Ornowski J, Meriggi F. Liver resections in cirrhotic patients: a Western experience. World J Surg 1986; 10:311–7.
11. Yasui M, Harada A, Torii A, Nakao A, Nonami T, Takagi H. Impaired liver function and long-term prognosis after hepatectomy for hepatocellular carcinoma. World J Surg 1995;19:439–43.
12. Ochiai T, Takayama T, Inoue K, Yamamoto J, Shimada K, Kosuge T, et al. Hepatic resection with and without surgical margins for hepatocellular carcinoma in patients with impaired liver function. Hepatogastroenterology 1999;46:1885–9.
13. Yoshida Y, Knematu T, Matsumata T, Takenaka K, Sugimachi K. Surgical margin and recurrence after resection of hepatocellular carcinoma in patients with cirrhosis. Further evaluation of limited hepatic resection. Ann Surg 1989;209:297–301.
14. Nagasue N, Yukaya H, Chang YC, Yamanoi A, Kohno H, Hayashi T, et al. Assessment of pattern and treatment of intrahepatic recurrence after resection of hepatocellular carcinoma. Surg Gynecol Obstet 1990;171:217–22.
15. Sasaki Y, Imaoka S, Masutani S, Ohashi I, Ishikawa O, Koyama H, et al. Influence of coexisting cirrhosis on long-term prognosis

after surgery in patients with hepatocellular carcinoma. Surgery 1992;112:515–21.
16. Poon RT, Fan ST, Ng IO, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. Ann Surg 2000;231:544–51.
17. Shirabe K, Shimada M, Kajiyama K, Gion T, Ikeda Y, Hasegawa H, et al. Clinicopathologic features of patients with hepatocellular carcinoma surviving more than 10 years after hepatic resection. Cancer 1998;83:2312–6.
18. Yamanaka N, Tanaka T, Tanaka W, Yamanaka J, Yasui C, Kuroda N, et al. Correlation of hepatitis virus serologic status with clinicopathologic features in patients undergoing hepatectomy for hepatocellular carcinoma. Cancer 1997;79:1509–15.