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A New Macroscopic Classification Predicts Prognosis for Patient With Liver Metastases From Colorectal Cancer

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Objective
The authors defined a new macroscopic classification of liver metastases from colorectal cancer.

Summary Background Data
There were different prognostic results after the same operative procedure for liver metastases with similar background factors.

Methods
Eighty-one resected liver metastases were classified into simple nodular (SN) or confluent nodular (CN) types according to the characteristics of the cut surface of the tumor.

Results
The 5-year survival rates after hepatectomy were 41.7% for the SN lesions (n = 39) and 23.1% for the CN lesions (n = 42). The difference between the survival curves was statistically significant (p = 0.0307). Multivariate analysis using Cox's proportional hazards model revealed that the macroscopic type (p = 0.023), the tumor diameter (p = 0.0001), and the presence of lymph node metastases (p = 0.0016) were statistically significant independent prognostic factors.

Conclusion
The new macroscopic classification may be valuable as a prognostic factor reflecting the biologic behavior of liver metastases.

Many studies have been made on surgery for patients with liver metastases from colorectal cancer. Some of them[1-12] have dealt with prognostic factors that may predict long-term survival after hepatic resection. Patients with various prognostic factors in common are often found to have divergent prognoses, even if treated with the same operative procedure. Cady and McDermott[7] interpreted such inexplicable results as a difference in the biologic behavior of liver metastases. We performed a retrospective study of our experience with hepatectomy for colorectal liver metastases to elucidate the independent prognostic factor representing biologic behavior.

METHODS

Patients

Over the 12-year period between April 1983 and March 1995, hepatectomies were performed on 101 patients with colorectal liver metastases. Extrahepatic metastatic lesions coexisted in 12 patients. Advanced primary cancers of other organs were present in three patients. Another three patients had received intraarterial chemotherapy for extensive liver metastases before surgery. These 18 patients, as well as 2 postoperative deaths, were excluded from the study. The data from the remaining 81 patients form the basis of this report.

Assessment of Liver Metastases

All surgical specimens were cut into 10-mm sections. Gross findings of the cut surface were classified into two types using Yasui's classification (Fig. 1). Metastatic lesions with a smooth, distinct border and medullary structure with or without necrotic foci were classified as the simple nodular type (SN) (see Fig. 1, A–C). Lesions with an irregular contour and a cut surface consisting of multiple nodules were classified as the confluent nodular type (CN) (see Fig. 1, D–F).

Meticulous macroscopic examination of the specimen was made in search of vessel or ductal infiltration (involving the portal vein, the intrahepatic bile duct, the hepatic vein, or the inferior vena cava), minute satellite lesions, direct invasion into the adjacent viscera, or regional lymph node metastases. These secondaries from the liver metastases have been designated as invasive factors of the tumor.[13] Macroscopic examination was followed by histopathologic confirmation.

Statistical Analysis

Cumulative survival rates were calculated by the Kaplan-Meier method.[14] The log-rank test[15] was used to evaluate the differences between the survival curves. For comparisons between the SN and CN groups, the chi square test was applied. Several clinicopathologic factors, including those found to be associated with patient survival by univariate analysis, were subjected to multivariate analysis using Cox's proportional hazards model.[16] Statistics were performed using SAS software (SAS Institution, Cary, NC). $P < 0.05$ was considered statistically significant.

RESULTS

Surgical Procedures

Anatomic hepatectomy with regional lymphadenectomy was performed in 73 of the 81 patients in the study. Of these, 61 patients (83.6%) underwent extended resection of two or more hepatic segments.[17]

Macroscopic Classification of the Tumors and Survival

There were 39 SN lesions and 42 CN lesions. No statistically significant differences were observed between the two types regarding sex, age (both mean and median), clinical stage of the primary lesion, histopathologic type of the primary and metastatic lesions, number of metastatic lesions, or ratio of synchronous metastatic lesions to metachronous lesions. The liver tumor size ranged from 0.5 to 16 cm (mean 5.0 cm, median 4.0 cm) for the SN type and 1.0 to 23 cm (mean 6.4 cm, median 6.0 cm) for the CN type. The difference in the mean tumor diameter was not statistically significant between the two types. The cumulative 3- and 5-year survival rates for the SN type (72.6% and 41.7%, respectively) were significantly higher ($p = 0.0307$) than those for the CN type (39.5% and 23.1%, respectively) (Fig. 2).

Macroscopic Type and Invasive Factors

Invasive factors were positive in 7 of 39 patients (17.9%) with SN lesions and 25 of 42 patients (59.5%) with CN lesions ($p = 0.0001$) (Table 1). Of the invasive factors, vessel infiltration was observed in 19 of the CN lesions (45.2%) and only 4 of the SN lesions (10.3%) ($p = 0.0005$). The incidence of direct invasion to the adjacent viscera was 28.6% (12 patients) in the CN group and

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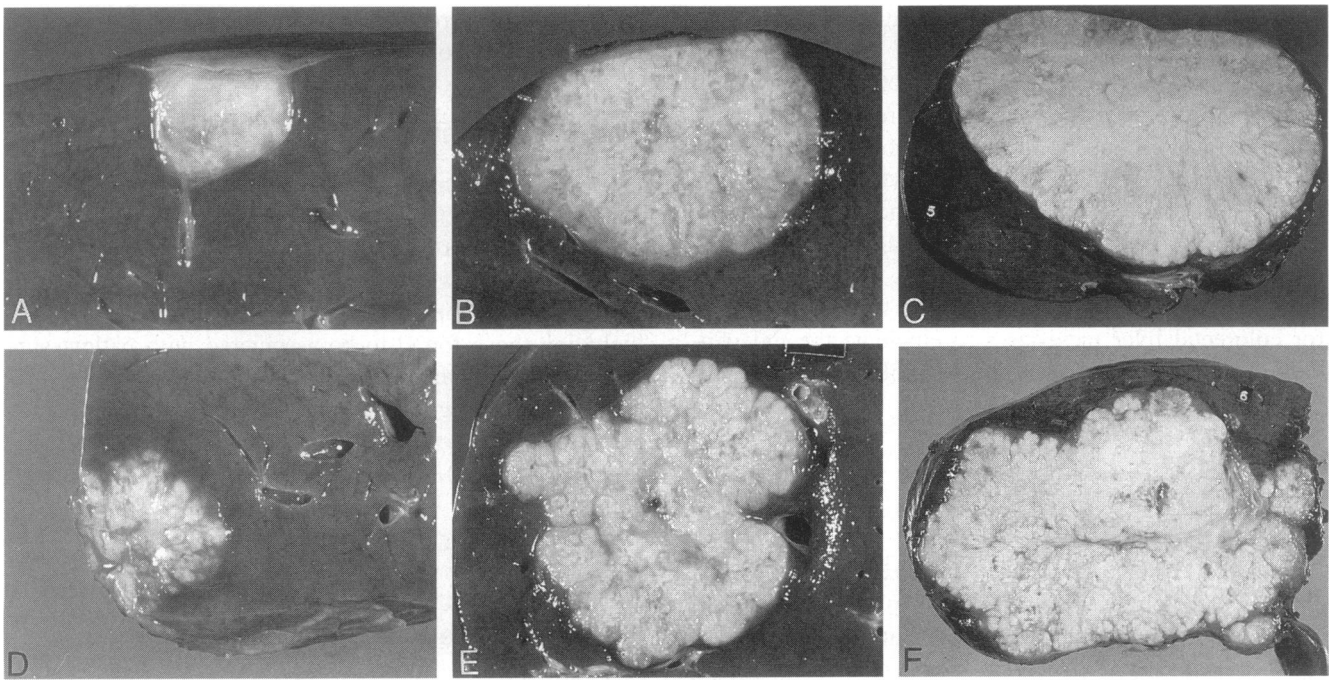

Figure 1. The macroscopic classification of liver metastasis from colorectal cancer (Yasui's classification). The simple nodular (SN) type has a smooth distinctive border and medullary structure with or without necrotic foci (A–C). The confluent nodular (CN) type is a multinodular tumor with an irregular border (D–F). Maximum diameter: A-2.0 cm, B-5.0 cm, C-15.0 cm, D-2.5 cm, E- 4.7 cm, F-16.0 cm.

7.7% (3 patients) in the SN group. The incidence of lymph node metastasis was 16.7% (seven patients) in the CN group and 10.3% (four patients) in the SN group.

Recurrence After Hepatic Resection

Tumor recurrence was found in 55 (67.9%) of the 81 patients. Of these, recurrence in the remnant liver was found in 23 patients (41.8%); pulmonary recurrences were found in 39 patients (70.9%). Recurrence in the hepatic remnant was found in 6 of the 22 recurrent SN tumors (27.3%) and 17 of the 33 (51.5%) recurrent CN tumors (p = 0.0109). Pulmonary recurrence was observed with statistically equal frequency in the SN and CN groups (77.3% and 66.7%, respectively).

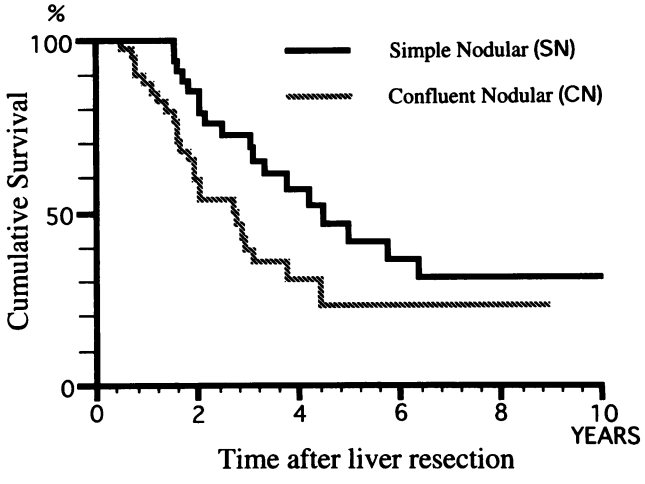

Figure 2. Cumulative survival curves after liver resection for patients with SN (n = 39) and CN (n = 42) tumors. The difference between the two groups was statistically significant (p = 0.0307).

Table 1. MACROSCOPIC INVASIVE FACTORS

Invasive Factor (complicated)	SN	CN	p Value*
Vessel infiltration	4	19	0.0005
Portal vein	4	15	0.0069
Bile duct	0	5	0.0261
Hepatic vein	0	1	0.3322
Inferior vena cava	0	4	0.0481
Minute satellite	3	2	0.5840
Direct invasion	3	12	0.0156
Regional lymph node metastasis	4	7	0.4001
Total	7/39 (17.9%)	25/42 (59.5%)	0.0001

SN = simple nodular type; CN = confluent nodular type.
* The chi square test was used.

Table 2. UNIVARIATE ANALYSIS OF POSSIBLE PROGNOSTIC FACTORS

Variable	Hazard Ratio	95% Confidence Limits		p Value
		Lower	Upper	
Maximum diameter				
<5 cm	1			
≥5 cm	3.480	1.853	6.539	0.0001
Macroscopic type				
Simple nodular	1			
Confluent nodular	1.977	1.063	3.678	0.0314
Invasive factors				
No invasive factors	1			
Lymph node metastasis	2.680	1.314	5.464	0.0067
Vessel infiltration	1.570	0.763	3.231	0.2205
Satellite	0.783	0.241	2.543	0.6837
Direct invasion	1.828	0.871	3.839	0.1108
Number of metastases				
Solitary	1			
Multiple	0.793	0.404	1.556	0.4999

Statistical Analysis of Prognostic Factors

Univariate analysis revealed that tumor diameter ≥5 cm, CN type, and lymph node metastasis were statistically significant risk factors influencing prognosis in patients with liver metastasis (Table 2).

Multivariate analysis was performed with the following factors as covariates: macroscopic type (SN or CN), tumor diameter (≥5 cm or <5 cm), lymph node metastasis (positive or negative), vessel infiltration (positive or negative), minute satellite lesions (positive or negative), and invasion to the adjacent viscera (positive or negative) (Table 3). Of these, macroscopic type ($p = 0.0230$), tumor diameter ($p = 0.0001$), and nodal metastasis ($p = 0.0016$) were found to be statistically significant as independent risk factors. Furthermore, the backward elimination procedure selected classification (hazard ratio 2.122), diameter (hazard ratio 2.997), and lymph node metastasis (hazard ratio 2.531) as independent risk factors.

DISCUSSION

Hepatectomy is considered the most effective method available for treating colorectal liver metastasis. However, several studies[1-4] of the surgical treatment of metastatic liver disease have highlighted the difficulty of complete tumor clearance, revealing the high incidence of recurrences in the remnant liver (59.4% to 78.9%). Some such recurrences might be attributable to minute satellite nodules that were unresected. In addition, the surgical procedures used may have been inadequate. Locoregional resection of the metastatic nodules might not always be sufficient, considering the mode of invasion[13] observed in the resected liver. The standard surgical procedure performed in the current study, therefore, was anatomic extended hepatectomy with regional lymphadenectomy, regardless of the size or site of the intrahepatic lesions. These procedures have resulted in the lowest rate of recurrence in the remnant liver (41.8%) thus far reported among studies involving substantial numbers of cases.

Recurrences in the remnant liver after hepatectomy for metastatic lesions emerge not only as a result of synchronous dissemination from the primary cancer that was unnoticed at the initial hepatectomy, but also as secondary spread[13] of the disease from the metastatic lesions through vessel infiltration (within the portal vein, intrahepatic bile duct, or hepatic vein) and minute satellite lesions. Some authors have reported that vessel infiltration is usually restricted to a minimal distance from the metastatic liver tumor.[18] However, we have confirmed[13,19] that tumor infiltration of the portal vein and bile duct is commonly observed and sometimes extends in the vessels far from the main lesion. These invasive factors must be taken into consideration when treating patients with hepatic metastasis.

Several clinicopathologic factors, including stage of the primary lesion,[5-6] number of metastases,[6-9] tumor diameter,[6,9-11,13] positive surgical margin,[6-7,9-10] coexistence of extrahepatic recurrence or metastases,[5-6,9-12] and presence of satellite lesions[11-12] have been described as prognostic factors in liver metastases. However, these factors have not always functioned as prognostic determinants. In fact, surgeons who apply the same operative procedure to patients with similar known prognostic factors sometimes find their patients' outcomes to be divergent.

In 1989, Steele and Ravikumar[20] wrote that key future goals will be to predict the biologic behavior of colorectal carcinomas with precision and to predict which regional

Table 3. MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS

Variable	Hazard Ratio	95% Confidence Limits		p Value
		Lower	Upper	
Macroscopic type	2.274	1.120	4.616	0.0230
Maximum diameter	4.250	2.025	8.919	0.0001
Lymph node metastasis	4.257	1.734	10.454	0.0016
Vessel infiltration	0.765	0.335	1.750	0.5261
Satellite	0.572	0.161	2.037	0.3889
Direct invasion	0.466	0.177	1.228	0.1224

metastases do not represent early markers of widespread systemic recurrence. One of the answers is that the current macroscopic classification of liver metastases (Yasui's classification) can predict their biologic behavior. This classification parallels the degree of invasiveness, such invasive factors being detected in 59.5% of CN lesions and only 17.9% of SN lesions. All the invasive factors, including vessel infiltration, lymph node metastasis, and direct invasion to the adjacent viscera, were more frequently found in the CN group. In particular, the incidence of vessel infiltration was higher in the CN group (45.2%) compared to the SN group (10.3%). Invasive and progressive characteristics of the metastatic lesions are thus reflected well in this novel classification of macroscopic type. The incidence of recurrence after hepatectomy is strongly linked to the macroscopic type: recurrence was seen in as many as 78.6% of CN lesions, as opposed to 56.4% of SN lesions. This was particularly true for recurrences to the remnant liver (51.5% *versus* 28.6%, respectively). The classification of macroscopic type, shown to be statistically valid as an independent risk factor by multivariate analysis, thus also reflects biologic behavior of the metastatic lesions.

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