Computed Tomographic Findings of Colorectal Liver Metastases Can Be Predictive for Recurrence After Hepatic Resection

Junzo Yamaguchi, MD; Ichiro Sakamoto, MD; Toshio Fukuda, MD; Hikaru Fujioka, MD; Kou Komuta, MD; Takashi Kanematsu, MD

Background: We recently reported that the pathologic mode of infiltrative growth (infiltrative [INF]-α, INF-β, and INF-γ) of colorectal liver metastases had characteristic morphologic findings, and furthermore showed that the INF type was a prognostic factor for disease-free survival after hepatic resection.

Hypothesis: Preoperative computed tomographic (CT) findings of the liver nodules may be predictive for pathologic tumor growth pattern.

Design: Retrospective study.

Setting: Departments of Surgery and Radiology at a university hospital in Japan.

Patients: A total of 25 CT examinations (1985-1998) were reviewed, and a comparison was conducted on CT findings of 2 groups with INF-α or INF-β (hereafter noted as INF-α-β) (n=9 [ie, a patient with INF-α plus 8 with INF-β]) and INF-γ (n=16) type liver metastases.

Main Outcome Measures: χ² Analysis of CT morphologic features was performed between the study groups. The result of multivariate analysis was obtained using the Cox proportional hazards model.

Results: The morphologic features observed by CT showed a significant difference between the 2 groups (INF-α-β, and INF-γ types) in the ratio of length to breadth of nodules (<1.5 vs ≥1.5, P=.008) and in the outline of nodules (regular vs irregular, P=.01). Of these CT imaging features, the outline of the nodule was an independent prognostic factor (P=.02).

Conclusion: Computed tomographic findings of colorectal liver lesions correlated with the pathologic tumor growth pattern and a prognosis.

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Many studies reported that hepatic resection of metastatic colorectal cancer was the best hope for prolonged survival, and many prognostic factors were shown. We classified the mode of infiltrative (INF) growth of colorectal liver metastases into 3 pathologic types (INF-α, INF-β, and INF-γ) and reported that the tumor growth pattern was a prognostic factor and a predictor of recurrence to the remnant of the liver after hepatic surgery. Briefly, in analysis of patients with liver metastases smaller than 6 cm or fewer than 4 nodules, 5-year disease-free survival rates were 64% and 14% in patients with INF-α or INF-β (hereafter, INF-α-β), and INF-γ type liver metastases, respectively, and recurrent liver disease after hepatic resection was found in 14% and 79% in the 2 groups, respectively. However, most prognostic factors including the INF type have been identified after surgery. Only a few factors preoperatively, that is, the size, number, and distribution of liver lesions, have been evaluated by imaging modalities and have been used both to plan effective surgery and to predict prognosis. However, it is our experience that these preoperative factors are insufficient to predict the prognosis in patients with metastatic liver tumors from colorectal cancer. The accurate preoperative assessment of tumor biology can contribute importantly to the therapeutic options including chemotherapy and to the prediction of prognosis. The present study was a retrospective analysis conducted to determine whether the pathologic growth pattern of liver metastases can be evaluated on the basis of computed tomographic (CT) imaging features.

METHODS

STUDY POPULATION

From January 1, 1981, through December 31, 1998, 42 curative hepatic resections were performed for 37 patients with isolated liver me-
tastases caused by colorectal cancer. In this study, a retrospective analysis was conducted on 25 of the 28 patients who underwent CT scanning (1985-1998). Four of the 25 patients were cases of recurrent liver disease after hepatic resection.

**CT PROTOCOLS**

Computed tomographic scanning including the acquisition of CT contrast-enhanced images, and nonenhanced images were performed in all 25 patients. Helical CT was performed in 11 patients and included nonenhanced, arterial-dominant-phase and portal-dominant-phase images through the liver. The arterial-dominant and portal-dominant phases were obtained with delays of 23 to 30 seconds and 60 to 70 seconds, respectively, after initiation of an intravenous bolus injection of contrast material. The remaining 14 patients who underwent conventional (nonhelical) CT had postcontrast scans with a delay of 60 to 70 seconds (portal-dominant phase) and nonenhanced scans. Section thickness was 5 to 7 mm for conventional and helical images. On average, patients received 100 mL of 60% iodinated contrast medium at both helical and conventional CT. For conventional CT, the contrast agent was intravenously administered at a rate of 1.5 to 2.5 mL/s; for helical multiphasic examinations, the rate was 2.0 to 3.0 mL/s, administered using a power injector. Helical CT studies were performed using the single-detector CT system (model Somatom Plus 4; Siemens Medical Systems, Erlangen, Germany) and conventional studies were performed with a CT scanner (model 9800; GE Medical Systems, Milwaukee, Wis).

**CT IMAGE ANALYSIS**

The portal-dominant phase was used to evaluate CT morphologic features of metastatic liver nodules. With regard to the ratio of length to breadth of the liver nodules, the median ratio was 1.5 (range, 1.0-2.0). Then the ratio was divided into smaller than 1.5 and larger than or equal to 1.5. The latter (≥1.5) included pear-shaped, kidney-shaped, or gourdlike masses. The outline of liver nodules was classified into regular and irregular contour. Size (maximum diameter) of metastases evaluated by CT was divided into smaller than 4 cm and larger than or equal to 4 cm. When multiple nodules existed in a patient, the nodule providing the best information on CT was evaluated. That is, the tumor size was not necessarily the largest liver metastasis seen in a patient. In addition, the boundary of nodules with adjacent liver tissues was classified into well defined and ill defined. These findings were independently evaluated by 2 radiologists (I.S. and T.F.) who did not have information on the outcome of the disease in these patients.

**MODE OF INF GROWTH OF LIVER METASTASES**

As previously described,7 microscopic findings of liver metastases were classified into INF-α, INF-β, and INF-γ. Briefly, as shown in the scheme (Figure 1), metastatic lesions with expansive growth but a sharp boundary with adjacent tissues were classified as INF-α type. Lesions with invasive growth and no boundary with adjacent tissues were classified as INF-γ type; the intermediate type between INF-α and INF-γ was classified as INF-β type.

**STATISTICAL ANALYSIS**

The x² analysis with Yates correction was used to test the differences between the 2 study groups. The tumor-free survival rates were calculated according to the Kaplan-Meier methods. Mean values (estimated values) of tumor-free survival time and the SD were calculated using STAT View 5 software (SAS Institute, Cary, NC). The result of multivariate analysis was obtained using the Cox proportional hazards model of prognostic factors for tumor-free survival. P<.05 were considered as statistically significant.

**RESULTS**

**CHARACTERISTICS OF PATIENTS WITH INF-α-β AND INF-γ TYPE LIVER METASTASES**

The groups with INF-α-β and INF-γ type liver metastases consisted of 9 and 16 patients, respectively. As given in Table 1, there was no difference in the clinical factors of time of diagnosis, number of metastases, diameter of the largest liver metastasis, and distribution between the 2 groups.
CT MORPHOLOGIC FEATURES IN PATIENTS WITH INF-α-β AND INF-γ TYPE LIVER METASTASES

Helical CT and nonhelical CT were performed in 4 and 5 patients, respectively, with INF-α-β type liver metastases and in 7 and 9 patients, respectively, with INF-γ type liver metastases. As given in Table 2 with regard to the ratio of length to breadth of nodules, 8 (89%) of 9 patients with INF-α-β type liver metastases had less than 1.5 nodules (Figure 2A) and 12 (75%) of 16 patients with INF-γ type had 1.5 or greater (Figure 2B) (P = .007). With regard to the outline of nodules, 7 patients (78%) with INF-α-β had regular contour nodules (Figure 2C),
and 13 patients (81%) with INF-γ had irregular contour (Figure 2D) \((P = .01)\). However, there was no significant difference in either size of metastases \((P = .07)\) or boundary with adjacent liver tissues \((P = .07)\) between the 2 groups. Figure 2E and F showed the boundary of nodules to be well defined and ill defined, respectively.

**CT FINDINGS AND DISEASE-FREE SURVIVAL AFTER HEPATIC RESECTION**

We then investigated whether CT features were prognostic. For patients with less than 1.5 \((n = 12)\) and those with 1.5 or more \((n = 13)\) liver metastases, the 5-year disease-free survival rate was 33% and 0%, respectively (estimated disease-free survival time \(\text{[SD]}\), 18.7 \([4.4]\) and 10.6 \([2.1]\) months, respectively) \((P = .04)\). For patients with regular \((n = 10)\) and irregular \((n = 15)\) contour liver metastases, the 5-year disease-free survival rate was 40% and 0%, respectively (estimated disease-free survival time \(\text{[SD]}\), 22.3 \([4.6]\) and 9.1 \([1.8]\) months, respectively) \((P = .02)\). However, multivariate analysis of 4 factors (ie, the ratio, outline, size, and boundary) showed that only the outline of nodules was statistically significant as an independent prognostic factor (hazard rate, 11.64; 95% confidence interval, 1.512-89.584; \(P = .02)\).

**COMMENT**

After hepatic resection of colorectal cancer liver metastases, 70% to 80% of patients experience a recurrent disease.\(^{12-14}\) Liver disease recurrence is frequently observed.\(^{15-17}\) However, it was not always easy to identify the high-risk patients preoperatively. The ability to do so would have great practical importance. Numerous technical advances have occurred in cross-sectional imaging techniques for evaluating hepatic malignancies. Preoperative hepatic imaging for patients with colorectal liver lesions also allows the collection of clinical information, such as the presence of lesions, precise distribution, resectability, and, to some extent, prognosis.\(^{8,10}\) Computed tomographic portography and/or liver magnetic resonance imaging must be performed in all patients prior to surgery.\(^8\) In the current study, we assessed the relation between the pathologic tumor growth pattern of liver metastases and the morphologic features seen on CT portography. Two groups (INF-α-β type and INF-γ type) had a characteristic morphology in the ratio of length to breadth of nodules and the finding of outlines of these nodules. The finding of outline of nodules was especially close correlated with the patient’s survival, despite a limited number of patients. These findings, therefore, provide evidence that the morphologic features seen on CT indicate the biological behavior of metastatic liver tumors from colorectal cancer.

We previously showed that simple nodular and confluent nodular-type liver metastases, the macroscopic classification reported to be a prognostic factor,\(^1\) were observed in 64% and 36% of patients with INF-α-β type liver metastases \((n = 14)\), respectively, and in 21% and 79% of patients with INF-γ type liver metastases \((n = 14)\), respectively.\(^7\) These observations might be reflected in differences of CT imaging features between the 2 groups in this study.

**CONCLUSIONS**

Pathologic tumor growth pattern of colorectal liver metastases seems to be elucidated by CT imaging features in most patients. The morphologic features might serve to provide information for treatment and also for survival.

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Corresponding author and reprints: Junzo Yamaguchi, MD, Department of Surgery, National Saga Hospital, 1-20-1 Hinode, Saga 849-0923, Japan (e-mail: junzo@crocus.ocn.ne.jp).

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