Intrahepatic Recurrences of Hepatocellular Carcinoma After Hepatectomy

Analysis Based on Tumor Hemodynamics

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Hypothesis: Surgical margin, ie, the area of possible local intrahepatic metastasis, is controversial in hepatectomy for hepatocellular carcinoma.

Design: The blood drainage area of tumor was identified preoperatively by abdominal helical computed tomographic scan under hepatic arteriography and excised as surgical margin. The specimens were pathologically examined on the basis of the corresponding computed tomographic images.

Setting: University hospital.

Patients: From June 2, 1997, to April 24, 2000, 67 patients with hepatocellular carcinoma who underwent curative hepatic resection.

Main Outcome Measure: Intrahepatic recurrence.

Results: Blood drainage area of tumor could be classified into the following types. The marginal type (drainage into the peritumorous area) was frequent (50 cases) and excised mostly by nonanatomic, limited resection. Portal vein type (drainage into the portal branches) was less common (12 cases) and resected mostly by anatomically systematic hepatectomy. The remaining 5 cases were of the hypovascular type and underwent limited resection. Multiple nodules were frequently found inside the drainage area (4 of 8 cases) and were moderate or poorly differentiated hepatocellular carcinoma, consistent with intrahepatic metastasis. Solitary nodules were mostly outside the drainage area (11 of 12 cases) and contained well-differentiated hepatocellular carcinoma (7 of 10 cases), suggesting multicentric carcinogenesis. Intrahepatic recurrences were commonly found in bilateral or contralateral lobes (17 of 19 cases) and divided into 2 groups with a few (≤4) and multiple (≥8) recurrent nodules.

Conclusions: Surgical margin varied according to tumor hemodynamics. Tumor recurrences may result not only from multicentric carcinogenesis but also from intrahepatic metastasis via systemic circulation.

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Hepatectomy is the treatment of choice for hepatocellular carcinoma (HCC), but the extent of hepatectomy is still controversial. If the functional reserve of the liver is adequate, anatomically systematic hepatectomy (eg, segmentectomy or lobectomy) is recommended because HCC is considered to spread via portal blood flow. On the other hand, nonanatomic, limited resection has also been recommended by clinical studies, particularly in patients with poor liver function. To determine the optimal extent of hepatectomy in HCC, survival rate or disease-free survival rate has commonly been studied. However, not only surgical resectability but also effectiveness of treatment for tumor recurrences may influence survival rate. Multicentric carcinogenesis from the underlying hepatitis or liver cirrhosis is also considered to affect the disease-free survival rate. Despite different evaluation methods, recent studies demonstrated similar, although considerably high, incidence of multicentric carcinogenesis in postoperative tumor recurrences, which ranged around 50%. These findings suggest that the optimal extent of hepatectomy for HCC has not been precisely evaluated, and that there is no conclusive evidence on it.

Theoretically, hepatectomy for HCC involves resection of not only the main tumor but also surgical margins, ie, the high-risk area of intrahepatic metastasis. However, the scientific identification of surgical margin in HCC, based on the mechanisms of tumor spread, has not been well investigated so far. Hepatocellular carcinoma is generally considered to spread via the bloodstream. Therefore, to determine surgical margin, ie, extent of hepatectomy for HCC, it is essential to evalu-
PATIENTS AND METHODS

PATIENTS

Seventy adult patients who had not received any treatment before admission underwent hepatectomy after CTHA between June 2, 1997, and April 24, 2000. Three patients with large tumors or tumor thrombi in the major branches of portal vein were excluded from the study because tumor hemodynamics could not be evaluated precisely as a result of abnormal portal blood flow. The resulting 67 patients (58 men and 9 women) were enrolled in this study. No patient received postoperative adjuvant therapy. A signed consent form was obtained from each subject.

ABDOMINAL CTHA

Helical CT scanning was performed over the whole liver after administration of a nonionic contrast medium (Omnipaque; Daiichi Pharmaceutical Co, Ltd, Tokyo, Japan) via the right, left, or proper hepatic artery, as described previously.22 Briefly, data acquisition commenced 5 to 8 seconds (early phase) and 45 to 30 seconds (late phase) after commencement of transcatheter injection of the contrast medium (150-160 mg/mL, 20-33 mL; injection rate, 1-2 mL/s). The CT scanning of the liver was performed with a section thickness of 7 to 10 mm and a table feed speed of 7 to 10 mm/s, and 23 to 25 images were reconstructed in 7- to 10-mm increments. The direction of scanning was cephalocaudal, and the duration of scanning was 23 to 25 seconds. From September 1999, data acquisition was performed in 3 phases (early phase: first, 10 seconds; second, 25 seconds; late phase, 55 seconds) by multidetector-row helical CT.23

RESULTS

HEPATECTOMY BASED ON TUMOR HEMODYNAMICS

The hemodynamics of tumors evaluated by CTHA differed from one case to another, but, for data analysis, tumors were classified into 3 types: marginal (Figure 1-A-D), portal vein (Figure 1E and F), and hypovascular. In the marginal type, the drainage of tumor blood was limited to the peritumorous area, which was clearly identifiable in the late phase of CTHA. This type was most frequent (50 [75%] of 67 patients). The adjacent tumor blood drainage area was completely resected with the main tumor, mostly by nonanatomic, limited resection (37 [74%] of 50 patients), as shown in Figure 1 and Table 1. In the portal vein type, the tumor was commonly located deep in the liver. The blood drainage area was larger than that of the marginal type and varied from a subsegment or less to a lobe, suggesting that tumor blood flowed in the branch(es) of the portal vein. The frequency of the portal vein type was 18% (12/67 patients). Anatomically systemic hepatectomy (eg, subsegmentectomy or segmentectomy) was performed in 8 (75%) of 12 patients with this type of tumor. In the remaining 5 patients with the hypovascular type, the blood drainage area could not be identified by CTHA because of the poor blood supply of the tumor. Nonanatomic, limited resection was performed in these patients.

DETERMINATION OF HEPATIC DISSECTION LINE

The early-phase CT scans demonstrated arterial blood filling of the tumor, while the late phases showed blood drainage into the noncancerous tissue, ie, the high-risk area of local intrahepatic spread, which is designated as the surgical margin. The surgical margin was determined on the relevant CT images and represented the distance between tumor edge and peripheral margin of the drainage area of tumor blood.21 By intraoperative ultrasonography, the dissection line was determined on the basis of the data from CTHA to resect the surgical margin and main tumor completely. The adequacy of the surgical margin was confirmed by ultrasonography during hepatic dissection.

HISTOPATHOLOGIC EXAMINATION

The resected specimens were fixed and cut at intervals of 5 to 10 mm so as to correspond to the CT images. The tumor and nontumor tissues were inspected macroscopically and then examined microscopically to determine the histopathologic diagnosis as described previously.24

FOLLOW-UP STUDIES

Patients were followed up at least once every 3 months after surgery by ultrasonography or CT scan, in addition to the measurement of serum α-fetoprotein and des-γ-carboxy prothrombin. The follow-up period ranged from 6 to 40 months (median, 18 months). When tumor recurrence was suspected, CT angiography and subsequent transcatheter arterial embolization were performed to confirm the number, size, and location of intrahepatic recurrences. Tumor recurrences in lungs were examined by chest CT scan.

PATHOLOGIC FINDINGS OF MAIN TUMOR AND SATELLITE NODULES INSIDE AND OUTSIDE OF DRAINAGE AREA OF TUMOR BLOOD

Most tumors of the marginal type (38 of 50 cases) and portal vein type (10 of 12 cases) were moderately or poorly differentiated HCC (Table 2). In 6 marginal-type tumors of 6 individual patients, so-called nodule-in-

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nodule tumor was observed, where moderately or poorly differentiated tumor developed inside a well-differentiated lesion. In contrast, in 5 hypovascular tumors, well-differentiated HCC was the sole (4 cases) or major (1 case) component of the main tumor. Satellite nodules were found both inside (8 of 67 cases) and outside (12 of 67 cases) of the drainage area. In 3 patients in the former group, numerous (8 or more) nodules were found. All satellite nodules inside the drainage area were moderately or poorly differentiated HCC, consistent with intrahepatic metastasis. In contrast, nodules outside the drainage area were solitary in 11 of 12 patients and contained well-differentiated lesions in 7 of 10 patients, suggesting multicentric carcinogenesis. Two patients had satellite nodules both inside and outside the drainage area. These patients had moderately or poorly differentiated HCCs inside the drainage area, while 1 patient had a well-differentiated lesion outside the drainage area.

### POSTOPERATIVE TUMOR RECURRENCE

During the follow-up period of 6 to 40 months after surgery, 19 patients (28%) developed intrahepatic tumor recurrences. There was no local recurrence in the vicinity of the cut surface. Almost all intrahepatic recurrences were multiple and located in either both liver lobes or the contralateral lobe (17 of 19 cases). Extrahepatic metastases were detected in 4 patients, including the lungs (3 cases) and extrahepatic bile duct (1 case). The numbers of recurrent hepatic nodules on CT scans ranged from 1 to 43, but they were divided into 2 groups: few (≤4) and multiple (>8) recurrent nodules. Ten (59%) of 17 patients with bilateral or contralateral recurrences developed at least 8 recurrent nodules, while the remaining 7 patients had few recurrent nodules.

### Table 1. Type of Hepatectomy Based on Tumor Hemodynamics

<table>
<thead>
<tr>
<th>Type of Hepatectomy</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal type</td>
<td>50</td>
</tr>
<tr>
<td>Partial hepatectomy</td>
<td>37</td>
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<tr>
<td>Subsegmentectomy</td>
<td>6</td>
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<tr>
<td>Segmentectomy</td>
<td>5</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>2</td>
</tr>
<tr>
<td>Portal vein type</td>
<td>12</td>
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<td>Partial hepatectomy</td>
<td>4</td>
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<tr>
<td>Subsegmentectomy</td>
<td>5</td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>5</td>
</tr>
<tr>
<td>Lobectomy</td>
<td>1</td>
</tr>
<tr>
<td>Hypovascular type</td>
<td>5</td>
</tr>
<tr>
<td>Partial hepatectomy</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>67</strong></td>
</tr>
</tbody>
</table>

**Figure 1.** Tumor blood drainage area demonstrated by computed tomography under hepatic arteriography. The late phase shows the drainage area of tumor blood flow. The drainage area was irregular and different in shape from one patient to another, but could be classified into the marginal type (A through D; tumor blood flowing to the peritumorous liver tissue) and portal vein type (E and F; tumor blood flowing to a larger area, e.g., subsegment or segment, via branch(es) of the portal vein). Hepatectomy was performed, including complete excision of the drainage area with the aid of intraoperative ultrasonography. Solid lines indicate the liver dissection line.
remaining 7 patients had 4 or fewer. Shown in Figure 4 are scans from one representative patient who developed multiple recurrences in both lobes 13 months after hepatectomy. Fifteen recurrent nodules of similar size were observed in the remnant liver.

**COMMENT**

The advantage of hepatectomy for HCC is the resection not only of the main tumor but also an adequate surgical margin, ie, the surrounding tissue that may contain nondetectable micrometastases. Extended hepatectomy or anatomically systemic hepatectomy based on portal blood flow has long been recommended. In contrast, nonanatomic, limited resection has also been recommended because of liver dysfunction commonly associated with liver cirrhosis or chronic hepatitis. These contradictions between surgical curability and preservation of liver function have been discussed for many years, but no clear resolution has emerged. This is partly because of the difficulty in differentiating between intrahepatic metastasis and multicentric carcinogenesis. Detection of micrometastases in the liver tissue also has been impossible. Therefore, the current policy is to perform the minimal, but essential, extent of hepatectomy, based on the mechanisms of the regional spread of HCC. These contradictions between surgical curability and preservation of liver function have been discussed for many years, but no clear resolution has emerged. This is partly because of the difficulty in differentiating between intrahepatic metastasis and multicentric carcinogenesis. Detection of micrometastases in the liver tissue also has been impossible. Therefore, the current policy is to perform the minimal, but essential, extent of hepatectomy, based on the mechanisms of the regional spread of HCC. Since intrahepatic metastasis is considered to occur via blood flow, it is essential to identify the drainage area of tumor blood, ie, the high-risk area of intrahepatic metastasis, because cancer cells first spread in this area before entering the systemic circulation.

Recent advances in hepatic imaging techniques have allowed direct visualization of the tumor hemodynamics, ie, inflow of arterial blood to the tumor and subsequent blood outflow from it. In the present study, we identified preoperatively the drainage area of tumor blood by CTHA and completely resected it, including the tumor, with the use of intraoperative ultrasonography as described earlier by our group. As shown in Figure 1, the drainage area of tumor blood varied greatly in shape.
and size. In other words, the surgical margin was different in each case with respect to tumor hemodynamics, and, even in the same tumor, its width differed according to the location on the tumor within the liver.

The pattern of tumor blood drainage could be basically classified into marginal and portal vein types. The drainage area of the marginal type was limited around the tumor. Tumor blood of this type drained into the adjacent liver tissues probably through capsular venules and finally flowed into the branches of the hepatic vein via hepatic sinusoids. Therefore, the extent of the blood drainage area might be determined by tumor blood flow or the difference of blood pressure between hepatic sinusoids and the capsular, drainage venules. Complete excision of the drainage area was mostly achieved by nonanatomic, limited hepatectomy in this type (Table 1). In the portal vein type, the drainage area of tumor blood was larger than that of the marginal type and sometimes corresponded to the anatomic segment or lobe, indicating that tumor blood flowed in the portal branches (Figure 1). Anatomically systematic hepatectomy was commonly performed in this type. In the remaining 5 patients without detectable tumor blood drainage (hypovascular type), the main tumors were well-differentiated carcinomas or consisted predominantly of well-differentiated carcinoma (Table 2). Since the hematogenous metastasis was considered negligible in this type of tumor, limited resection was performed in these 5 patients.

The concept of a high-risk area for intrahepatic metastases in the blood drainage area was supported by pathological findings of resected specimens (Figure 2). Satellite nodules in the drainage area were frequently multiple and moderately or poorly differentiated carcinomas (Table 2), consistent with the characteristics of intrahepatic metastases. In contrast, satellite nodules outside the drainage area were commonly solitary and frequently contained well-differentiated carcinoma, suggestive of multicentric carcinogenesis.

In both the marginal and portal vein types, the blood drainage area could be clearly identified and completely resected in all patients. The adequacy of each resection line was subsequently confirmed by histopathologic examination, as shown in Figure 2. Follow-up studies indicated no recurrence in the vicinity of the cutting wedge of the liver, suggesting that local, hematogenous spread of tumor (local intrahepatic metastasis) could be completely prevented by this method. However, 17 of 67 patients developed multiple bilateral or contralateral recurrences, indicating other mechanisms of tumor spread. Two types of tumor recurrence were noted: few (≤4) and multiple (≥8), as shown in Figure 3. The former type may result mainly from multicentric carcinogenesis because of the limited number of recurrent nodules. In the multiple type, intrahepatic nodules were not only numerous, but uniformly small and similar in size, as shown in Figure 4. Since it was confirmed in this study that there was no direct inflow of tumor blood into the remnant liver tissue, these findings suggest that a proportion of HCC recurrences may develop through intrahepatic metastases via systemic circulation. That such a mechanism can explain intrahepatic metastasis is supported by the clinical evidence that multiple intrahepatic recurrences frequently develop after liver transplantation in patients with HCC. Furthermore, the presence of cancer cells in the peripheral blood was suggested by reverse transcription polymerase chain reaction in patients with advanced HCC. The hypothetical mecha-
nisms of intrahepatic metastasis via local blood flow and systemic circulation are depicted in Figure 5.

The present findings emphasize the clinical importance of detection of cancer cells in peripheral blood when the extent of hepatectomy is determined. Complete resection of the tumor blood drainage area is probably not necessary when cancer cells are detected in peripheral blood, because cancer may have already spread to distant organs through hematogenous dissemination. However, the presence of cancer cells in blood should not necessarily equate with the development of tumor recurrences; prospective comparative studies on tumor recurrences in patients with and without positive peripheral cancer cells have to be performed in the future.

In conclusion, the HCC tumor blood drainage area, ie, the high-risk area for regional intrahepatic recurrence, should be determined individually, based on at least tumor hemodynamics.

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REFERENCES


