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Pathologic Support for Limited Hepatectomy in the Treatment of Liver Metastases from Colorectal Cancer

Junji Yamamoto, M.D.,* Kenichi Sugihara, M.D.,* Tomoo Kosuge, M.D.,* Tadatoshi Takayama, M.D.,* Kazuaki Shimada, M.D.,* Susumu Yamasaki, M.D.,* Michiie Sakamoto, M.D.,† and Setsuo Hirohashi, M.D.†

From the Department of Surgery, National Cancer Center Hospital, and the Pathology Division,† National Cancer Center Research Institute, Tokyo, Japan*

Objective
The authors determined an appropriate surgical treatment for liver metastases from colorectal cancers. Clinicopathologic features of metastatic lesions of colorectal cancers were studied.

Summary Background Data
Major hepatic resection is the usual procedure for treatment of hepatic metastases from colorectal cancers.

Methods
Forty consecutive patients who underwent hepatic resections were prospectively studied, for a total of 89 metastatic liver tumors.

Results
Metastatic tumor often extended along Glisson's capsule, including invasion to the portal vein (9 cases), the hepatic vein (3 cases), the bile duct (16 cases), and the nerve (6 cases). The main tumor had small satellite nodules in only one patient, and there were no microscopic deposits in the parenchyma, even within 10 mm from the metastatic tumors. Fibrous pseudocapsule formation was observed in 28 patients.

Discussion
The rarity of intrahepatic metastasis from metastatic tumor supports nonanatomic limited hepatic resection as the procedure of choice for metastatic colorectal cancer in the liver. The spread via Glisson's capsule should be taken into consideration for complete tumor clearance.

Liver metastases complicates in 20% to 30% of the cases of colorectal cancer.[1,2] Determining how to treat this hematogenous metastases is a vital problem in improving the prognosis of such patients. Recent advances in liver surgery have made surgical therapy common for the treatment of hepatic metastatic disease, especially in patients with metastases from colorectal cancers. Many authors have discussed criteria for patient selection and the predictable prognostic factors based on their experiences with hepatic resection for colorectal liver metastases.[3–10]

Our standard procedure for metastatic liver tumor is nonanatomic limited resection,[2] although most surgeons

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Address reprint requests to Junji Yamamoto, M.D., Department of Surgery, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104, Japan.

recommend extensive hepatic resection.[10,11] A few reports have been published on the pathologic aspects of colorectal metastatic cancer.[12,13] In the current report, we prospectively studied the mode of extension of colorectal metastatic deposits in the liver to determine the appropriate surgical treatment for metastatic colorectal cancer.

MATERIALS AND METHODS

A total of 89 metastatic liver tumors in 40 consecutive patients who underwent hepatic resection between March 1991, and February 1992 at the National Cancer Center Hospital were studied prospectively.

All surgical specimens were sliced 5-mm thick, fixed in 10% formaldehyde solution, embedded in paraffin, and stained with hematoxylin and eosin. Macroscopically, the location, number, size, and gross extension pattern of each tumor were recorded. Microscopic examination included histologic differentiation; invasion to the portal vein, hepatic vein, intrahepatic bile duct, and nerve; histology of noncancerous liver parenchyma; extent of necrosis; the presence of fibrous tissue between tumors and the liver parenchyma; and the presence of cancer cells at the surgical margin. In patients with multiple metastases, the pathologic findings of the largest tumor represented those of other tumors because each tumor showed similar pathologic features.

The histologic type of tumors was determined according to the classification of the World Health Organization.[14] The fibrous tissue between tumors and the liver parenchyma was classified as follows: none—no fibrous tissue observed; thin—tumor was separated by several layers of collagen bundles; thick—tumor was separated by ten or more layers of such bundles (Fig. 1A–C). The extent of tumor necrosis was defined as either slight (under 20% of the area of the maximum cut surface of tumors), medium (between 20%–80%), or severe (more than 80%). The surgical margin was considered to be free of cancer when the entire tumor edge was covered with layers of hepatocytes.

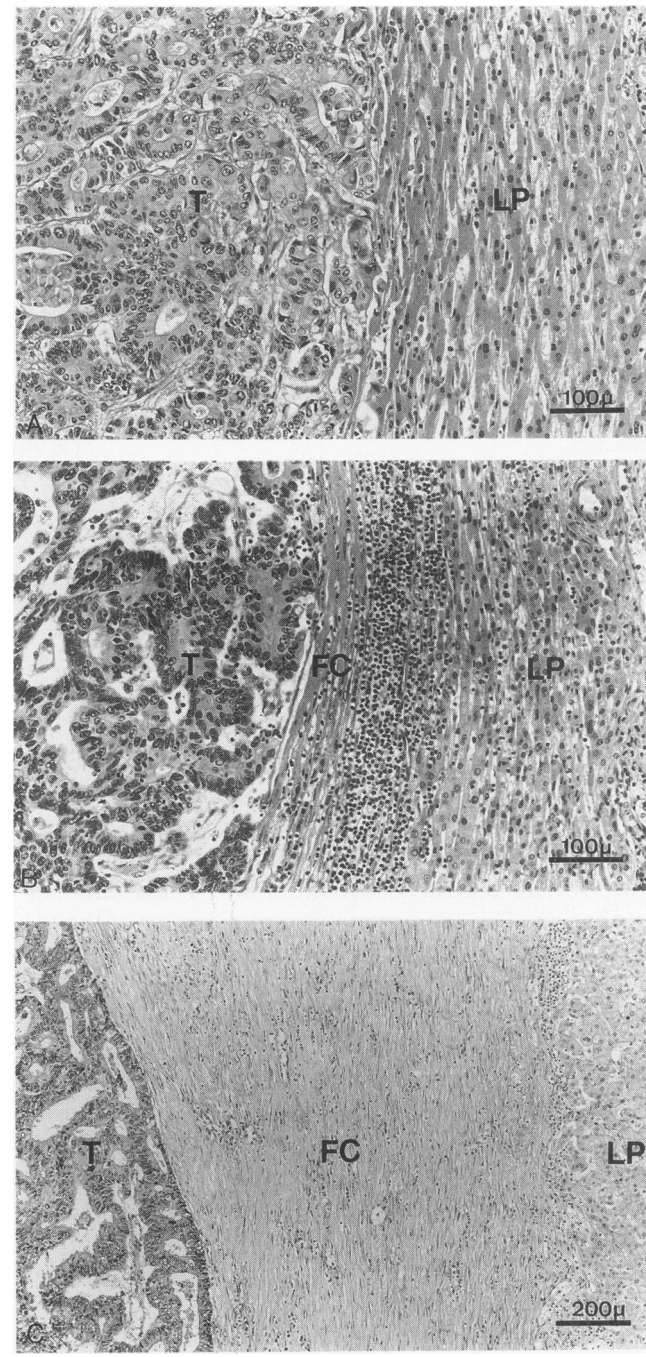

Figure 1. Fibrous tissue between tumor and surrounding hepatic parenchyma. (A) Tumor cells directly infiltrating hepatic sinusoid. (B),(C) Fibrous pseudocapsule (FC) has developed between tumor (T) and parenchyma (LP); thin (B) and well-developed (C). (hematoxin & eosin, original magnification A, B: × 200, C: × 100)

RESULTS

Clinical Data

The patients consisted of 26 men and 14 women with a median age of 62 years (range: 40–81 years). The site of the primary tumor was the rectum in 11 patients, the sigmoid colon in 16, the descending colon in 1, the transverse colon in 3, the ascending colon in 1, and the cecum in 3. Three patients had double primary tumors of the transverse and sigmoid colon, the descending and sigmoid colon, and the sigmoid colon and rectum. Thirty-two patients underwent operations for metachronous metastases and eight underwent operations for synchronous lesions. The operative procedures included 4 hemihepatectomies plus limited resection of the contralateral lobe; 5 hemihepatectomies; 5 segmentectomies, 14 single limited resections; and 12 multiple limited resections. None of the patients had received transarterial chemoinfusion before liver resection.

Table 1. CHARACTERISTICS OF METASTATIC NODULES FROM COLORECTAL CANCER IN THE LIVER

	Solitary Metastasis (n = 18)	Multiple Metastases (n = 22)	Total (n = 40)
Size (maximum cm)	3.5 ± 1.9 (1.7–8.5)	4.5 ± 2.5 (1.5–10.5)	4.1 ± 2.3 (1.5–10.5)
Histologic typing			
Well differentiated adenocarcinoma	8 (20%)	8 (20%)	16 (40%)
Moderately differentiated adenocarcinoma	8 (20%)	12 (30%)	20 (50%)
Mucinous carcinoma	2 (10%)	2 (10%)	4 (10%)
Invasion to			
Portal vein	4 (22.2%)	5 (22.7%)	9 (22.5%)
Hepatic vein	1 (5.6%)	2 (9.1%)	3 (7.5%)
Bile duct	7 (38.9%)	9 (40.9%)	16 (40%)
Nerve	2 (11.1%)	4 (18.2%)	6 (15%)
Noncancerous liver			
Normal	15 (83.3%)	21 (95.5%)	36 (90%)
Chronic hepatitis	2 (11.1%)	1 (4.5%)	3 (7.5%)
Liver cirrhosis	1 (5.6%)	—	1 (2.5%)
Positive surgical margin	1 (5.6%)	7 (25%)	8 (20%)

Pathologic Findings (Table 1)

Eighteen patients had solitary tumors, 11 had two tumors, 6 had three tumors, and the other 5 patients had four, five, six, seven and nine metastatic deposits, respectively. Among 22 patients with multiple metastatic tumors, 18 had bilobar distribution, and 4 had unilobar distribution. The average maximum diameter of the tumors was 4.1 cm (range: 1.5–10.5 cm).

All of the tumors were well circumscribed, and only one patient was observed to have small satellite deposits very close to the main tumor. Nine patients had gross extension in Glisson's capsule; eight patients had bile duct invasion; and one patient had neural invasion. Bile duct invasion appeared as papillary growth in the ductal lumen extending from the tumor. Proximal extension was common, and the distance from the edge of the tumor to the tip of the extension ranged from 4 mm to 23 mm (Fig. 2). There was no relationship between the distance and the tumor size (Table 2).

Microscopically, the tumors invaded the portal venous branch more frequently than the hepatic vein. Invasion to the bile ducts was observed in 16 patients (40%) (Fig. 3). Six patients (15%) also had neural and perineural invasion. Thus, overall microscopic invasion to the Glisson's capsule was seen in 22 of 40 cases (55%). Microscopic examinations have not found additional satellite deposits in the parenchyma, even within 10 mm from the metastatic tumors. The surgical margin was more frequently positive for cancer in patients with multiple metastases than in those with solitary deposits. The positivity of the surgical margin had no relation to the surgical procedure used. Necrosis was noted in all of the nodules examined; it was slight in 9 patients (22.5%), moderate in 21 patients (52.5%), and severe in 10 patients (25%). Fibrous tissue between tumors and the liver parenchyma was observed in 28 cases (70%); it was thin in 13 patients and thick in 15 patients.

DISCUSSION

Our study showed that metastatic tumors from colorectal cancers rarely spread discontinuously in the liver. Hepatocellular carcinoma has a high affinity for the portal vein and spreads in the liver via portal flow.[15,16] Intrahepatic cholangiocarcinoma often accompanies intrahe-

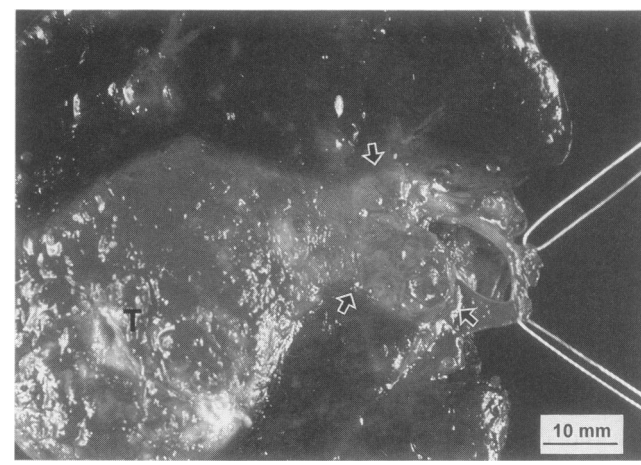

Figure 2. Macroscopic bile duct invasion of the tumor (indicated by arrows) appeared as papillary growth in the bile duct. In this case, the metastatic tumor (T) was located near the posterior portal pedicle, and the bile duct invasion extended 14 mm from the tumor in the right hepatic duct (tensioned with threads).

Table 2. MACROSCOPIC INVASION TO GLISSON'S CAPSULE BY COLORECTAL METASTATIC TUMORS

Case No.	Tumor Size (mm)	Invaded Structure	Distance from Tumor to Tip of Invasion (mm)	Direction of Invasion
1	27	Bile duct	4	Proximal
2	55	Bile duct	7	Proximal
3	20	Bile duct	11	Proximal
4	22	Bile duct	11	Proximal
5	15	Bile duct	12	Proximal and distal
6	20	Bile duct	12	Proximal and distal
7	50	Bile duct	14	Proximal
8	40	Bile duct	23	Proximal
9	23	Nerve	13	Proximal

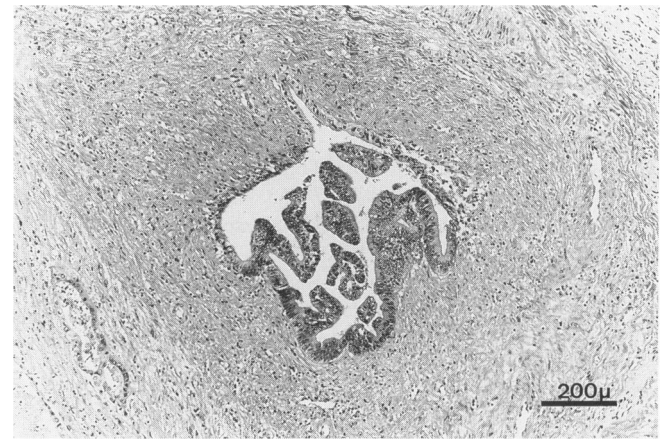

Figure 3. Invasion to the bile duct by the tumor. The cancer shows papillary growth in the lumen of the bile duct. (hematoxin & eosin, original magnification × 100)

patic metastases around the main tumor, especially when it shows vascular invasion.[12,17,18] In the current studies, however, multiple lesions did not exhibit vascular invasion more often than solitary lesions. The absence of small satellite lesions around the tumor, except in one patient, suggested that multiple lesions were derived from multiple metastatic foci of the primary disease, rather than from re-metastasis of the metastatic tumor.

Invasion to Glisson's capsule, which includes the bile duct, the portal and hepatic veins, and nerve, is common in colorectal metastases, as well as in cholangiocarcinoma.[12,17,18] However, these cancers showed different modes of bile duct invasion; metastatic colorectal cancer showed papillary growth in the bile duct (Figs. 2 and 3), whereas cholangiocarcinoma frequently spreads along the duct wall and periductal tissues.[12,17]

Several studies have reported reduced survival rates and an increased rate of recurrence after complete removal of tumors when the surgical margin is less than 10 mm.[3,4,6,9] The observations in our study did not support these results because microscopic satellite foci were not found in the parenchyma within 10 mm from metastatic tumors. Cancer-containing surgical margins are related to multiple metastases because multiple tumors often require multiple liver resections where transection surfaces may more frequently be close to the tumor margin. Our current results do not recommend an anatomic and extensive liver resection as surgical treatment for metastases from colorectal cancer. A generous surgical margin is not required for resection. Surgeons can remove a tumor by shaving the noncancerous liver tissue, especially when it has a thick fibrous pseudocapsule, as was observed in one third of the cases.

However, the high incidence of invasion to Glisson's capsule and its various structures suggest that the portal area of the feeder that is close to the tumor should be resected. In addition, gross extension of the tumor, which was noted in eight patients for the bile duct and in one patient for the nerve of Glisson's capsule, is important from a surgical perspective. Surgeons must be aware of such substantial tumor spread along Glisson's capsule to achieve complete resection because they often can extend more than 10 mm from the tumor. In our series, three patients had incomplete resection because of such extension. Macroscopic invasion often was recognized as a thick Glisson's capsule by inspection or by ultrasound during surgery.

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