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Outcome of Surgical Treatment of Synchronous Liver Metastases from Colorectal Cancer

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Abstract

Background: We retrospectively identified the prognostic factors in cases of synchronous liver metastases from colorectal cancer and established a clinical strategy at our institution.

Methods: One hundred eight patients with hepatic metastases from colorectal cancer underwent a first radical hepatic resection. Of these, 67 were diagnosed with hepatic synchronous metastases from colorectal primaries (S group) and 41 were diagnosed with metachronous metastases (M group). Hepatic lesions were diagnosed concurrently with the primary lesions in 45 of the 67 patients in the S group. Of these 45 patients, 37 underwent synchronous hepatectomy (SH group) and 8 underwent metachronous hepatectomy (MH group).

Results: The overall 3-, 5- and 10-year survival rates were 51.4%, 41.6%, and 30.9%, respectively. There were no significant differences between the S and M groups in overall survival. Univariate analysis of the S group revealed significant differences in survival based on tumor factor, pathological lymph node metastases of the primary tumor, and the tumor-free margin. There were no significant differences between the SH and MH groups in overall survival.

Conclusions: Patients with synchronous liver metastases from colorectal cancer should undergo radical resection of the primary lesion and simultaneous hepatectomy with an adequate tumor-free margin as a standard surgical course.
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Key words: liver metastases from colorectal cancer, synchronous metastases, prognostic factor, survival rates, tumor-free margin

Introduction

Surgical resection is now accepted as a viable treatment for colorectal cancer metastases to the liver. The overall 3- and 5-year survival rates after hepatic resection in recent reports have ranged from 44% to 59% and 30% to 40%, respectively. The median survival time in these reports has ranged from 35 to 40 months[1–5]. In most cases the surgery is indicated for patients without local recurrence, other hematogenous metastases, or lymph node

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metastases in the hepatoduodenal ligament and for patients in whom curative hepatic resection is considered feasible.

Although the prognostic factors in cases of liver metastases from colorectal cancer remain unconfirmed, all of the following have been reported to be significantly associated with a poor prognosis: tumor size, number of metastatic lesions, tumor-free margin, extrahepatic metastases, stage of the primary tumor, disease-free interval, and the level of preoperative carcinoembryonic antigen[1–5,8–12,14]. Studies of cases of particularly synchronous liver metastasis have not clarified how the interval between the primary procedure for colorectal cancer and liver resection influences prognosis[2–4,11].

Our group retrospectively evaluated the prognostic factors in cases of synchronous liver metastases from colorectal cancer and established a clinical strategy for how surgery for the colorectal lesion should be performed and how and when hepatectomy should be performed at our institution.

Patients and Methods

From 1990 through 2004, 132 patients with hepatic metastases from colorectal cancer underwent hepatic resection at the First Department of Surgery of Nippon Medical School, Tokyo. Selection criteria for surgery were a reasonable likelihood of success in an oncologically radical operation and a reasonable likelihood of at least 40% of the normal hepatic parenchyma being preserved. Resectable lung metastases were not considered exclusion criteria.

Nine patients underwent a second hepatectomy, 1 patient underwent a third hepatectomy, and resections were ruled out in 14 patients because of gross residual disease within or outside the liver. In these 14 patients, lymph node metastases in the hepatoduodenal ligament were found in 4 patients and direct invasion to the diaphragm was found in 2. All 24 of these patients were excluded from the study. The remaining patients included 60 men and 48 women, with a median age of 64.0 years (range, 30 to 79 years).

Hepatic metastases detected from 0 to 12 months after primary resection were defined as metastases synchronous with primary colorectal tumors. These metastases were diagnosed in 67 cases, and metachronous metastases were diagnosed in 41. Hepatic lesions were diagnosed at colorectal resection in 45 cases, and hepatic metastases were diagnosed within 12 months in 22 cases. We performed synchronous hepatectomy in 37 patients, in keeping with our policy of resecting hepatic lesions found synchronously. Another 6 patients underwent separate operations for the primary resection and liver resection, and 2 patients underwent chemotherapy before hepatic resection because of multiple hepatic metastases.

The operative procedures for the anatomic resections were defined by the following terminology proposed by Strasberg[15]: segmentectomy (resection of Couinaud's segment)[16,17], sectionectomy (resection of Healey's segment)[18], and hemihepatectomy. Of the 108 patients, 51 underwent systematic anatomical hepatic resection and 57 underwent nonanatomical limited resection.

The hepatectomy procedures were selected on the basis of the numbers, sizes, and locations (proximity to the hepatic pedicle) of the hepatic metastatic tumors. These selection criteria were thought to optimize our chances of removing all tumors with sufficient tumor-free margins (about 5 mm).

Univariate and multivariate analyses were performed to determine whether any of the following could be considered prognostic factors: sex, age (younger than 60 years vs. 60 years or older), primary tumor site (rectum vs. colon), stage (I, II vs. III, IV), tumor factor of the pathological TNM classification of the primary tumor (Tis, T1, T2 vs. T3, T4), pathological vascular invasion of the primary tumor, pathological lymphatic invasion, pathological lymph node metastases of the primary tumor, number of liver tumors (solitary vs. multiple), maximum diameter of the liver lesions (<3 cm vs. ≥ 3 cm), intrahepatic distribution (unilateral vs. bilateral), type of operative procedure (anatomic resection vs. nonanatomic resection), and tumor-free margin (<5 mm vs. ≥ 5 mm).

Statistical comparisons between groups were

Table 1 Patient characteristics in the synchronous and metachronous groups

	S group (n=67)	M group (n=41)	P value
Sex (M : F)	35 : 32	25 : 16	0.3752
Age (years)	63.0 ± 10.5	63.3 ± 11.8	0.6828
Primary lesion			
Site (Rectum : others)	42 : 25	27 : 14	0.7391
Tumor factor (Tis, T1, T2 : T3, T4)	19 : 44	10 : 23	0.9883
Lymph node metastases (n0 : n1, n2, n3, n4)	42 : 21	22 : 11	0.9999
Lymphatic invasion (ly0 : ly1, ly2, ly3)	51 : 12	28 : 5	0.8957
Vascular invasion (v0 : v1, v2, v3)	57 : 6	22 : 11	0.0097
Hepatic lesion			
Intrahepatic distribution (Unilateral : Bilateral)	42 : 25	60 : 36	0.3347
Maximum diameter (mm)	39.5 ± 35.3	36.5 ± 21.0	0.4306
Number of lesions	2.36 ± 1.55	1.86 ± 1.41	0.0418
Hepatectomy			
Type of resection (anatomic : non-anatomic)	39 : 28	18 : 23	0.2125
Tumor-free margin (≥5mm : <5mm)	55 : 12	36 : 5	0.6036

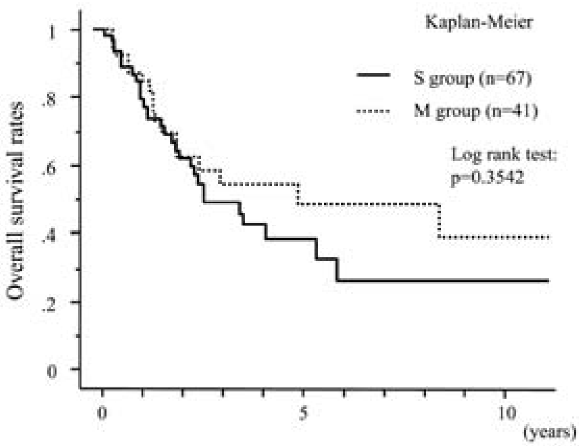

Fig. 1 Overall survival in the synchronous group (S group) and metachronous group (M group). There were no significant differences in survival rates between these two groups. (P=0.3542)

performed using the Mann-Whitney U test or the chi-square test. Survival was analyzed using the Kaplan-Meier method, with the date of the hepatic resection as a starting point. All patients were followed up to December 2004 or until death as an end point. Overall survival curves were compared with the log-rank test. A multivariate stepwise Cox's regression analysis was performed to identify significant contributors among the factors independently associated with death on univariate analysis. A P value of less than 0.05 was considered to indicate significance.

Results

Demographics and Operative Date

The characteristics of the patients in the synchronous and metachronous groups are summarized in **Table 1**. There were no significant differences between the groups in terms of patient sex, age, primary tumor site, stage, tumor factor, pathological lymphatic invasion, pathological lymph node metastases, maximum diameter of the liver lesions, intrahepatic distribution, type of operative procedure, or tumor-free margin. Significant differences between the groups were noted in the pathological vascular invasion of the primary tumor and the number of metastatic liver tumors.

Surgical Results

The mean follow-up period was 31 months (median, 19 months; range, 1～134 months). There were no deaths in the first 30 days after surgery. The overall 1-, 3-, 5-, and 10-year survival rates of the 108 patients were 85.5%, 51.4%, 41.6%, and 30.9%, respectively. The overall 1-, 3-, and 5-year survival rates were 49.5%, 39.0%, and 26.7% in the synchronous group and 58.1%, 49.1% and 39.2% those in the metachronous group **(Fig. 1)**. There were no significant differences between the overall survival

Table 2 Univariate analysis of prognostic factors in all cases

	P value	Relative risk	95%CI
Sex (M : F)	0.8971	1.038	0.593 ～ 1.816
Age (≥60 : <60)	0.2176	1.490	0.790 ～ 2.809
Temporal relationship (synchronous : metachronous)	0.5206	1.205	0.682 ～ 2.131
Primary lesion			
Site (Rectum : others)	0.3455	0.763	0.435 ～ 1.338
Tumor factor (Tis, T1, T2 : T3, T4)	0.1426	0.545	0.242 ～ 1.227
Lymph node metastases (n0 : n1, n2, n3, n4)	0.1083	0.546	0.261 ～ 1.143
Lymphatic invasion (ly0 : ly1, ly2, ly3)	0.5230	0.766	0.338 ～ 1.737
Vascular invasion (v0 : v1, v2, v3)	0.9793	0.990	0.457 ～ 2.146
Hepatic lesion			
Intrahepatic distribution (unilateral : bilateral)	0.3302	1.323	0.753 ～ 2.325
Maximum diameter (≥30mm : <30mm)	0.9851	1.005	0.570 ～ 1.774
Number of lesions (solitary : multiple)	0.0400	1.841	1.028 ～ 3.295
Hepatectomy			
Type of resection (anatomic : non-anatomic)	0.0838	1.666	0.934 ～ 2.972
Tumor-free margin (≥5mm : <5mm)	0.0001	5.834	3.050 ～ 11.157

Table 3 Univariate analysis of prognostic factors in the synchronous group (S group)

	P value	Relative risk	95%CI
Sex (M : F)	0.1104	0.546	0.260 ～ 1.148
Age (≥60 : <60)	0.2668	1.584	0.703 ～ 3.569
Primary lesion			
Site (Rectum : others)	0.2296	0.637	0.305 ～ 1.330
Tumor factor (Tis, T1, T2 : T3, T4)	0.0421	0.329	0.113 ～ 0.961
Lymph node metastases (n0 : n1, n2, n3, n4)	0.0491	0.396	0.157 ～ 0.996
Lymphatic invasion (ly0 : ly1, ly2, ly3)	0.2744	0.555	0.193 ～ 1.596
Vascular invasion (v0 : v1, v2, v3)	0.1885	2.052	0.707 ～ 5.993
Hepatic lesion			
Intrahepatic distribution (unilateral : bilateral)	0.4395	1.329	0.646 ～ 2.737
Maximum diameter (≥30mm : <30mm)	0.5281	1.274	0.600 ～ 2.703
Number of lesions (solitary : multiple)	0.0967	1.947	0.887 ～ 4.273
Hepatectomy			
Type of resection (anatomic : non-anatomic)	0.3369	1.438	0.685 ～ 3.019
Tumor-free margin (≥5mm : <5mm)	0.0001	5.606	2.513 ～ 12.507

rates of the two groups.

Analysis of Prognostic Factors in All Cases

Table 2 shows correlations of the patient characteristics, features of the primary and metastatic tumors, and operative procedures with good prognosis in the overall study population. None of the following factors were correlated with patient survival: sex, age, temporal relationship, primary tumor site, stage, tumor factor of the pathological TNM classification of the primary tumor, pathological vascular invasion of the primary tumor, pathological lymphatic invasion, pathological lymph node metastases of the primary tumor, maximum diameter of the liver lesions, intrahepatic distribution, type of operative procedure, and the number of hepatic resections. The tumor-free margin and the numbers of liver tumors were both significantly associated with good prognosis (**Table 2**).

Analysis of Prognostic Factors in Cases of Synchronous Metastasis

Univariate analysis of the 13 factors considered to be possible prognostic factors in the synchronous group alone revealed significant differences in

Table 4 Multivariate analysis of prognostic factors in the synchronous group (S group)

	P value	Relative risk	95%CI
Sex (M : F)	0.8626	1.074	0.478 ～ 2.413
Tumor factor (Tis, T1, T2 : T3, T4)	0.3284	0.422	0.075 ～ 2.381
Lymph node metastases (n0 : n1, n2, n3, n4)	0.4305	0.544	0.120 ～ 2.472
Number of lesions (solitary : multiple)	0.0698	2.210	0.938 ～ 5.208
Tumor-free margin (≥5mm : <5mm)	0.0002	5.033	2.151 ～ 11.774

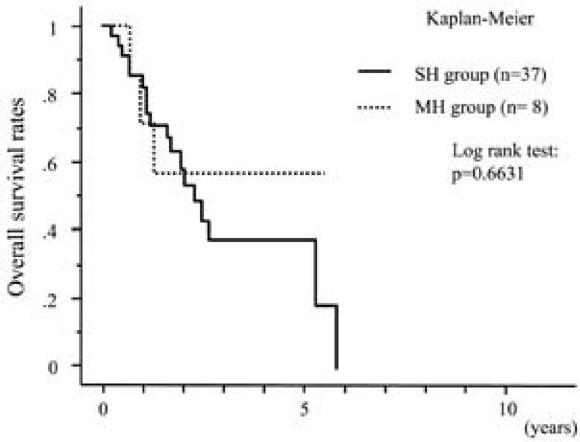

Fig. 2 Overall survival in the synchronous hepatectomy group (SH group) and metachronous hepatectomy group (MH group). Hepatic lesions and primary lesions were diagnosed simultaneously in 44 patients. There were no significant differences in survival rates between these two groups. (P=0.6631)

survival based on tumor factor (P=0.0421), pathological lymph node metastases of the primary tumor (P=0.0491), and tumor-free margin (P=0.0001). The number of liver tumors was not significant, with a P value of around 0.10 (**Table 3**). Tumor-free margin was the only significant prognostic factor in a multivariate analysis of the stratified group (**Table 4**).

Survival Rates of Patients with Hepatic and Primary Lesions Detected Simultaneously

Of the 45 patients with hepatic and primary lesions detected simultaneously, 37 underwent synchronous hepatectomy (SH group) and 8 underwent metachronous hepatectomy (MH group). The overall 1-, 3-, and 5-year survival rates were 81.8%, 37.8%, and 37.8% in the SH group and 71.4%, 57.1%, and 57.1% in the MH group, respectively (**Fig. 2**). No significant differences in overall survival were found between these two groups.

Discussion

Surgical resection is widely accepted as an effective method for treating colorectal carcinoma metastases to the liver[1-5]. Resection is the treatment of choice for metachronous liver metastases, as almost all of these metastases are resectable. Patients surgically treated for colorectal cancer are usually monitored by follow-up imaging studies such as ultrasonography, computed tomography, and magnetic resonance at 6-month intervals during the first 3 years after the primary procedures. Therefore, smaller and/or fewer hepatic metastases can be detected. In short, almost all metachronous liver metastases are resectable. Patients with synchronous liver metastases, on the other hand, sometimes develop advanced primary cancers and lung metastases. Our objectives in the present study were to evaluate differences in the prognoses of synchronous and metachronous liver metastases and to establish a clinical strategy for synchronous liver metastases at our institution.

The overall survival rates of the synchronous and metachronous groups did not differ in our Kaplan-Meier analysis. The temporal relationship was not a significant factor in our univariate analysis in any cases. The tumor-free margin and the number of liver tumors were the only factors significantly associated with a good prognosis.

Some groups have identified a tumor-free margin of less than 1 cm as a significant prognostic factor[1,2,8,19]. Others have deemed the safety margin adequate when no part of the lesion is exposed on the cut surface of the resection[4,5,13,14]. In our study, a tumor-free margin of less than 5 mm significantly affected the prognosis. This 5-mm tumor-free margin is achieved when no lesion is exposed on the cut surface or comes into contact with a main branch.

The value of the tumor-free margin as a prognostic factor is compromised when satellite nodules remain in the remnant liver. Some studies have found a positive correlation between the maximum diameter of the main tumor and the frequency of satellite nodules[19–21]. In others studies, the appearance of satellite nodules around the main metastatic lesion is rare[13,14]. In any case, the relationship between satellite nodules and tumor recurrence in the remnant liver remains controversial.

A tumor-free margin in hepatectomy was the only significant predictor of a favorable prognosis in the synchronous group in our multivariate analysis. Under this criterion, the tumor-free margin should be defined as no exposure of the tumor on the cut surface and no contiguity to a main branch.

We also observed a significant difference in survival when patients were grouped according to the number of lesions, even though tumor clearance was complete in every case. Some groups have reported significant differences in survival between patients with single and multiple lesions[3–5,8,9]. Wanebo et al. have identified four or more lesions as a contraindication for surgery[22]. Minagawa's group, on the other hand, have found no significant difference in prognosis between patients with a single nodule and patients with more than four nodules. Accordingly, they have recommended liver resection whenever technically feasible for patients with four or more lesions[5]. In our study the survival rate of patients with a single nodule was higher than that of patients with multiple lesions. The presence of multiple lesions was found to significantly influence the prognosis in our univariate analyses. Although multiple liver metastases are not considered a contraindication for hepatic resection, their presence seems to be a weak prognostic indicator.

The stage of the primary tumor has often been identified as a significant prognostic factor[2–6,9]. The tumor factor and lymph node metastases of the primary lesion were significantly associated with a favorable prognosis in our analysis of patients with synchronous liver metastases. This suggests that the survival of patients with advanced colorectal cancer depends not on hepatic metastatic factors, but on the primary tumor factor. On the basis of this result, we conclude that adequate surgical treatment for colorectal carcinoma improves the survival of patients with liver metastases.

In the treatment of patients with synchronous hepatic metastases and primary lesions, it remains unclear whether prognosis differs between patients undergoing simultaneous surgical resections and patients undergoing surgery in stages.

Simultaneous resection is considered risky in several respects. First, intestinal resection may increase the risk of intraoperative bacterial contamination of the cut liver surface. Second, the effects of transient portal clamping and impaired liver function due to the decrease in hepatic mass after hepatectomy may increase the risk of postoperative anastomotic leakage. Finally, the volume of resectable liver parenchyma in patients requiring parenchymal resection cannot be accurately determined, given that simultaneous hepatic resections have been reported primarily for minor hepatectomies[23]. Synchronous hepatectomy has been identified as a predictor of poor survival in many previous reports[7,24,25]. Scheele et al. have reported that prognoses are poor in patients with synchronous hepatectomy and have speculated that micrometastatic lesions may remain unresected in patients undergoing simultaneous resections of liver and primary colorectal tumors[25].

Recent studies in Japan have found no significant differences in prognosis between synchronous and metachronous hepatectomy under certain conditions[9,26]. These studies have recommend synchronous hepatectomy for four types of patients: those with a adequate tumor-free hepatic margin, those requiring resection of only one hepatic section to remove the liver metastases, those 70 years or younger, and those without poorly differentiated or mucinous adenocarcinoma as the primary lesion.

Our policy is to resect hepatic lesions and the primary lesions at the same time whenever the lesions are found synchronously. Our study found no significant differences in overall survival between patients undergoing synchronous hepatectomy and those undergoing metachronous hepatectomy. However, our study was not randomized and included to few patients in the analyses to support definitive conclusions. In light of advances in the techniques and instruments for hepatectomy, however, we will continue favoring synchronous hepatectomy at our institution.

Conclusion

No significant differences in the overall survival rates were found between patients with synchronous liver metastases from colorectal cancer and patients with metachronous liver metastases. Patients with synchronous liver metastases from colorectal cancer should undergo radical resection of the primary lesion and simultaneous hepatectomy with an adequate tumor-free margin as a standard surgical course.

Hepatic lesions should be resected together with primary lesions when they are found synchronously.

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