



Proposal of criteria to select candidates with colorectal liver metastases for hepatic resection: Comparison of our scoring system to the positive number of risk factors

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Abstract

AIM: To select accurately good candidates of hepatic resection for colorectal liver metastasis.

METHODS: Thirteen clinicopathological features, which were recognized only before or during surgery, were selected retrospectively in 81 consecutive patients in one hospital (Group I). These features were entered into a multivariate analysis to determine independent and significant variables affecting long-term prognosis after hepatectomy. Using selected variables, we created a scoring formula to classify patients with colorectal liver metastases to select good candidates for hepatic resection. The usefulness of the new scoring system was examined in a series of 92 patients from another hospital (Group II), comparing the number of selected variables.

RESULTS: Among 81 patients of Group I, multivariate analysis, i.e. Cox regression analysis, showed that multiple tumors, the largest tumor greater than 5 cm in diameter, and resectable extrahepatic metastases were significant and independent prognostic factors for poor survival after hepatectomy ($P < 0.05$). In addition, these three factors: serosa invasion, local lymph node metastases of primary cancers, and post-operative disease free interval less than 1 year including synchronous hepatic metastasis, were not significant, however, they were selected by a stepwise method of Cox regression analysis ($0.05 < P < 0.20$). Using these six variables, we created a new scoring formula to classify patients with colorectal liver metastases. Finally, our new scoring system not only classified patients in Group I very well, but also that in Group II, according to long-term outcomes after hepatic resection. The positive number of these six variables also classified them well.

CONCLUSION: Both, our new scoring system and the positive number of significant prognostic factors are useful to classify patients with colorectal liver metastases in the preoperative selection of good candidates for hepatic resection.

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Key words: Colorectal cancer; Liver metastasis; Hepatic resection; Prognostic factor

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INTRODUCTION

It is well accepted that hepatic resection for colorectal liver metastases is beneficial; it has been reported survival rates improve to as high as almost 30% to 50% at 5 years after curative hepatic resection recently^[1-10]. However, the feasible criteria for surgery are still controversial. The purpose of the present study is to implement a useful classification system to select optimal candidates for hepatic resection among patients with colorectal liver metastases.

MATERIALS AND METHODS

Patients

Group I : 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. Every hepatectomy was considered curative because of complete macroscopic resection of hepatic tumors. Even though extrahepatic metastases were excised, hepatectomy was performed if extrahepatic metastatic tumors could be completely resected as well macroscopically. During the post-operative period, two patients died in the hospital. One died secondary to aspiration pneumonia and the other by

developing severe intra-abdominal sepsis (mortality rate: 3.1%). Therefore, the remaining 81 patients were followed until death or their last outpatient visit up to December 31, 2004. The follow-up period ranged from 4 to 197 mo. with a median of 53.0 mo. After discharge from the hospital, patients were closely monitored at the outpatient clinic or affiliated institutions. During visits, measurement of serum carcinoembryonic antigen (CEA) levels and ultrasonography were performed at least once every two months for early detection of recurrence. In addition, computed tomography was performed approximately twice a year. Almost all cases of cancer recurrence were diagnosed by these investigative tests. When the diagnosis was unclear, angiography and/or needle biopsy under ultrasonic guidance was performed to establish a firm diagnosis.

Group II: Between January 1, 1981 and December 31, 2003, 92 consecutive patients underwent partial hepatectomy for colorectal liver metastases at the Department of Surgery, Teikyo University Hospital. During the post-operative period, two patients died in the hospital from post-operative hepatic failure (mortality rate: 5.6%). The remaining 92 patients were followed up 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. After discharge from the hospital, each patient was closely monitored at the outpatient clinic or affiliated institutions in a manner similar to the patients at University of Tokyo hospital.

Prognostic factors

We examined the statistical significance of thirteen factors that were expected to influence long-term prognosis in patients in Group I. Each factor could only be determined preoperatively or during surgery. These included gender; male or female, age at hepatectomy; < 60 or ≥ 60 years, chronology of hepatic metastases; synchronous or metachronous, and post-operative disease free interval, ≤ 1 year including synchronous metastasis or > 1 year; number of hepatic metastases; solitary or multiple, maximum diameter of the hepatic metastases; ≤ 5 cm or > 5 cm, unilobar or bilobar hepatic involvement, resectable extrahepatic distant metastasis, which included pulmonary metastases, localized peritoneal metastases, or hepatoduodenal lymph node metastases, serum carcinoembryonic antigen level (CEA) at hepatectomy; less or higher than 10 times of the upper normal level, serosa invasion, and regional lymph node metastases of the primary colorectal carcinoma, type of hepatic resection; lobectomy or limited resection less than lobectomy, and macroscopical surgical resection margin; < 1 cm or ≥ 1 cm. The demographic characteristics and tumor-related features, which are statistically analyzed later, are summarized in Table 1.

Statistical analysis

Survival rates after hepatectomy were calculated using data obtained from patients in Group I and Group II by the Kaplan-Meier method. Only deaths attributable to recurrent cancer were treated as events. Patients who died secondary to other causes without recurrence were treated

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

Variable	n
Gender (male/female)	61/20
Age at hepatectomy($< 60/\geq 60$ yr)	32/49
Chronology of hepatic metastasis (synchronous/metachronous)	41/40
Disease free interval after colectomy (synchronous or ≤ 1 yr/ > 1 yr)	56/25
Extrahepatic distant metastases (no/yes)	9/72
CEA (≤ 10 times of normal value/ > 10 times of normal value)	57/24
Primary lesion	
Depth of invasion (up to subserosa/more)	57/24
Lymph node metastasis (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
Therapeutic factor	
Type of hepatectomy (limited/lobectomy)	56/25
Surgical margin (< 1 cm / ≥ 1 cm)	61/20

as censored. Selection of independent and significant prognostic variables was performed by multivariate analysis in patients of Group I with the stepwise analysis of Cox proportional hazard regression model. The stepwise variable selection was performed at a 0.20 significant level in this study. The creation of a scoring formula was based on the results of the multivariate analysis as above. Each selected independent and significant prognostic factor was respectively given a coefficient. The total score of each patient ($y1$) was calculated according to a formula that consisted of these selected prognostic factors.

The scoring formula was applied to patients in Group II as well as Group I. Patients were divided into sub-groups depending on their total scores ($y1$) as follows; $y1 = 0, 0 < y1 \leq 1, 1 < y1 \leq 2, 2 < y1 \leq 3, 3 < y1 \leq 4, 4 < y1 \leq 5, 5 < y1 \leq 6, 6 < y1$. Survival rates according to the sub-groups were calculated using the Kaplan-Meier method. On the other hand, survival rates according to the positive number of selected significant prognostic factors ($y2$) were also calculated, and compared to the results of the scoring formula ($y1$). They were analyzed using the log-rank test.

RESULTS

The overall cancer-related survival rates after surgical resection in the 81 patients in Group I were 88.2% at 1 year, 67.7% at 2 years, 56.0% at 3 years, 51.6% at 4 years, and 49.1% at 5 years, respectively (Figure 1). The results from the multivariate analysis of those variables expected to influence cancer-related survival after surgical resection in Group I are provided in Table 2. Only variables selected by the stepwise analysis of the Cox proportional hazard regression model are shown in the table ($P < 0.20$). Multiple hepatic metastatic tumors, hepatic metastatic tumors that were greater than 5 cm in maximum diameter, and resectable extrahepatic distant metastases were significant and independent variables that influenced cancer-related survival ($P < 0.05$). In addition, serosa

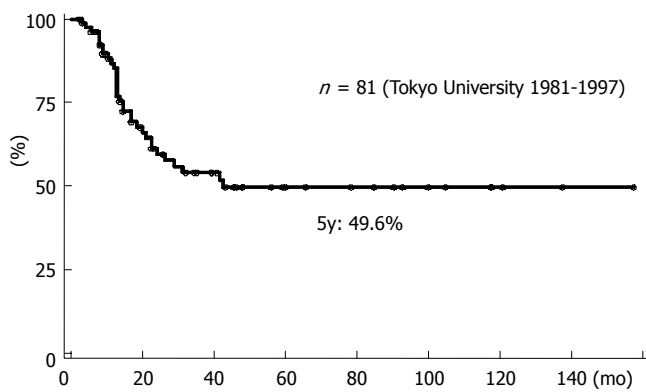


Figure 1 Kaplan-Meier cancer-related survival curve after hepatic resection for colorectal liver metastases in patients of Group I.

Table 2 Multivariate analysis for clinicopathological variables with the stepwise analysis of Cox proportional hazard regression model $n = 81$ (Tokyo Univ 1981-1997)

Variable	Parameter	P	Hazard ratio (95% CI)
Diameter > 5 cm	1.35657	0.0013	3.883 (1.703-8.852)
Extrahep met (+)	1.19430	0.0133	3.301 (1.282-8.502)
Number ≥ 2	0.85412	0.0265	2.349 (1.105-4.997)
DF interval < 1 yr	0.67838	0.1602	1.971 (0.765-5.080)
n (+) of primary	0.60034	0.1352	1.823 (0.829-4.007)
\geq se (+) of primary	0.54877	0.1676	1.731 (0.794-3.774)

$P > 0.2$; Age ≥ 60 , Gender, Synchronous, Bilobar invasion, CEA, Major hepatectomy (lobectomy), Surgical margin < 1 cm.

Table 3 The scoring formula (y_1) and the positive number of risk factors (y_2)

Score (y_1) = $1.35657 \times (\text{Diameter} > 5 \text{ cm})$
 $+ 1.19430 \times (\text{Extrahep.met})$
 $+ 0.85412 \times (\text{Multiple})$
 $+ 0.67838 \times (\text{D.F.I.} < 1 \text{ yr})$
 $+ 0.60034 \times (\text{n+ of Primary})$
 $+ 0.54877 \times (\geq \text{se of Primary})$
 $y_1: 0 \leq y_1 \leq 5.2324$
 Score (y_2) = Number of Factors
 $y_2: 0, 1, 2, 3, 4, 5, 6$

invasion and regional lymph nodes metastases of primary colorectal cancer, and recurrent hepatic metastases within one year after resection of primary colorectal cancer including synchronous hepatic metastases were considered close to significant ($0.05 < P < 0.20$).

As described above, multivariate analysis indicated six variables that more independently influenced cancer-related survival after hepatic resection. In the next step of creating a scoring formula, we use these six variables to classify patients as shown in Table 3. In this formula, each variable had a coefficient, which was indicated as a parameter estimate by Cox regression analysis, as shown in Table 2. If the factor was positive, it was given a score of one point. If it was negative, it was given a score of 0 points. Thereafter the total score of each patient (y_1) could be calculated. On the other hand, the positive number of

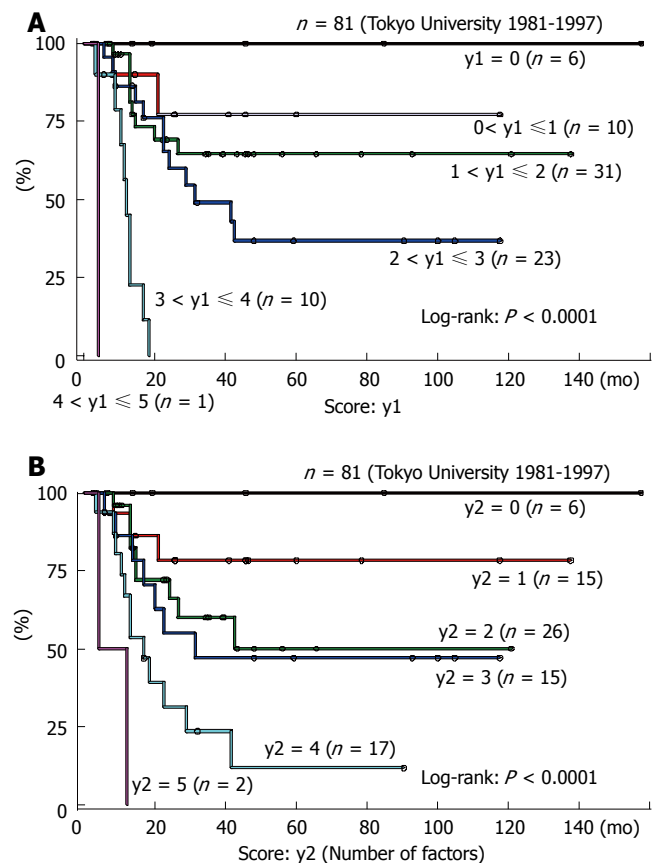


Figure 2 Kaplan-Meier cancer-related survival curves after hepatic resection for colorectal liver metastases. **A:** According to the total score (y_1) in patients of Group I; **B:** According to the positive number of risk factors (y_2) in patients of Group I.

these six variables (y_2) of each patient was also calculated

Classification of patients and survival

The total scores of patients (y_1) in Group I were distributed between 0 and 5.2324. The survival curves of patients based on the total score (y_1) are shown in Figure 2A. Which were accurately and significantly classified ($P < 0.0001$). We clearly found that the prognosis of patients with a total score of (y_1) > 3 were very poor. On the other hand, the survival curves of patients based on the positive number (y_2) are shown in Figure 2B. They were well and significantly classified as well ($P < 0.0001$). We clearly found that the prognosis of patients with positive number ≥ 5 were very poor.

The survival curves of all patients in Group II are shown in Figure 3. The overall cancer-related survival rates of the 92 patients in Group II after surgical resection were 83.2% at 1 year, 62.6% at 2 years, 49.4% at 3 years, 41.0% at 4 years, and 36.4% at 5 years, respectively. We applied our scoring system to 92 patients in Group II. The total scores of these patients (y_1) were distributed between 0 and 5.2324. The survival curves of patients based on the total score (y_1) are shown in Figure 4A. They were also significantly classified ($P < 0.0001$). We clearly found that the prognosis of patients with total score (y_1) > 3 were very poor. On the other hand, the survival curves of patients based on the positive number (y_2) are shown in Figure 4B. They were significantly classified as well ($P < 0.0001$). We

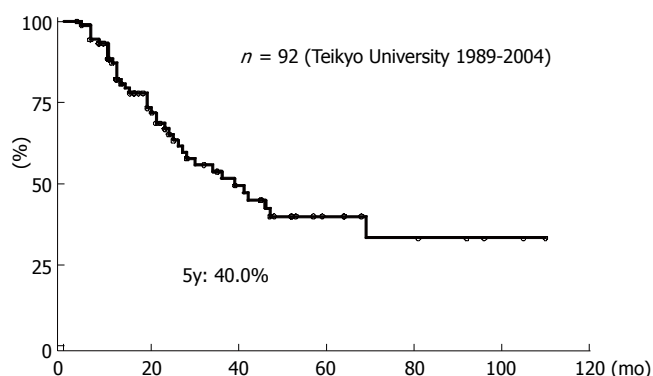


Figure 3 Kaplan-Meier cancer-related survival curve after hepatic resection for colorectal liver metastases in patients of Group II.

clearly found that the prognosis of patients with positive number ≥ 5 were very poor.

DISCUSSION

Clinical and pathological factors have been identified as important prognostic determinants of survival after surgical resection for colorectal liver metastases. These include sex^[11], age at hepatectomy^[1,12], stage of the primary tumor^[1,3,4,11-15] (including local lymph node metastases and depth of invasion), synchronous or metachronous hepatic metastases^[1-3,6,8,10,12,13,16] (including disease free interval between resection primary tumor and presence of hepatic metastasis), number^[1-4,6,7,11,12,15,17-19], size^[1,2,8,9,11,13,17,20], and distribution^[6,12,14] of hepatic metastases; serum carcinoembryonic antigen (CEA) level^[1,3,4,7,20,21], extrahepatic distant metastases^[4-6,8,10,11,15,20] (including lymph node metastasis of hepatic hilum), type of hepatectomy^[14], surgical margin^[5,7,9,11-13,15,17,18,20], and adjuvant chemotherapy^[8,22,23].

In the present study, we aimed to create a new classification system of patients with colorectal liver metastases to distinguish patients who would be good candidates for hepatic resection. There have been some classification systems for these patients so far^[1-3,12], however, they are not accepted world wide yet. We selected clinicopathological features that could be recognized as prognostic factors only before or during surgery, because we had to decide how to treat those patients pre- or intraoperatively. We included some therapeutic factors as well in this study because we intended to determine whether those therapeutic factors were significant or not. We believed that any therapeutic factors that may be significant should also be included in the classification scoring system. However, we excluded adjuvant chemotherapy because it has been arbitrarily performed in past years and we could not evaluate its efficacy. We considered positive surgical margins to be a very important factor^[5], however, we excluded it because it was an incidental factor and could only be recognized after surgery.

Among the thirteen clinicopathological factors we proposed, we found and selected the following to be more significant and independent prognostic factors for poor survival after hepatectomy: multiple hepatic metastatic tumors; hepatic metastatic tumor greater than 5 cm in

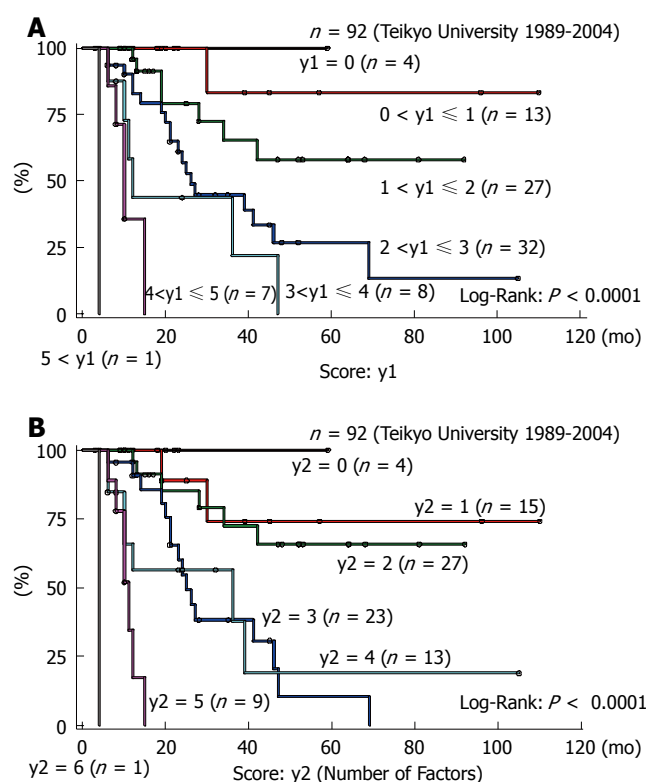


Figure 4 Kaplan-Meier cancer-related survival curves after hepatic resection for colorectal liver metastases. **A:** According to the total score ($y1$) in patients of Group II. **B:** According to the positive number of risk factors ($y2$) in patients of Group II.

diameter; resectable extrahepatic distant metastases; recurrent hepatic metastases within one year after resection of primary colorectal cancer including synchronous hepatic metastases; regional lymph node metastases and serosa invasion of primary colorectal cancers. On the other hand, none of the therapeutic factors we proposed were selected as significant prognostic factors. We found that a 1 cm negative surgical margin and type of hepatectomy were not important as long as the tumor was resected completely for colorectal liver metastases. The goal of the present study was to establish a new scoring system to classify patients with colorectal liver metastases. Hence, this would allow an accurate prediction of long-term prognosis after surgical resection in these patients. Such a system would enable better selection of candidates for surgical resection. At last, our new scoring system, which includes six prognostic factors described above, significantly classified not only a group of patients in one hospital but also a group of patients in another hospital. We are not aware of a similar scale system for predicting the long-term outcome of surgical resection for colorectal liver metastases. According to our scoring system, patients with a total score of $0 \leq y1 \leq 3$ were suitable candidates for hepatectomy. On the other hand, patients with a total score of $y1 > 5$ should not undergo hepatectomy. We believe that patients with a total score of $3 < y1 \leq 5$ should undergo hepatectomy first, since there is no other treatment superior to hepatectomy at present.

In addition, we realized that the positive number of significant prognostic factors also classified patients well with colorectal liver metastases. The prognosis of pa-

tients with positive number ≥ 5 was very poor. It seemed that our scoring formula and the positive number of risk factors had almost equal usefulness to select good candidates for hepatic resection at present. The former is more accurate, but complicated to calculate, while the latter is less accurate, but simple. Further investigation should be necessary to prove their superiority.

In conclusion, we identified six important and independent prognostic factors that were recognized before or during surgery. We used multivariate analyses from a retrospective review of patients who underwent hepatic resection for colorectal liver metastases in one hospital. We proposed a new scoring system to classify those patients according to the long-term outcome after hepatectomy. Our scoring system accurately classified a different group of patients from another hospital as well. In addition, the positive number of significant prognostic factors also classified with those patients with good accuracy. Further investigation is necessary in the future.

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