Proposal of a new and simple staging system of colorectal liver metastasis

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AIM: To create a new, simple and useful staging system for colorectal liver metastasis analogous to the Tumor Node Metastasis classification system of International Union Against Cancer.

METHODS: A retrospective review was undertaken of 81 consecutive patients who underwent partial hepatectomy for colorectal liver metastases (group 1). Clinical and pathological features of both primary and metastatic liver cancers were entered into a multivariate analysis to determine independent variables helpful in accurately predicting long-term prognosis after hepatectomy. Using selected variables, we created a new staging system like TNM classification. The usefulness of the new staging system was examined in a series of 92 patients from another hospital (group 2).

RESULTS: Multivariate analysis showed that 81 patients in group 1 had significant multiple hepatic tumors with the largest tumor being more than 5 cm in diameter, resectable extrahepatic distant metastases, and independent prognostic factors for poor survival after hepatectomy. Using these three variables, we created a new staging system to classify patients with colorectal liver metastases. Finally, our new staging system classified the patients both in group 1 and in group 2.

CONCLUSION: Our new staging system of colorectal liver metastasis is simple and useful for staging patients.

INTRODUCTION

It is well accepted that hepatic resection of colorectal liver metastases is a beneficial clinical procedure in that it reportedly improves 5-year survival rates of affected patients by as high as 30%-50% following curative hepatic resection[1-14]. Although this procedure is performed worldwide by a number of liver surgeons, it is often hazardous to compare results from different studies due to the fact that there is no universally accepted classification system for staging colorectal hepatic metastatic diseases. Several recent papers have offered classification systems based on a variety of variables of colorectal liver metastasis[1,4], including the number of metastatic nodules[1,4,4-6], the size of metastases[6,6], the sites of unilateral or bilobar involvement[6,6], the extent of liver involvement (≤ 25%, and ≤ 50%)[1,3], the chronology of synchronous or metachronous disease[1,5,4], the invasion to major vessels or bile ducts[6], the presence of extrahepatic metastasis[3-4], the performance status and serum alkaline phosphatase[8].

However, it is uncertain whether these classification systems are accepted and adopted outside the confines of proposing institutions. In the present study, we aimed to create a new, simple and useful classification system for colorectal liver metastases analogous to the Tumor Node Metastasis (TNM) classification system of International Union Against Cancer (UICC).

MATERIALS AND METHODS

Patients

Group 1: Between January 1, 1981 and March 31, 1997, 83 consecutive patients underwent partial hepatectomy for colorectal liver metastases at the First Department of Surgery (presently the Department of Surgical Oncology), Tokyo University Hospital. During the post-operative period, two patients died in the hospital. One died of secondary aspiration pneumonia and the other died of severe intra-abdominal sepsis (mortality rate: 3.1%). The remaining 81 patients were followed up either until death or their last outpatient visit up to December 31, 2002. The follow-up period ranged from 4 to 197 mo with a median of 53.0 mo. The demographic characteristics and tumor-
related features, which were statistically analyzed later, are summarized in Table 1.

**Group 2:** Between January 1, 1989 and December 31, 2003, 95 consecutive patients underwent partial hepatectomy for colorectal liver metastases at the Second Department of Surgery, Teikyo University Hospital. During the post-operative period, three patients died in the hospital. Two died of hepatic failure due to massive hepatectomy and the other died of severe intra-abdominal sepsis (mortality rate: 3.2%). The remaining 92 patients were followed up either until death or their last outpatient visit up to December 31, 2004. The follow-up period ranged from 4 to 110 mo with a median of 39.0 mo.

Every hepatectomy was considered curative since surgeons were confident of the complete macroscopic resection of hepatic tumors at the time of surgery. Hepatectomy was performed even in the presence of extrahepatic metastases if surgeons were reasonably assured of the complete macroscopic resection of extrahepatic metastases as well. After discharge from the hospital, the patients were closely monitored either at the outpatient clinic or at the affiliated institutions. Measurement of serum carcinoembryonic antigen (CEA) levels and ultrasonography were performed during post-operative visits at least once every two months in an effort to detect early recurrence. In addition, computed tomography was performed approximately twice a year. Almost all cases of cancer recurrence were diagnosed by these investigative tests. If the diagnosis was unclear, angiography and/or needle biopsy was performed, under ultrasonic guidance in an effort to confirm or rule out recurrence of the disease.

**Prognostic factors**

Eleven factors that were expected to influence the long-term prognosis were evaluated for statistical significance. These factors could only be determined preoperatively or during surgery (therapeutic factors were excluded and not considered). Factors that were considered included gender, age at hepatectomy (< 60 or ≥ 60 years), chronicity of synchronous or metachronous hepatic metastases, and post-operative disease-free interval ≤ 1 year, the number of solitary or multiple metastatic nodule hepatic metastases, the maximum diameter of hepatic metastases (≤ 5 cm), unilobar or bilobar hepatic involvement, resectable extrahepatic metastasis (pulmonary metastases, localized peritoneal metastases, or hepatoduodenal lymph node metastases, each was completely resected), serum CEA levels at hepatectomy (less or higher than 10 times the upper level of normal), serosal exposure to the primary colorectal tumor, and regional lymph node metastases of the primary colorectal tumor.

**Statistical analysis**

Survival rates after hepatectomy were calculated using data obtained from patients by the Kaplan-Meier method. Only deaths attributable to recurrent cancer were treated as deaths due to disease. Patients who died of secondary or other causes without recurrence were treated as censored.

Prognostic variables concerned with cancer-related survival rate were entered into multivariate analysis. The Cox stepwise analysis proportional hazard regression model was used to select independent and significant prognostic variables. Stepwise variable selection was performed at a value of P < 0.20 level of significance. P < 0.05 was considered statistically significant.

**RESULTS**

**Group 1**

Significant prognostic factors: The overall 1-, 2-, 3-, and 5-year cancer-related survival rates after surgical resection in the 81 patients were 89.6%, 67.7%, 56.0%, 54.2%, and 49.6%, respectively (Figure 1A). The results of the multivariate analysis of the variables expected to influence cancer-related survival rate after surgical resection are provided in Table 1. Only variables selected by the stepwise analysis at a value of P < 0.20 level of significance, using the Cox proportional hazard regression model, are also shown in Table 2. Multiple tumors, tumor over 5 cm in diameter, and resectable extrahepatic metastases were significant and independent variables influenced cancer-related survival rate (P < 0.05). On the other hand, serosal exposure and regional lymph node metastases of the primary colorectal tumor, and recurrent hepatic metastases within one year after resection of the primary colorectal cancer including synchronous hepatic metastases, were the factors selected by stepwise analysis as the possible indication of poor prognosis, but they were not statistically significant (P > 0.05 or P < 0.20).

Classification of patients and survival: In devising our classification system, we considered three variables selected by the multivariate analysis, including the number and size of hepatic metastases (H-factor), and the presence of extrahepatic metastases (M-factor), which were resected completely. Results were shown as follows: H1: single metastasis with diameter ≤ 5 cm; H2: single metastasis with diameter > 5 cm or multiple metastases with diameter ≤ 5 cm; H3: multiple metastases with diameter > 5 cm; M0: extrahepatic metastasis (−); M1: extrahepatic metastasis (+, resectable). Staging system (A): stage I: H1 and M0; stage II: H2 and M0; stage III: H3 and M0; stage IV: H1-3 and M1; staging system (B): stage I: H1&M0; stage II: H1 and M1 or H2 and M0; stage III: H2 and M1 or H3 and M0; stage IV: H3 and M1.

**Table 1** Prognostic factors entered into multivariate analysis based on proposed clinical and histopathological features

| Variable                          | Patients (n) |
|----------------------------------|--------------|
| Gender (male/female)             | 61/20        |
| Age at hepatectomy (< 60/≥ 60)   | 32/49        |
| Chronology of hepatic metastasis (synchronous/metachronous) | 41/40 |
| Disease free interval after colectomy (< 1 yr/≥ 1 yr) | 56/25 |
| Extrahepatic distant metastases (no/yes) | 72/9 |
| CEA (< 10 times of normal value/≥ 10 times of normal value) | 57/24 |
| Primary lesion                   |              |
| Depth of invasion (up to subserosa/more) | 57/24 |
| Lymphnodemetastasis (no/yes)     | 39/42        |
| Hepatic metastasis               |              |
| Number (single/multiple)         | 45/36        |
| Maximum diameter (≤ 5 cm/ > 5 cm) | 59/22        |
| Lobe involved (unilobar/bilobar)  | 64/17        |
The survival curves of patients in group 1 based on the staging system (A) are shown in Figure 1B. They were statistically significant (P = 0.0057). However, the survival curve of patients with stage IV cancer seemed to be better than that of those with stage III cancer. The 5-year survival rates of patients with cancer in stage I (n = 26), stage II (n = 38), stage III (n = 8), and stage IV (n = 9) were 74.8%, 49.2%, 15.6%, and 25.0%, respectively. Their median survival time was 52, 18, and 10 mo, respectively, with that unsettled in stage I patients.

**Staging system (B):** The survival curves of patients in group 1 based on the staging system (B) are shown in Figure 2B. They were statistically significant (P = 0.0003). The 5-year survival rates of patients with cancer in stage I (n = 26), stage II (n = 43), and stage III (n = 12) were 74.8%, 49.8%, and 9.5%, respectively. Their median survival time was 52, 52, and 18 mo, respectively. By coincidence, there were no patients with stage IV disease in this group.

**Group 2**

The overall 1-, 2-, 3-, 4-, and 5-year cancer-related survival rates after surgical resection in the 92 patients were 82.2%, 65.2%, 51.6%, 42.5%, and 40.0%, respectively (Figure 2A). The survival curve of patients with stage IV cancer seemed to be better than that of those with stage III cancer. The 5-year survival rates of patients with cancer in stage I (n = 24), stage II (n = 44), stage III (n = 8), and stage IV (n = 15) were 75.0%, 44.5%, 0%, and 0%, respectively. Their median survival time was 46, 13.5, and 20 mo, respectively, with that unsettled in stage I patients.

**Staging system (B):** The survival curves of 92 patients in group 2 based on the staging system (B) are shown in Figure 2C, and findings were statistically significant (P < 0.0001). The survival curve of patients with stage IV cancer seemed to be better than that of those with stage III cancer. The 5-year survival rates of patients with cancer in stage I (n = 24), stage II (n = 48), stage III (n = 16), and stage IV (n = 3) were 75.0%, 43.0%, 0%, and 0%, respectively. Their median survival time was 41, 12, and 10 mo, respectively, with that unsettled in stage I patients.

**DISCUSSION**

At present, there is no universally accepted classification system for patients with colorectal liver metastasis. Our first step in this investigation was to determine the important clinical and pathological variables that significantly influence prognosis following surgical resection of colorectal liver metastases. Many studies have identified factors which are thought to represent important prognostic determinants, including age at hepatectomy[6,7], sex[23], stage of the primary tumor[24,5,7,11,15-20,22,23,28,29], extrahepatic metastases[22-28], and adjuvant chemotherapy[12,32,33]. Therapeutic factors, such as adjuvant chemotherapy[12,32,33]...

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**Table 2 Regression statistics for the stepwise cox proportional hazard model**

| Variable | Parameter | P | Hazard Ratio (95% CI) |
|----------|-----------|---|----------------------|
| Diameter > 5 cm | 1.36675 | 0.0113 | 3.883 (1.703-8.852) |
| Extrahep. Met (+) | 1.19463 | 0.0331 | 3.301 (1.282-8.502) |
| Number ≥ 2 | 0.85412 | 0.0265 | 2.349 (1.105-4.997) |
| D.F.Interval < 1 yr | 0.67938 | 0.1602 | 1.971 (0.765-5.080) |
| n (+) of primary | 0.66934 | 0.1352 | 1.312 (0.829-2.007) |
| ≥ se (+) of primary | 0.54977 | 0.1676 | 1.791 (0.794-3.774) |

1Only those variables selected by the stepwise analysis, at the P-value of 0.20 level of significance, are shown. n = 81 (Tokyo Univ. 1981-1997). Age ≥ 60, gender, synchronous, bilobar invasion, CEA, P > 0.2.

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**Figure 1** Kaplan-Meier cancer-related survival curve after hepatic resection for patients with colorectal liver metastases in group 1. A: Staging system (A) (log-rank test, P = 0.0057); B: staging system (B); C: stage I through stage III (log-rank test, P = 0.0003).
The long-term outcome after hepatectomy. We hope that it can promote a prospective study on the efficacy of some other therapies such as adjuvant chemotherapy. Although the present study population sample is small, our staging system is simpler and more useful than any other previous classification systems. Further investigation utilizing a larger patient population is necessary.

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