Analysis of Preoperative Prognostic Factors for Long-term Survival After Hepatic Resection of Liver Metastasis of Colorectal Carcinoma

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Hepatic resection is the most effective therapy for liver metastasis of colorectal carcinoma. To clarify indications for this therapy, the clinicopathologic and follow-up data of 103 consecutive patients who underwent hepatic resection for metastases of colorectal carcinoma were analyzed. Factors influencing overall survival rate were investigated by multivariate analysis. Thereafter, patients who underwent resection were stratified according to the number of independent risk factors present, and their outcomes were compared with those of 14 nonresection patients with fewer than six liver tumors and without extrahepatic metastasis. The overall survival rate of the 103 resection patients was 43.1%. The clinicopathologic factors shown to affect on long-term survival after hepatic resection were the interval between colorectal and hepatic surgery (<12 months), preoperative carcinoembryonic antigen level (≥10 ng/ml), and number of hepatic metastases (four or more). The 5-year overall survival rates were 75.0% with no risk factors (n = 16), 53.6% with one risk factor (n = 46), 23.0% with two risk factors (n = 36), and 0% with three risk factors (n = 5). Survival rates did not differ between resection patients with three risk factors and nonresection patients. Therefore, hepatic resection may be appropriate for patients with fewer than three risk factors. (J Gastrointest Surg 2005;9:374–380) © 2005 The Society for Surgery of the Alimentary Tract

KEY WORDS: Colorectal carcinoma, liver metastasis, hepatic resection, risk factor, prognosis

The incidence of colorectal carcinoma has increased worldwide, and synchronous or metachronous liver metastasis occurs in about 30% of cases. Hepatic resection is considered the most effective therapy for metastasis of colorectal carcinoma to the liver, and the overall survival rate after hepatic resection is reported as 26%–51%. ^{1–10} Several clinicopathologic factors predictive of patient survival after hepatic resection have been identified: status of the primary colorectal carcinoma (tumor stage and grade), ^{1,2,4,6,8,9} interval between colorectal and hepatic surgery, ^{1,2,4,5,9} number of hepatic metastases, ^{1,3–9} distribution of hepatic tumors, ^{3,7} size of the liver tumor, ^{3,4,5} preoperative serum carcinoembryonic antigen (CEA) level, ¹⁰ and nodal metastasis in the hepatic hilum. ^{1,3,8} Most investigators agree that the interval between colorectal and hepatic surgery, number of hepatic tumors, and status of the primary colorectal cancer are the most important predictors of long-term survival.

Several investigators have proposed staging of colorectal liver metastasis; stages would predict postoperative survival of patients.^{3,4,9,11} Fortner et al.¹¹ listed the risk factors as invasion of a major intrahepatic vessel or bile duct, distribution of the hepatic tumors, invasion of perihepatic organs, and distant metastasis including nodal metastasis. Gayowski et al.³ listed factors such as the number of metastatic tumors (solitary versus multiple), size of metastasis (larger or smaller than 2 cm in diameter), location of the liver tumor (one or both lobes), major vessel invasion, and extrahepatic metastasis. Ueno et al.⁹ proposed a preoperative staging system based on the primary tumor features (degree of tumor budding and nodal status), time to the diagnosis of liver metastases, and number of liver tumors. Unfortunately, all three of these staging systems include many factors and are too complex for preoperative use. The search continues

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for a simple preoperative staging system for liver metastasis of colorectal carcinoma.

The prognosis of patients with colorectal liver metastasis who undergo nonsurgical treatment or who do not undergo treatment remains very poor, despite advances in chemotherapy. 12-15 The median survival time of patients who receive nonsurgical treatment is reportedly less than 20 months. ^{12–15} In a randomized controlled study of the outcomes of patients who underwent various treatments for multiple (<15) resectable colorectal liver metastases, Wagman et al.¹⁴ observed no significant difference between resection and nonresection patients. Their results and results of other investigations into risk factors have led to the notion that careful selection of patients for hepatic resection of metastases from colorectal cancer is necessary to improve long-term survival, but the indications for hepatic resection for liver metastasis of colorectal cancer have not been well established. Absolute contraindications for resection of liver metastases from colorectal carcinoma have not been clearly defined, but most investigators agree that patients should not be offered hepatic resection if they have uncontrolled primary disease or such widespread hepatic involvement that residual liver function after resection would be inadequate. 16 Aggressive surgical management of multiple colorectal liver metastases has reportedly improved survival of selected patients. 17,18

In the present study, we attempted to clarify the preoperative risk factors affecting long-term survival after hepatic resection for colorectal liver metastasis and to propose a staging system for predicting long-term postoperative results. In addition, to clarify the indications for resection in cases of liver metastasis of colorectal carcinoma, we compared the long-term survival of resection patients stratified by risk factors with that of nonresection patients.

MATERIAL AND METHODS

During the period of January 1985 through December 2003, 125 patients with liver metastases from colorectal cancer underwent hepatic resection at the Department of Surgery I, Oita University Faculty of Medicine. Twenty-two patients were excluded from the study: three (2.4%) who died of postoperative complications within 30 days, two who had obvious residual tumor at the time of surgery, seven who underwent hepatic resection and thermal ablation therapy for residual hepatic tumors, seven who had extrahepatic metastasis before or at the time of hepatic resection, one who was lost to follow-up, and two for whom clinicopathologic data were unclear. All 103 patients were regularly followed at our outpatient

clinic and monitored for recurrence by assessment of serum tumor markers every 2 months and by ultrasonography or contrast-enhanced computed tomography scanning every 4 to 6 months.

We investigated 10 clinicopathologic variables pertaining to patient characteristics, clinical data, and histopathologic findings such as gender, age, interval between colorectal and hepatic resection, number of hepatic metastases, tumor diameter, preoperative CEA level, site of primary tumor, Dukes classification, tumor differentiation of primary tumor, and extent of surgical resection (Table 1). The extent of surgical resection was defined according to Couinaud's classification system; minor hepatic resection as resection of less than two segments and major hepatic resection as resection of two or more segments. Patient outcomes were determined on the basis of clinical data obtained from files as of January 31, 2004. Thus, the mean and median followup periods of the 103 patients after hepatic resection were 37.8 and 24.0 months, respectively (range, 1–226 months). The prognostic significance of clinicopathologic factors in relation to cancer-related overall survival rates was investigated by univariate and multivariate analyses. Data were censored in the analysis of overall survival if a patient was living or had died of unrelated disease and in the analysis of disease-free survival if a patient was living or had died of unrelated disease without recurrent colorectal carcinoma. Survival rates were calculated by the Kaplan-Meier method and compared statistically by univariate log-rank analysis. Variables with a value of P < 0.1 in univariate analysis were used in subsequent multivariate analysis based on Cox's proportional hazards model.

During the same period, 27 patients with colorectal liver metastasis and no extrahepatic metastasis received nonsurgical treatment at our hospital. Fourteen of these patients who had fewer than seven liver metastases were compared on the basis of clinicopathologic factors and outcome after admission with the 103 resection patients stratified by the number of risk factors. In the comparisons of clinicopathologic factors and treatment methods, continuous variables were analyzed by Kruskal-Wallis test, and nominal variables were analyzed by Fisher's exact probability test. A value of P < 0.05 was considered significant in all analyses. Statistical analysis was performed with JMP software (JMP, SAS Institute Inc., Cary, NC).

RESULTS Patient Characteristics

The 103 patients who underwent hepatic resection with a curative intent included 56 men and 47

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