Indicators for Treatment Strategies of Colorectal Liver Metastases

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Objective
To analyze the survival predictors of patients undergoing hepatectomy for colorectal liver metastasis to determine useful indicators for therapy selection.

Summary Background Data
Although recurrence develops in more than two thirds of patients undergoing hepatectomy for colorectal liver metastasis, preoperative characteristics that might predict such recurrence have yet to be clearly identified.

Methods
Clinicopathologic data of 85 consecutive patients with colorectal cancer who underwent a curative resection of primary lesions and metastatic liver diseases at one institute were analyzed using the multivariate method with respect to both the metastatic state and the primary lesion.

Results
Multivariate analysis indicated that the aggressiveness of the primary tumor, early liver metastasis, and a large number of liver metastases were the characteristics that could be detected before hepatectomy and that independently indicated a worse survival. A three-ranked classification based on these coefficients (H-staging) was significantly related to both the recurrence rate within 6 months (7% in H-stage A, 30% in B, and 44% in C) and the 5-year survival rates (55%, 14%, and 0% respectively). An additional scoring system (H'-staging) based on the aggressiveness of the primary tumor and the level of carcinoembryonic antigen 1 to 3 months after hepatectomy was found to be related to the mode of subsequent recurrence and surgical resectability of the recurrent foci.

Conclusions
H-staging can provide useful prognostic information for the treatment of liver metastasis. H'-staging could also help in predicting the possible mode of recurrence after hepatectomy and in determining the most suitable mode of additional therapy. Further multiinstitutional studies based on a large collective database will confirm the utility of these two staging systems.

Hepatic resection is at present the treatment of choice for patients with colorectal metastases because it offers a reasonable chance of long-term survival. Nevertheless, because recurrence develops in many patients in a short period after hepatectomy, an improved set of indicators for surgical treatment is needed. Numerous investigators have reported the significance of several prognostic parameters, including liver-related characteristics (number,2,3 distribution,4 tumor diameter,5,6 macroscopic type,7 and satellite metastases3), the time to liver metastasis,1 the existence of extrahepatic disease,8 the extent of liver resection,1,3–6 age,5 level of carcinoembryonic antigen (CEA),3,5 and stage of the primary tumor.5 To date, however, few reliable selection criteria have been established with regard to treatment policies based on these variables.5

To assess the prognostic indicators, we reviewed a consecutive series of our patients with colorectal cancer and associated liver metastases. We examined several parameters and their relation to the prognostic outcome to determine whether any of these factors might be predictors of poor outcome and therefore useful in assessing the need for surgical resection and in determining the appropriate postoperative follow-up system. We addressed the factors associated with metastatic lesions and also the primary tumor characteristics.
PATIENTS AND METHODS

Among the patients who underwent a curative resection of primary colorectal cancer at the First Department of Surgery of the National Defense Medical College Hospital between January 1985 and March 1996, 88 consecutive patients with liver metastases underwent either a synchronous or metachronous curative hepatic resection. Three patients died of postoperative complications or other disease within 3 months after the hepatectomy, and thus 85 were available for further prognostic evaluation.

The surgical procedures comprised 27 single limited resections, 8 multiple limited resections, 3 segmentectomies, 5 segmentectomies plus limited resections, 31 hemihepatectomies, 9 hemihepatectomies plus limited resections, 1 trisegmentectomy, and 1 trisegmentectomy plus a limited resection. Since 1989, intraarterial injection of 5-fluorouracil (5-FU) has been used at our institution as a postoperative preventive chemotherapy, and 37 patients (43.5%) received such treatment (average dose 6,341 mg; range 500–24,500 mg). The median follow-up period of the patients was 52 (range 13–118) months.

The baseline prognostic indicators consisted of 19 variables in five fields—patients, primary site, liver, time of diagnosis of liver metastases, and tumor marker. All characteristics are shown in Table 1. The extent of nodal involvement was subdivided into two categories: no nodal involvement or positive paracolic/pararectal lymph nodes in the limited segment close to the primary tumor (N_a), and more distant paracolic/pararectal lymph node involvement or positive upward spread along the named vascular trunk (N_b). The former category was consistent with N_0 and N_1, the latter with N_2 and N_3 in the Japanese Classification of Colorectal Carcinoma.9

Tumor budding is a pathologic finding just ahead of the tumor invasive front that refers to either microtubular cancer nests or microscopic clusters of undifferentiated cancer cells.10,11 It is divided into four grades: no, mild, moderate, and severe budding (Fig. 1).11 The intramural spread length was measured by pathologic examination of longitudinal formalin-fixed samples at both the proximal and distal sites of the tumor.

The posthepatectomy CEA serum value was measured 1 to 3 months after hepatectomy.

After transformation of the numeric variables into two categories, the survival was estimated using the Kaplan–Meier method and then was checked for statistical differences between various subgroups using the nonparametric linear Mantel-Cox (log-rank) test. The specific contribution of prognostic variables was examined by a multivariate Cox’s proportional hazards model. A stepwise procedure and likelihood ratio tests were used to select the variables for the final models.

RESULTS

Liver Resection

The disease-free rate 2 and 5 years after hepatectomy was 35.8% and 20.5%; the overall survival rate at 2 and 5 years was 64.7% and 27.9%, respectively. Twenty patients (23.5%) had recurrent disease within 6 months after hepatectomy.
tectomy, and they showed a significantly worse survival (Fig. 2). There were no survivors at 3 years among these 20 patients, whose median survival was 13 months, whereas the 5-year survival rate of patients who showed no signs of recurrence at 6 months after hepatectomy was 34.9%. Sixteen patients received intraarterial 5-FU infusion after hepatectomy of $>5$ g, and eight received such infusion after hepatectomy of $>10$ g. None of the groups receiving 5-FU had a significantly better survival than the corresponding groups receiving no or a reduced dose of 5-FU.

**Primary Tumor Characteristics**

The tumor depth, nodal state, tumor budding, and intramural spread all had a significant influence on survival based on a univariate analysis ($P = .0004-.0123$), whereas none of the other characteristics had a significant effect on survival (Table 2).

In the analysis by Cox’s regression model, marked tumor budding (moderate or severe) and extended nodal involvement ($N_{i}$) were found to worsen survival independently with almost an equal hazard ratio (Table 3). To represent the degree of primary tumor aggressiveness, a categorization based on these two findings was performed. Patients who had neither marked tumor budding nor extended nodal involvement were defined as a low-grade group; those with either or both of these unfavorable factors were classified as a high-grade group.
Establishment of Prognostic Staging Before Hepatectomy

The time to liver metastasis was significant at $P = .0074$. Long-term survival in metachronously (>1 year after primary surgery) detected metastases was superior to that of either synchronous metastasis or that within 1 year after primary surgery (see Table 2). The number of liver metastases was also selected as a significant prognostic indicator ($P = .0122$) (see Table 2). An elevated postoperative serum CEA level was associated with a less favorable crude survival, whereas the effect of the preoperative CEA level was not statistically significant (see Table 2).

Among the significant prognostic characteristics, the biologic aggressiveness of the primary site (degree of tumor budding and nodal involvement), the number of liver metastases, and the time to diagnosis were chosen as the factors that could be detected before hepatectomy. They were examined by a multivariate analysis using Cox’s proportional hazards model. These three variables were all estimated to be independent significant prognostic indicators (Table 4).

Based on the results of this multivariate analysis, we developed the H-staging prehepatectomy categorization system that classified patients into three stages according to the estimated prognosis after liver resection (Table 5). Survival curves of the patients classified by the proposed H-staging are shown in Figure 3. The 5-year survival rate of each group was stage A, 54.8%; stage B, 14.2%; and stage C, 0%. The median survival of stage C patients was 14 months.

### Table 2. Significant Prognostic Determinants Based on Univariate Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
<th>$P$ Value</th>
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<tbody>
<tr>
<td>Primary Site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor depth</td>
<td>Subserosa (n = 60)</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Serosa or invasion to other organs (n = 25)</td>
<td>1.985</td>
<td>1.160–3.397</td>
<td>.0123</td>
</tr>
<tr>
<td>Nodal state</td>
<td>$N_n$ (n = 61)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$N_p$ (n = 24)</td>
<td>2.545</td>
<td>1.447–4.484</td>
<td>.0012</td>
</tr>
<tr>
<td>Tumor budding</td>
<td>None or mild (n = 43)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate or severe (n = 42)</td>
<td>2.740</td>
<td>1.575–4.785</td>
<td>.0004</td>
</tr>
<tr>
<td>Intramural spread</td>
<td>≤5 mm (n = 52)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5 mm (n = 33)</td>
<td>2.169</td>
<td>1.258–3.745</td>
<td>.0053</td>
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<td>Liver</td>
<td>Number of metastases</td>
<td>1.2 (n = 69)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 or more (n = 16)</td>
<td>2.183</td>
<td>1.185–4.016</td>
<td>.0122</td>
</tr>
<tr>
<td>Time to Diagnosis of Liver Metastasis*</td>
<td>Latter term (n = 26)</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Early term (n = 59)</td>
<td>2.358</td>
<td>1.258–4.405</td>
<td>.0074</td>
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<tr>
<td>Tumor Marker (Post/hepatectomy CEA)</td>
<td>Within normal range (n = 69)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated level (n = 16)</td>
<td>3.707</td>
<td>2.025–6.786</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* Latter term, >1 year from primary operation; early term, synchronous or <1 year from primary operation.

### Table 3. Multivariate Analysis of Primary Site Variables by Cox’s Proportional Hazards Model

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Coefficient</th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor budding</td>
<td>0.734</td>
<td>2.084</td>
<td>1.079–4.025</td>
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<td>Nodal state</td>
<td>0.670</td>
<td>1.954</td>
<td>1.081–3.529</td>
<td>.0265</td>
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<td>Tumor depth</td>
<td>0.412</td>
<td>1.510</td>
<td>0.861–2.646</td>
<td>.1501</td>
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<tr>
<td>Intramural spread</td>
<td>0.226</td>
<td>1.254</td>
<td>0.660–2.382</td>
<td>.4892</td>
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</table>

### Table 4. Statistically Significant Indicators for Posthepatectomy Survival*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient</th>
<th>Hazard Ratio</th>
<th>95% Confidence Limits</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor feature</td>
<td>1.177</td>
<td>3.243</td>
<td>1.724–6.099</td>
<td>.0003</td>
</tr>
<tr>
<td>Time to diagnosis of liver metastases</td>
<td>0.724</td>
<td>2.063</td>
<td>1.075–3.958</td>
<td>.0294</td>
</tr>
<tr>
<td>Number of liver metastases</td>
<td>0.649</td>
<td>1.913</td>
<td>1.038–3.525</td>
<td>.0375</td>
</tr>
</tbody>
</table>

* Detectable before hepatectomy by stepwise regression analyses using Cox’s proportional hazards model.
† Primary tumor aggressiveness was classified into two types—high-grade, marked tumor budding and/or extended nodal involvement ($N_p$) were positive; low-grade, both were negative.
Wald $\chi^2 = 23.916$, Akaike’s Information Criteria = 405.420
Establishment of Prognostic Staging After Hepatectomy

A second multivariate analysis, which added the CEA levels at 1 to 3 months after hepatectomy to the three significant variables above, was performed using a stepwise regression model. The results showed that the primary site characteristics and CEA level after hepatectomy were significant prognostic determinants (Table 6). However, the number of metastases and the time to diagnosis failed to achieve statistical significance. Because the relative risks associated with each risk factor were comparable, a simple grading system was developed. A three-ranked staging (H-staging) was established based on the presence of these two significant risk factors: H-stage A, no factors; H-stage B, one factor; and H-stage C, two factors. The actual survival curves constructed for these three groups were distinct, with the 5-year survival rates decreasing from 63.6% for H-stage A to 11.0% for H-stage B and 0% for H-stage C (Fig. 4).

Prognostic Significance of Each Model

The disease-free survival curve in the H-stage A group was much better than that in the H-stage B and H-stage C groups (Fig. 5). The rate of further recurrences within 6 months was only 6.7% in H-stage A patients; it was 30.4% in H-stage B and 44.4% in H-stage C patients (Table 7). Disease-free intervals of the patients with recurrence were significantly shorter in H-stage B and C patients compared with H-stage A patients.

In addition to H-staging, H'-staging further subclassified patients according to their disease-free survival (Fig. 6). In patients with recurrence, the disease-free interval and survival after recurrence both tended to be longer in patients in H'-stage A (Table 8). The proportion of patients having remnant liver recurrence but no other extrahepatic recurrent foci was much higher in H'-stage A (71.4%) than in H'-stage B (26.1%) or H'-stage C (14.3%). Table 9 shows the rate of surgical resection for recurrent disease by H'-stag-
The surgical resectability of recurrent disease decreased according to the staging, in terms of recurrence not only in the remnant liver but also in the lung. Five H-stage A patients who received intraarterial chemotherapy of >10 g 5-FU are all currently surviving (except for one patient who died of another disease at 65 months after hepatectomy), whereas the 5-year survival rate of 24 patients without 5-FU infusion was 58.4%.

DISCUSSION

According to recent reports, the 5-year survival rate for patients with colorectal cancer after hepatectomy is 24% to 48%.1,2,4-6,8,12,13 In the present series, although 27.9% of the posthepatectomy patients survived >5 years and clearly benefited from surgery, there was a subset of resection candidates who did not benefit from surgery. The main purpose of this study was to provide criteria for excluding these patients before surgery.

The prognosis of patients who show recurrence within 6 months after hepatectomy is still disappointing; in this series, the median survival for such patients was only 13 months, and no patients survived for >3 years. An unfavorable H-staging was significantly related to a relapse within 6 months after hepatectomy—in fact, patients with H-stage C died within a surprisingly short period (median survival 14 months) even if the hepatectomy had been successfully performed. Wagner et al14 reported a median survival of 21 and 15 months in patients with an unrected single liver metastasis and with multiple unilobar lesions, respectively. Steele and Ravikumar15 reported a median survival of 24 months in asymptomatic patients with three or fewer unrected metastases and 10 months for those with four or more. Scheele et al16 reported a median survival of 14 months for patients with one to three unrected liver metastases, and Yamamura et al17 reported a median survival of 13 and 12 months for patients with unrected metastases in one lobe and fewer than four metastases in both lobes, respectively.

Based on the results of these retrospective reports on the survival of patients with unrected disease, we recommend that patients with H-stage C undergo less invasive therapy first and that surgical indications are reevaluated afterward (i.e., 6 months later). However, surgical intervention should not be delayed for patients with a favorable H-staging.

In terms of the need for additional therapy after liver resection, the possibility of recurrence and the potential recurrence sites should be reevaluated after surgery. Our results regarding the CEA level at 1 to 3 months after hepatectomy correlated with Hohenberger et al’s18 findings, in which elevated posthepatectomy CEA levels were considered to indicate that tumor had been left behind after surgery. The H’-staging described here, which subdivides patients according to the biologic characteristics of the primary tumor and the posthepatectomy CEA value, can thus supply more accurate information regarding the prognosis. Patients who had no risk factors (H’-stage A patients) had a significantly lower recurrence rate and a superior survival than H’-stage B or C patients. In patients with recurrence, both the disease-free interval and the survival after recurrence were longer in H’-stage A patients than in H’-stage B or C patients.

Of the patients with remnant liver recurrence, the propor-

<table>
<thead>
<tr>
<th>H-Stage</th>
<th>Recurrence Within 6 Months After Hepatectomy</th>
<th>Disease-Free Interval in Patients with Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 30)</td>
<td>2/30 (6.7%)*</td>
<td>708.3days†</td>
</tr>
<tr>
<td>B (n = 46)</td>
<td>14/46 (30.4%)</td>
<td>358.2days</td>
</tr>
<tr>
<td>C (n = 9)</td>
<td>5/9 (44.4%)</td>
<td>327.4days</td>
</tr>
</tbody>
</table>

* Comparison among three groups: P = .0170. † H-stage A vs. B: P < .0001, H-stage A vs. C: P = .0028.

Figure 5. Comparison of the disease-free survival of patients undergoing liver resection based on the initial H-staging. * log-rank test among three groups.

Figure 6. Comparison of the disease-free survival of patients undergoing liver resection based on the follow-up H-staging. * log-rank test among three groups.
tion who had no extrahepatic recurrent foci was 71.4% in H'-stage A patients. Although several treatment modalities are being considered for liver metastases (including systemic adjuvant chemotherapy, intraarterial infusion chemotherapy,19 –23 and a combination thereof),24 no data have yet been found to establish selection criteria for offering additional preventive therapy after hepatectomy. Because from a pharmacologic standpoint intraarterial chemotherapy is more effective than systemic therapy for treating liver diseases,22,25 the development of regional preventive chemotherapy will improve the survival of patients who have a high possibility of recurrence only in the remnant liver (i.e., H'-stage A patients). In fact, H'-stage A patients who received intraarterial chemotherapy of 10 g 5-FU had a favorable prognosis in this series, although the scale of the database was small.

The efficacy of repeat hepatectomy26 –29 and lung resection after hepatectomy30 has been reported by several institutes. In the present study, a relation was observed between the H'-staging and the operability for recurrence, not only for repeat hepatectomy but also for lung resection. H'-stage A patients with recurrence are therefore thought to have a chance of obtaining a surgical cure. However, the clearly worse prognosis for the unfavorable groups (H'-stage B and C) confirms the need for intensive adjuvant or alternative treatment.

With the use of H-staging and H'-staging, which could be made without the need for specialized equipment, we were able to obtain useful information for the selection of an appropriate treatment strategy for liver metastasis, as well as for the selection of suitable follow-up therapy. Among the parameters used in these two stagings, the biologic aggressiveness of the primary tumor, represented by the budding at the invasive front and the extent of nodal involvement, was the most powerful prognostic predictor. Although few investigators have focused on primary tumor grading as a prognostic factor in patients undergoing hepatectomy, Scheele et al1 reported that a grade III/IV classification in the Broader system was associated with a less favorable crude survival. The tumor features at the invasive front demonstrate the degree of cancer invasiveness, and thus tumor budding has been proposed to be a pathologic finding with excellent potential for use in tumor grading.10,11,31 A limitation of H-staging is that it should be applied only after the resection of a primary lesion to select the optimal strategies for synchronous liver metastasis. Therefore, as for synchronous liver metastasis, the simultaneous resection of primary and metastatic tumors is not thought to be beneficial, in terms of the lack of H-staging information.

To corroborate or modify the staging system, further studies based on a large collective database will be necessary. Only after such corroboration should widespread application be considered.

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### References


