

A New Staging System for Colorectal Carcinoma with Liver Metastasis

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Abstract. *Purpose: The prognosis of colorectal carcinoma (CRC) with liver metastasis varies from case to case. A standardized classification system for evaluation of the prognosis and the treatment is needed. Therefore, we developed a new staging system for CRC with liver metastasis (HM-stage) based on the survival data. Patients and Methods: We evaluated 148 CRC patients with liver metastasis treated between 1985 and 1999. Prognostic factors were identified based on a multivariate analysis. According to the final prognostic factors and hazard ratios, we defined the HM- stage. Results: Three factors, including extent of liver metastasis, depth of tumor invasion and peritoneal metastasis, were identified to be the final prognostic factors. These factors were then assigned points. The patients were classified as being HM-stage I to IV by the sum total. The median survival time for each HM-stage were 37 months for HM-stage I, 23 months for II, 10 months for III and 7 months for IV, respectively. A significant difference among each stage was recognized ($p < 0.0001$). Conclusion: This new staging system for CRC with liver metastasis is simple and should be clinically useful for both estimation of the prognosis and evaluation of the therapy in patients.*

The most common distant metastasis of primary colorectal carcinoma (CRC) is metastasis to the liver. Already at the time of the primary tumor, 15-25% of the patients present with liver metastases, while without any treatment the median survival after the detection of liver metastases is approximately 9 months, depending on the extent of the

disease at the time of diagnosis (1). And, the 5-year survival rate for patients having undergone surgical resection is reported to be 30-40% (2-8), and further improvement of therapeutic outcomes is anticipated. However, some patients have recurrence even after hepatic resection, while some patients without surgery have good outcome due to effective chemotherapy.

CRCs with synchronous liver metastasis are all classified indiscriminately under stage IV (9, 10). The prognosis varies among individuals, however, and is largely dependent on the extent of liver metastasis, the presence or absence of metastasis to distant organs other than the liver, and residual tumor after resection (11, 12).

On the other hand, recurrences occur in approximately 20% of patients who have been treated by curative resection for CRC. The liver is the major metastasis site, occurring in 25% of all recurrent cases (13-16). There is no staging classification for recurrence as liver metastasis. Accordingly, the formulation of a new set of criteria for staging classification is considered necessary for the assessment of therapeutic responses and prognosis in CRCs with synchronous and metachronous liver metastasis.

We have devised a new staging system for CRC with liver metastasis on the grounds of survival rate data, and have assessed its validity and usefulness.

Patients and Methods

The study population comprised 148 CRC patients with liver metastasis (synchronous; 106 cases and metachronous; 42 cases) treated at Tokyo Women's Medical University, Daini Hospital, Japan, between 1985 and 1999. These cases accounted for 16.9% of all cases of CRC treated during the same period. In terms of treatment for liver metastasis, 47 patients underwent a hepatic resection, 46 patients were mainly treated by chemotherapy via hepatic artery infusion, while 55 patients received only systemic chemotherapy. Primary CRC and regional lymph nodes were resected in all cases.

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Table I. Univariate analysis (Cumulative survival rate).

Prognostic factor	p-value
Liver metastasis* (H1: H2: H3)	$p < 0.0001$
Depth of tumor invasion** (T1-3: T4)	$p < 0.0001$
Peritoneal metastasis* (P-: P+)	$p = 0.002$
Lymph node metastasis** (pN0: pN1-2)	$p = 0.0025$
Lymphatic invasion* (ly-: ly+)	$p = 0.0035$
Venous invasion* (v-: v+)	$p = 0.0062$
Distant metastasis* (M-: M+)	$p = 0.0188$

Prognostic factors were described according to Japanese classification of CRC* and AJCC cancer staging manual**.

Univariate analysis. Univariate analysis of data was performed with respect to age, gender, synchronicity/metachronicity, and the clinicopathological factors as follows: *i.e.*, extent of liver metastasis; H1 vs. H2 vs. H3, tumor location, depth of tumor invasion; pT1-T3 vs. pT4, peritoneal metastasis; P- vs. P+, histological grade; G1 vs. G2-4, lymph node metastasis; pN0 vs. pN1-2, lymphatic invasion; ly0 vs. ly1-3, venous invasion; v0 vs. v1-3, and distant metastasis; M(-) vs. M(+), serum CEA level; low (<5.0ng/ml) vs. high (≥ 5.0 ng/ml), CEA doubling time (16); long (>100days) vs. short (≤ 100 days) and serum CA19-9 level; low (<26ng/ml) vs. high (≥ 26 ng/ml). The description in this paper was in agreement with AJCC Cancer Staging Manual and Japanese Classification of CRC (9, 10).

We particularly use Japanese Classification of CRC on the extent of liver metastases. H1 expresses metastasis limited to one lobe, H2 is some metastases to both lobes (4 lesions or less), and H3 means numerous metastases to both lobes (5 lesions or more), respectively.

In cases of metachronous liver metastasis, three variables such as depth of tumor invasion, vascular invasion and histological grade were used at the time of operation for primary lesion(s).

Multivariate analysis. Proper prognostic factors were subjected to Cox's proportional hazards model multivariate analysis (18, 19) in order to select the final prognostic factors.

Prognostic factor scoring and staging of CRC with liver metastasis. The final prognostic factors, determined by multivariate analysis, were scored using their hazard ratios, taking into account the weight of individual factors; this was then used to devise a staging system for CRC with liver metastasis that would permit variance in the survival rate.

Survival rate as classified according to staging of CRC with liver metastasis. To verify the validity of the new staging system we devised, the prognostic stage of each patient in this study was assessed using this classification scheme.

Statistical analysis. The length of survival was measured from the date of the start of the treatment for liver metastases until death from any cause or June 30, 2004 whichever event occurred first. Deaths due to "surgical mortality" were not excluded. Cumulative overall survival rates were calculated using Kaplan-Meier's method

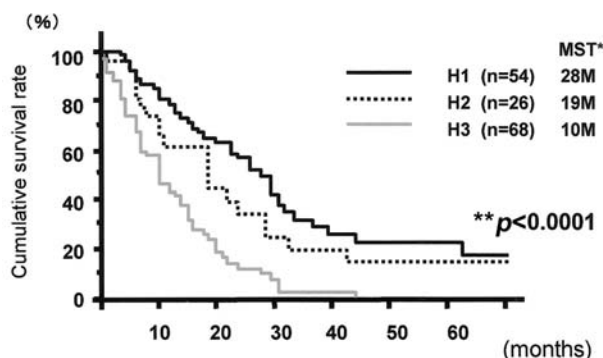


Figure 1. Survival curves by the extent of liver metastasis. *Mean survival time

in the univariate analysis, and the log-rank test was employed to test any differences for statistical significance. Multivariate analysis was carried out using the Cox's proportional hazards model and Walt's test. Any intergroup differences were considered statistically significant at $p < 0.05$.

Results

Univariate analysis. Significant differences in terms of survival rate factors were noted in the extent of liver metastasis, depth of tumor invasion, peritoneal metastasis, lymph node metastasis, lymphatic invasion, venous invasion and distant metastasis, whereas no such statistical differences were observed with respect to any other factors (Table I).

Survival curves are presented for the three factors: extent of liver metastasis (Figure 1), depth of tumor invasion (Figure 2) and peritoneal metastasis (Figure 3).

Multivariate analysis. Of the seven factors noted to show significant differences on univariate analyses, the following three factors were considered to significantly affect prognosis: extent of liver metastasis ($p = 0.0001$), depth of tumor invasion ($p = 0.002$) and peritoneal metastasis ($p = 0.049$) (Table II).

Staging of CRC with liver metastasis (HM-stage). The three final prognostic factors determined in the multivariate analysis were scored based on their hazard ratios, taking into account the weight of individual factors. Scores were assigned as follows: extent of liver metastasis; H1: 0, H2: 1, and H3: 2, depth of tumor invasion; pT1 or pT2: 0, pT3 or pT4: 1, and peritoneal metastasis; P (-): 0, P (+): 1.

Thus, the staging for CRC with liver metastasis was defined according to the sum of the scores: 0; HM-stage I, 1; HM-stage II, 2 to 3; HM-stage III, and 4; HM-stage IV (Table III).

Survival rates by HM-stage of CRC with liver metastasis. For the overall study population, the mean survival time (MST)

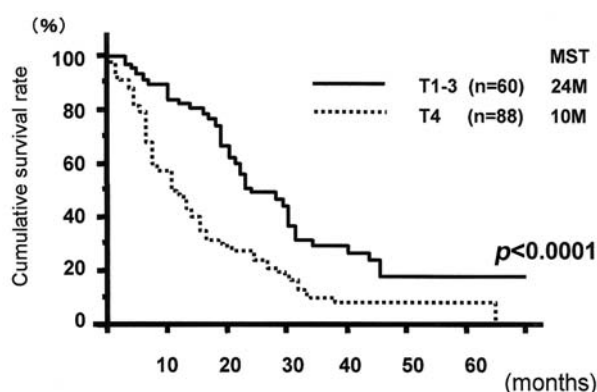


Figure 2. Survival curves by depth of tumor invasion.

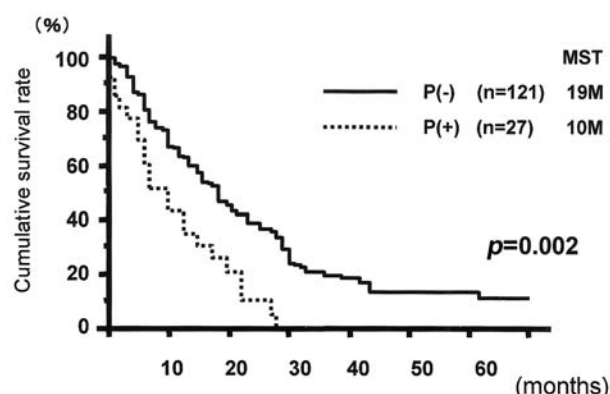


Figure 3. Survival curves by peritoneal metastasis.

was 16 months and the cumulative 5-year survival rate was 11.0%. They were 37 months and 39.8%, respectively, for HM-stage I patients, hence a remarkably favorable prognosis. For HM-stage II patients, the figures were 23 months and 18.7%, for HM-stage III patients, 10 months and 1.8%, and for HM-stage IV patients, 7 months and 0%, representing a grave prognosis. Significant inter-stage differences were noted in both parameters (Figure 4, $p < 0.0001$).

Discussion

Primary CRCs with distant metastasis or with peritoneal metastasis are all classified under stage IV (9, 10). The 5-year survival rate for such patients is reported to be 16.7% for colon cancer and 12.7% for rectal carcinoma (13). There is no curative treatment for peritoneal metastasis or distant lymph node metastasis, where the 5-year survival rate remains lower than 15% (20). In liver metastasis, without any treatment the median survival after the detection of liver metastases is approximately 9 months, depending on the extent of the disease at the time of diagnosis (1). However, it is not infrequent that the metastatic lesion is resectable and the 5-year survival rate of the patients with hepatic resection is reportedly 30-40% (2-5) and has been improving in recent years.

It would be extremely useful in clinical terms to formulate a new staging classification of CRC with liver metastasis. In view of this, we have newly devised a staging system for CRC with liver metastasis, based on an analysis of survival rates for patients with CRC with liver metastasis, and have assessed the validity and usefulness, and the clinical significance of this staging system.

In the univariate analysis, the extent of liver metastasis, depth of tumor invasion, peritoneal metastasis, lymph node metastasis, lymphatic invasion, venous invasion and distant metastasis were listed as factors related to prognosis in CRC

Table II. Multivariate analysis (Cox's proportional hazard model).

Prognostic factor	Hazard ratio	p-value
Liver metastasis* (H1: H2: H3)	1: 1.73: 3.23	$p < 0.0001$
Depth of tumor invasion** (T1-3: T4)	1: 2.01	$p < 0.002$
Peritoneal metastasis* (P-: P+)	1: 1.83	$p = 0.049$
Lymph node metastasis** (pN0: pN1-2)	1: 1.39	$p = 0.283$
Lymphatic invasion* (ly-: ly+)	1: 1.16	$p = 0.517$

Prognostic factors were described according to Japanese classification of CRC* and AJCC cancer staging manual**.

Table III. Staging of CRC with liver metastasis (HM-stage).

Prognostic factor	Scores assigned		
Liver metastasis	H1	H2	H3
Depth of tumor invasion	pT1-3	pT4	
Peritoneal metastasis	P(-)	P(+)	
Sum of scores	0	1	2
HM-stage	I	II	III
			IV

patients with liver metastasis. Factors such as treatments for liver metastasis and the extent of liver metastasis have generally been implicated as prognostic factors for CRC patients with liver metastasis (11). Treatment undoubtedly constitutes a major prognostic factor, and whether the metastatic lesion in the liver has been resected or not has a profound bearing on prognosis.

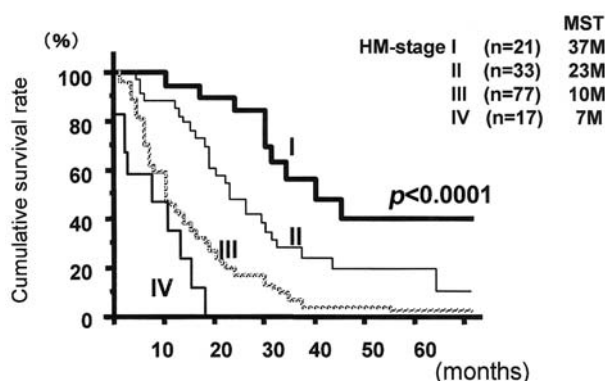


Figure 4. Survival curves of each HM-stage.

Yasui *et al.* (21) classified macroscopic types of hepatic metastatic lesions into simple nodular (SN) and confluent nodular (CN) in patients after resection of liver metastases and reported their relationship with prognosis. A recent study has attempted to identify metastasis-associated genes by detecting the gene expression pattern of colon cancer with liver metastasis using the cDNA microarray technique, and they identified the genes with expression levels that are altered with metastasis (22). Although there are currently many parameters for inclusion in the analysis (23), our analysis primarily constituted the factors specified in the Japanese Classification of CRC (9) for the sake of clinical convenience and simplicity.

As a result of multivariate analysis, the extent of liver metastasis, depth of tumor invasion and peritoneal metastasis were selected as the final prognosis-determining factors. The extent of liver metastasis represents an important factor that determines the feasibility of resecting metastatic lesions in the liver. The depth of tumor invasion determines the degree of progression of the primary lesion, and hence the most profound effect on metastasis and recurrence. Peritoneal metastasis, in particular, is one of the most important factors that clinically affects prognosis, in as much as it is meaningless to resect the liver metastasis if the case is positive for peritoneal metastasis.

A new staging system for CRC with liver metastasis has been devised by combining the three factors described above. As for prognosis by stage, there were statistically significant differences in survival rate among the stages, thus providing evidence in support of the validity and usefulness of this classification scheme. Nordlinger *et al.* (24) reported that a simple prognostic scoring system was proposed to evaluate the chance of cure of patients after resection of liver metastases from CRC using numerical assessments of seven factors, *i.e.* age, size of largest metastasis, CEA level, stage of primary tumor, disease-free

interval, number of liver nodules and resection margin. However, the subjects in their study were limited to patient resected liver metastases. The present staging classification has a broader scope of clinical utilization in that it may be employed to predict prognosis and select therapy in all cases of liver metastasis.

With this new system it has become practicable to compare the prognosis for patients at each stage by type of treatment, thus enabling evaluation of the respective efficacy of different treatments. This new staging system is a simple classification scheme determined by three factors: extent of liver metastasis, depth of tumor invasion and peritoneal metastasis. Therefore, it may be used commonly at all medical institutions dealing with CRCs.

It may be concluded that this staging system is simple, easy-to-use and clinically useful for both making an accurate estimate of the prognosis and evaluating the treatment.

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