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Prognostic impact of anatomical resection on early and late intrahepatic recurrence in patients with hepatocellular carcinoma

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Abstract
Background/Purpose. Little has been addressed regarding the impact of the type of resection, which can be anatomical or nonanatomical, for patients with hepatocellular carcinoma (HCC), from the viewpoint of early (≤2-year) and late (>2-year) intrahepatic recurrence. The aim of the present study was to investigate this issue.
Methods. Between 1990 and 2004, we performed 365 potentially curative liver resections. Among these, 233 patients with a solitary tumor were the subjects of this study. They were classified into two groups: anatomical resection ($n = 106$) and nonanatomical resection ($n = 127$). We evaluated the following outcomes: (1) early and late recurrence rates; (2) topography of the recurrent tumors; and (3) risk factors for early recurrence.
Results. The early recurrence rate after anatomical resection was significantly lower than that after nonanatomical resection: recurrence rates at 1 and 2 years were 13.8% and 29.8%, respectively, in the former group; while they were 22.6% and 46.3%, respectively, in the latter group ($P = 0.01$; log-rank test). However, late recurrence rates were similar in the two groups ($P = 0.36$). Local recurrence was observed in 25 of the 89 patients with intrahepatic recurrence after nonanatomical resection (28%), whereas it was observed in 3 of the 64 patients with intrahepatic recurrence after anatomical resection (5%), showing a significantly lower local recurrence rate in the anatomical resection group ($P = 0.0002$). Cox multivariate analysis identified the type of resection employed as one of the variables contributing to early HCC recurrence (nonanatomical resection: hazard ratio, 1.84; 95% confidence interval [CI], 1.01–3.37).
Conclusions. Anatomical resection would be a more appropriate strategy than nonanatomical resection for preventing early intrahepetic recurrence in patients with solitary HCC. However, the type of resection has no significant influence on late recurrence.

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Key words Hepatocellular carcinoma · Anatomical resection · Early and late recurrence

Introduction

The outcome of liver resection for hepatocellular carcinoma (HCC) has steadily improved as a result of advances in surgical techniques and perioperative care.[1–3] However, the long-term outcome is still unsatisfactory because of a high incidence of intrahepatic recurrence,[4,5] intrahepatic metastasis (IM), and/or multicentric occurrence (MO) of a new tumor.[6–8] Previous studies have shown that IM occurs mainly in the early phase after hepatectomy for HCC, whereas MO does so in the later phase.[9–11]

Considering that IM can occur via the portal venous system, it seems that anatomical resection, i.e., resection of the tumor with the surrounding portal territory, would be an ideal treatment for HCC. If anatomical resection is able to eradicate minute intrahepatic metastatic foci adjacent to the primary tumor, it can be hypothesized that early intrahepatic recurrence might be prevented. Since Makuuchi et al.[12] developed a technique of ultrasonically guided subsegmentectomy in 1985, several studies have been conducted to evaluate the effect of anatomical resection on overall survival and/or disease-free survival.[13–17] However, no studies have precisely evaluated the role of such resection from the viewpoint of the period until disease relapse.

In this communication, we discuss the potential effect of anatomical resection on early and late intrahepatic recurrence, in comparison with nonanatomical resection.

Methods

Between January 1990 and December 2004, we performed 365 potentially curative hepatectomies for patients with HCC, using consistent treatment and follow-up strategies, at the First Department of Surgery, Shinshu University Hospital. Potentially curative resection means removal of all gross tumors with a clear margin. With regard to the surgical margin, resection with a 0-mm margin was defined as curative in this study, as long as no tumor invasion was evident at the cut surface. Among these patients, 132 with multiple tumors, including those with macroscopic intrahepatic metastases adjacent to the main tumor, were excluded from the evaluation, in order to clarify the spatial relationship between the primary tumor and the recurrent ones. Finally, 233 patients were entered into the analysis: 106 patients who underwent anatomical resection and 127 who underwent nonanatomical resection. Anatomical resection was considered to include hemihepatectomy, sectionectomy, and segmentectomy, which are defined as the resection of a hemiliver, a section, and a segment of the liver, respectively.[18] Limited resection and tumor enucleation were considered to be types of nonanatomical resection. We decided on the type of liver resection according to the criteria of Makuuchi et al.[17] In brief, if ascites could not be controlled with diuretics preoperatively, liver resection was not indicated. The serum bilirubin value and the indocyanine green retention rate at 15 min (ICG-R) were the major parameters for determining the extent of resection. Although we have not routinely performed preoperative transcatheter arterial chemoembolization (TACE), some patients had undergone TACE preoperatively at other hospitals. The details of the surgical techniques and perioperative management have been described in previous reports.[19]

Briefly, liver resection was performed by the clamp crushing method under Pringle's maneuver or by the hemihepatic vascular occlusion technique.[20] Intraoperative ultrasonography was performed in all cases to assess occult tumors that were not detected by preoperative imaging modalities and to confirm the spatial relationships between the tumors and vascular structures.[21] Bleeding from the raw surface of the transected liver was controlled by meticulous placement of surface ligatures. Perioperative blood transfusion (BTF) was defined as the transfusion of whole blood and/or packed red cells, either during the operation or within 1 week afterwards.

Follow-up

After discharge, patients were closely followed up at our outpatient clinic. All patients underwent routine examinations for recurrence every 3 months, including ultrasonography (US) and measurement of α-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP) levels, one of the tumor markers for HCC[22,23] Computed tomography (CT) with contrast medium was performed every 6 months. Suspected intrahepatic recurrence was confirmed using CT during arterial portography and CT during hepatic arteriography. Recurrence was diagnosed when these imaging modalities showed a new lesion with typical radiologic features of HCC. The indications for repeat hepatectomy of recurrent HCC were basically decided in a manner similar to those used for the first liver resection.[24,25] TACE was indicated for patients who had a large number of tumors, refused repeat hepatectomy, or had poor liver function.

In this study, early and late intrahepatic recurrences were defined as recurrence within or after 2 years after the initial liver resection, in accord with previous studies.[26–28] A preliminary analysis also confirmed that these time periods were the most discriminant choice for the time points of early and late recurrences when compared with other time intervals.

Regarding the site of recurrence, recurrence in the remnant liver was classified as marginal recurrence, recurrence in the same segment, recurrence in the same section, recurrence in the same hemiliver, recurrence in a distal segment, and multisegmental recurrence. Recurrence was defined as local when it arose in the same section as that where the primary tumor had been located.[14]

Histological study of the recurrent tumors was possible for patients who underwent repeat liver resection. We classified these tumors as IM or MO according to previously described criteria.[29,30] IM was defined as a recurrent tumor consisting of moderately or poorly differentiated HCC with the same or a lower degree of differentiation compared with that of the primary tumor. MO was defined as follows: (1) the recurrent tumor consisted of well-differentiated HCC occurring in a hepatic segment, different from that of the moderately or poorly differentiated preexisting HCC; (2) both the primary and recurrent tumors were well-differentiated HCCs; or (3) the recurrent tumor contained regions of adenomatous hyperplasia in peripheral areas.

Variables analyzed

The factors studied were classified as host-, cancer-, or surgery-related. The host-related factors were: age (older vs younger than 65 years), sex, hepatitis B antigen (HBsAg), hepatitis C antibody (HCVAb), Child-Pugh class, ICG-R (15% or more vs less than 15%), and histologically proven liver cirrhosis (cirrhosis vs noncirrhosis). The cancer-related factors included tumor size

(3 cm or more vs less than 3 cm); microscopic portal invasion, which was defined as tumor-cell infiltration identified by postoperative histological assessment of the resected specimen (present vs absent); tumor-cell differentiation according to the Edmondson and Steiner classification (grade 1 vs others); serum AFP level (20 ng/ml or more vs less than 20 ng/ml); and plasma DCP level (positive vs negative). The surgery-related factors included type of resection (anatomical vs non-anatomical), surgical margin (5 mm or more vs less than 5 mm), amount of bleeding (1000 ml or more vs less than 1000 ml), and BTF.

Statistical analysis

Values for continuous variables were expressed as medians and ranges. The Mann-Whitney test was used to compare data in the two groups. Cumulative recurrence rate curves were constructed by the Kaplan-Meier method, and compared by the log-rank test. Multivariate regression analysis was performed using the Cox proportional hazard model. Variables to be entered into the regression analysis were chosen on the basis of the results of univariate analysis. A P value of less than 0.15 was set as a cutoff for the elimination. All statistical analyses were performed using StatView 5.0J software (SAS Institute, Cary, North Carolina, USA).

Results

Background characteristics

The 106 anatomical resections included 66 segmentectomies, 27 sectionectomies, 7 left hemihepatectomies, and 6 right hemihepatectomies. In the nonanatomical resection group, there was a significantly higher proportion of patients with histologically proven liver cirrhosis and a significantly higher ICG-R value (Table 1). The width of the surgical margin in the nonanatomical resection group was narrower than that in the anatomical resection group (2 mm; range, 0–20 mm, vs 4 mm; range, 0–40 mm; $P = 0.001$). The number of patients who underwent preoperative TACE was similar in the two groups. As for microscopic intrahepatic metastasis, the incidence was comparable in the two groups: two (1.9%) in the anatomical resection group versus 4 (3.1%) in the nonanatomical resection group.

Table 1. Clinicopathological data of patients who underwent anatomical and nonanatomical resections

Variables	Anatomical ($n = 106$)	Nonanatomical ($n = 127$)	P value
Age (years)[a]	65 (21–83)	67 (33–88)	NS
Sex			NS
Male/female	75/31	93/34	
HBsAg			NS
Positive/negative	25/81	31/96	
HCV Ab			NS
Positive/negative	66/40	86/41	
Child-Pugh class			0.03
A/B	102/4	112/15	
ICG-R (%)[a]	15 (5–30.0)	21 (2–58)	<0.0001
Underlying liver disease			
Cirrhosis/noncirrhosis	25/81	69/58	<0.0001
Tumor size (cm)[a]	3.0 (1.1–14.0)	2.8 (1.0–14.5)	NS
Microscopic portal invasion[b]			NS
Yes/No	31/73	36/84	
Histological differentiation (E & S)[b]			NS
1	20	31	
2	67	70	
3	17	18	
4	0	1	
α-Fetoprotein (ng/ml)			0.01
≥20/<20	44/62	72/53	
Des-γ-carboxy prothrombin			NS
Negative/positive	58/44	75/48	
Surgical margin (mm)			0.002
<5/≥5	56/50	92/35	

NS, not significant; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; ICG-R, indocyanine green retention rate at 15 min; E & S, criteria of Edmondson and Steiner

[a] Values are medians with ranges

[b] Microscopic portal invasion and tumor cell differentiation were not evaluated in two patients after anatomical resection and in seven after nonanatomical resection because of total necrosis of the tumor due to preoperative TAE

Tumor recurrence

The mean and median follow-up periods for the entire cohort were 68 months and 59 months, respectively (range, 5–192 months). During the follow-up period, recurrence was observed in 160 patients, and the remnant liver was the first site of recurrence in 153 of them (although lung, lymph node, or bone metastasis occurred later in some). Among these 153 patients, 86 had an early recurrence and 67 had a late one (Table 2).

The 2-year recurrence rate after anatomical resection was significantly lower than that after nonanatomical resection (29.8% vs 46.3%; $P = 0.01$; Fig. 1). On the other hand, recurrence rates after 2 years; namely, late recurrence, were similar in the two groups ($P = 0.36$; Fig. 2). Similar results in favor of anatomical resection were obtained after the stratification of patients for ICG-R (> or ≤15%), background liver (cirrhosis or noncirrhosis), and surgical margin (< or ≥5 mm; Table 3).

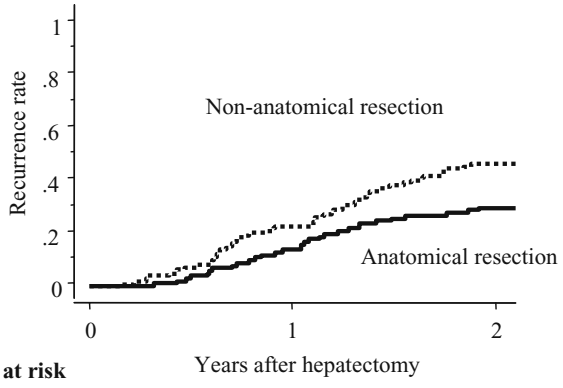
Local recurrence was observed in 25 of the 89 patients with intrahepatic recurrence after nonanatomical resection (28%), and it was observed in 3 of the 64 patients with intrahepatic recurrence after anatomical resection (5%), showing a significantly lower local recurrence rate in the anatomical resection group ($P = 0.0002$; Table 4). In the nonanatomical resection group, 17 of the 25 patients (68%) with local recurrence had disease relapse within 2 years.

Of the 12 resected early recurrent tumors from the 12 patients in the anatomical resection group, 5 (42%) were classified as IM and 7 (58%) as MO. On the other hand, of the 13 resected HCCs from the 13 patients after nonanatomical resection, 11 (85%) were IM and 2 (15%) were MO, indicating a tendency for a higher percentage of IM after nonanatomical resection.

Cox multivariate analysis identified HCV Ab positivity and type of resection as factors contributing to early intrahepatic recurrence (Table 5).

Discussion

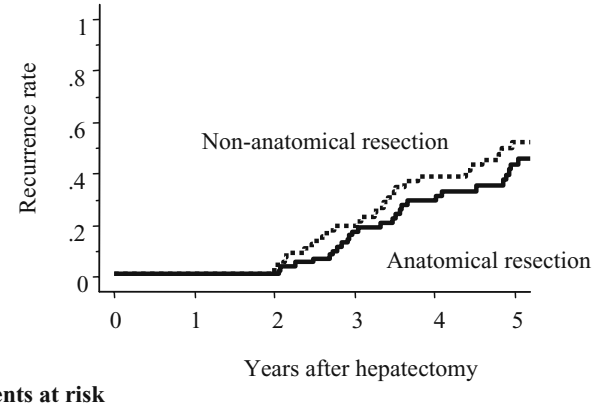
In the present series we demonstrated that anatomical resection was superior to nonanatomical resection in



Patients at risk

Anatomical	106	86	69
Non-anatomical	127	95	62

Fig. 1. Early-phase recurrence curves after anatomical ($n = 106$) and nonanatomical ($n = 127$) resection. The 2-year recurrence rate after anatomical resection was significantly lower than that after nonanatomical resection (29.8% vs. 46.3%; $P = 0.01$)



Patients at risk

Anatomical	69	52	40	27
Non-anatomical	62	45	30	21

Fig. 2. Late-phase recurrence curves after anatomical ($n = 69$) and nonanatomical ($n = 62$) resection. Recurrence rates after 2 years were similar between the two groups ($P = 0.36$)

Table 2. Number of recurrences in anatomical and nonanatomical resection groups

	Anatomical ($n = 106$)	Nonanatomical ($n = 127$)	Total
Total number of recurrences	67	93	160
Intrahepatic recurrence	64	89	153
Time to intrahepatic recurrence			
Early (≤2 years)	30	56	86
Late (>2 years)	34	33	67

Table 3. Early recurrence rates after stratification for ICG-R, surgical margin, and background liver status

		2-Year recurrence rate (%)		
	No. pts[a]	Anatomical	Nonanatomical	*P* value
ICG-R				
>15%	42/94	24.4	50.5	0.006
≤15%	64/33	33.6	33.4	NS
SM				
<5 mm	56/92	39.5	50.1	NS
≥5 mm	50/35	19.1	37.1	0.06
Background liver				
Cirrhosis	25/69	20.8	46.7	0.03
Noncirrhosis	81/58	32.7	45.8	NS

ICG-R, indocyanine green retention rate at 15 min; NS, not significant; SM, surgical margin
[a] Numbers of patients who underwent anatomical and nonanatomical resections, respectively

Table 4. Topography of recurrent tumors in anatomical and nonanatomical resection groups

	Anatomical	Nonanatomical	*P* value
Site of intrahepatic recurrence			<0.0002*
Local	3 (5%)	25 (28%)	
Marginal	0	3	
Same segment	1	14	
Same section	2	8	
Same hemiliver	20 (31%)	20 (23%)	
Distal segment	19 (30%)	19 (21%)	
Multiple segments	22 (34%)	25 (28%)	
Total	64	89	

* *P* value; comparison between local and other types of recurrence
Percentages in parentheses represent proportions of total number of intrahepatic recurrences in each group

Table 5. Independent risk factors contributing to early intrahepatic recurrence (≤2 years)

Variables	Hazard ratio	95% CI	*P* value
HCV Ab-positive	3.33	1.72–6.49	0.0004
Nonanatomical resection	1.84	1.01–3.37	0.04

HCV Ab, hepatitis C antibody

terms of the incidence of early intrahepatic recurrence in patients with solitary HCC. In general, there is an assumption that IM can occur mainly in the early phase, whereas MO occurs in the later phase after hepatectomy for HCC.[9–11] This is supported by some previous studies suggesting that different risk factors are involved in each type of recurrence.[26,31] In short, adverse tumor factors such as vascular invasion and/or intracapsular infiltration are responsible for early recurrence. On the other hand, factors associated with late recurrence are thought to be those reflecting increased underlying carcinogenesis in the liver. Of note, Yamamoto et al.[10] reported that nine of ten patients with a normal liver, which supposedly would be less likely to have MO, suffered intrahepatic recurrence of HCC within 2 years after resection. Hence, our finding of a lower early-phase recurrence rate after anatomical resection indicated that this type of resection seems to be advantageous for reducing IM.

Sites of intrahepatic recurrence after anatomical resection have not been clearly demonstrated in previous studies. Regimbeau et al.[14] showed that anatomical resection significantly prevented local recurrence adjacent to the primary tumor, in comparison with nonanatomical resection. In the present study, the local recurrence rate after nonanatomical resection was significantly higher than that after anatomical resection (28% vs 5%; $P = 0.0002$). Interestingly, 68% of local recurrences were observed within 2 years after nonanatomical resection, indicating that such patients are likely

to harbor undetected micrometastases around the main tumor. These results may indicate the superiority of anatomical resection for the possible eradication of minute IM foci by resecting tumor-bearing portal branches and the corresponding liver parenchyma.

The definition of local recurrence after resection of HCC has not been clearly demonstrated in previous studies. However, considering the mechanism of cancer spread via the portal venous system, local recurrence is thought to be due to residual intrahepatic metastatic foci adjacent to the primary HCC, which could not be detected before and during surgery. Takayama et al.[28,32] defined local recurrence as a tumor within 2 cm of the surgical margin or in the same segment as the initial tumor. Similarly, Regimbeau et al.[14] defined local recurrence as a tumor arising in the same section as that where the primary tumor was located. In the present study, we defined local recurrence in accordance with the latter study.

Of note, anatomical resection had no significant influence on late recurrence in the present series. In general, it has been reported that late recurrence after resection of HCC is ascribable mainly to MO.[9–11] Previous studies have shown that a chronically damaged liver is responsible for the appearance of de-novo primary HCC.[10,33] Hence, it is understandable that the surgical procedure employed, whether it be anatomical or nonanatomical resection, would not affect late recurrence after hepatectomy for HCC.

There may be criticism that the lower early recurrence rate in our anatomical resection group was merely a reflection of the better functional liver reserve or wider resectional margin. Nevertheless, the results after stratification for ICG-R value, presence or absence of liver cirrhosis, and surgical margin appear to support the feasibility of the anatomical resection for HCC. Furthermore, the difference between our anatomical and nonanatomical groups was more pronounced in patients with impaired liver function; namely, those with ICG-R more than 15% (24.4% vs 50.5%; $P = 0.006$) and those with cirrhosis (20.8% vs 46.7%; $P = 0.03$). Our multivariate factor analysis, which identified the type of resection as one of the independent factors contributing to early recurrence, further supports its clinical importance irrespective of functional liver reserve and width of surgical margin. Because the number of patients in the present study was limited and because the study was not a prospective randomized one, it cannot be concluded, on the basis of our results alone, that anatomical resection can reduce early intrahepatic recurrence.

Histological analysis of the early recurrent tumors was possible only in patients who underwent repeat liver resection, because we did not routinely perform needle biopsy for recurrent tumors. Classification of the tumors revealed that there was a trend toward a higher proportion of IM after nonanatomical resection compared with anatomical resection, indicating that the latter type of resection appears to be a more appropriate strategy for preventing IM. However, there was a degree of limitation in this analysis because our results may not reflect all of the early recurrent tumors.

In the present study, we defined recurrence within 2 years after resection of HCC as an early recurrence. The rationale for this definition is based on a previous report suggesting that adenomatous hyperplasia, which has been proven to be a precancerous lesion, requires 2 years or more for transformation into HCC.[34] In fact, previous studies revealed that a second peak of intrahepatic recurrence was observed after 2 years from the initial liver resection.[10,26]

In conclusion, anatomical resection could be a more appropriate strategy than nonanatomical resection for preventing early intrahepatic recurrence in patients with a solitary HCC. However, the type of resection had no significant influence on late recurrence.

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