Resection of Hepatic Metastasis from Colorectal Cancer : Survival, Factors Influencing Prognosis, and Follow-up

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ABSTRACT. The purpose of this retrospective study was to analyze the surgical results of hepatic resection in our patients with colorectal hepatic metastasis. During a 26-year period, 223 patients among 1,484 patients with colorectal cancer suffered liver metastasis. In 44 curatively resected patients, the one-, three- and five-year cumulative survival rates were 85.9%, 44.9% and 23.0%, respectively. The prognostic importance of seven factors was eveluated. Synchronous or metachronous resection, the type of liver resection, and histologic differentiation did not influence the prognosis, whereas the number and size of metastases, and lymph node involvement did significantly affect prognosis as single factors. The mean diameter of metastatic lesions in the liver was 2.5 cm in the synchronous group and 4.5 cm in the metachronous group, the difference being significant ($p=0.0005$). The presence of tumors with large diameters in the metachronous group might mean our failure of early detection of the recurrence of hepatic metastases. It is necessary to make steady efforts such as introducing regular follow-up imaging of colorectal cancer. The median interval between the primary operation and liver metastasis resection was 15.7 months in the lymph node involvement group and 37.7 months in the no lymph node involvement group. In 19 patients among 21 metachronously resected patients, the hepatic resection was done within three years. In conclusion, it was considered that hepatectomy could be done safely, that detection of an earlier lesion could improve the surgical results, and that follow-up for liver metastasis should be done intensively between 12 and 36 months after colorectal cancer surgery.

Key words : Colorectal cancer — Follow-up — Hepatic resection — Liver metastasis — Prognostic factors

The effectiveness of hepatic resection for metastatic colorectal cancer is well established,[1] but many factors that influence the prognosis after hepatic resection still remain controversial, even though the prognostic importance of various patient and tumor variables have been evaluated by many authors.[1-3]

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Furthermore, intensified follow-up for hepatic metastasis could theoretically lead to earlier detection and higher resectability of liver lesions, resulting in a better prognosis for patients. However, it is unknown if, or to what extent, follow-up after resection of colorectal cancer benefits the patient, and its value has been questioned.[4-7]

In this retrospective study, we examined the surgical results of liver metastasis resection in our patients and then analyzed the prognostic factors of curative hepatic resection cases in detail. In addition, the median interval between the primary colorectal cancer operation and liver metastasis resection, and the accumulated percentage of liver metastasis resections according to the interval in a metachronous group were analyzed to find a clue to earlier detection of hepatic metastasis.

PATIENTS AND METHODS

A total of 1,484 patients underwent operation for colorectal cancer at the Kawasaki Medical School Hospital during the 26-year period from December 1974 to December 2000. Metastases were simultaneously found in 153 of the patients (10.3%) at the time of hospitalization for the colorectal cancer surgery. In 70 of 1,331 patients (excluding the above-mentioned 153 patients, 5.3%), the metastases were discovered during the follow-up period after the first operation for colorectal cancer. A total of 223 patients (15.0%) out of the 1,484 who underwent colorectal cancer surgery developed liver metastasis.

The intervals and selected diagnostic tests for follow-up were different at the time of performance of the first operation because of the long duration of this study. The patients were seen at least three times a year during the first three year after surgery, and were seen annually after that. They underwent blood chemistry tests and the carcinoembryonic antigen (CEA) assay after that, with other diagnostic tests; i.e., ultrasonography (US) and computed tomography (CT), being employed when necessary.

Hepatic resections were performed in 51 out of 223 metastasized patients (22.9%). There were 37 males and 14 females, ranging in age from 38 years old to 84 years old. Hepatic resection was done simultaneously at the time of the first operation for colorectal cancer in 28 out of 153 metastasized patients (18.3%, synchronous group) and during the follow-up period in 23 out of 70 metastasized patients (32.9%, metachronous group). No patients died within 30 days after liver resection, but two patients died in the hospital without discharge. Hepatic resection was judged to be a non-curative operation in five patients by a postoperative pathological examination. Tumor cells were clearly observed on the cut surface of the resected specimen in three patients. In two patients, positive nodal metastasis was found in a lymph node picked up beyond the nodal dissection area.

As factors influencing the prognosis after hepatic resection, we selected seven factors; that is, the time of diagnosis of liver metastasis, the type of liver resection, the number of liver metastases, the size of the liver metastasis, the location of the primary colorectal cancer, histopathological differentiation of the colorectal cancer, and nodal metastasis at the time of

the colorectal cancer operation. The analysis of these factors was done using 44 curatively-resected cases.

The grouping of each prognostic factor selected and the number of patients are shown in Table 1. The factor "time of diagnosis of liver metastasis" includes a synchronous group and a metachronous group. As for the factor "type of liver resection", it was divided into minor and major types of resection. The minor types included partial hepatic resection and segmentectomy. Major ones were lobectomies with or without added partial hepatic resection. Partial resection was performed in 20 patients, segmentectomy in 10, and lobectomy with or without partial resection in 14 (right lobectomy in five, left lobectomy in eight and left lobectomy with partial resection in one). Nine patients also received hepatic arterial infusion chemotherapy after surgery. In addition, two patients underwent hepatic resection twice and one patient underwent partial lung resection for pulmonary metastasis in the metachronous group. As for the "number of metastases", which was detected by US and/or CT, patients with more than two metastases were grouped into the multiple group (two metastases in five patients, three in two, five in one and six in one). As for the "size of liver metastasis", patients with lesions of 2 cm or less than 2 cm were grouped into the small group. The largest size was employed when liver metastases were multiple. As for the "location of the primary colorectal cancer", cancer developed in the cecum (one patient), ascending colon (three), transverse colon (one), descending colon (two), and sigmoid colon (10). Primary rectal cancer developed in Rs (four patients), Ra (14) and Rb (nine) according to the rules of the Japanese Society for Cancer of the

TABLE 1. Prognostic factors analyzed, grouping of each factor and number of patients

Prognostic factor	grouping	No. of pts.
Time of diagnosis of liver metastasis	Synchronous G	23
	Metachronous G	21
Type of liver resection	Minor G	30
	Major G	14
Number of liver metastasis	Single G	34
	Multiple G	10
Size of liver metastases	Small G (≦2 cm)	15
	Large G (>2 cm)	28
	Unknown	1
Location of PCC	Colon G	17
	Rectal G	27
Histopathological differentiation of PCC	Well G	16
	Mod G	27
	Poor G	1
Nodal metastases at the time of PCC operation	N(+)G	26
	N(−)G	18

No. of pts. : number of patients, PCC : primary colorectal cancer, N(+) : nodal metastasis positive, N(−) : nodal metastasis negative

Colon and Rectum.[8] Tumors were histologically differentiated into three groups ; that is, well-, moderately- and poorly-differentiated adenocarcinomas. As for "nodal metastasis at the time of the colorectal cancer operation", patients were grouped into a negative group (N(−)) and a positive group (N(+)). The accumulated percentage of liver metastases according to the interval between the primary colorectal cancer operation and liver metastasis was also demonstrated in the metachronous group.

Survival time was calculated from the date of hepatic resection until death. Postoperative cumulative survival (PCS) curves and rates were calculated by the Kaplan-Meier method. The log rank test was used to compare the survival curves. Statistical analysis fo PCS rates for each year was done by the Z-test, and the Mann-Whiteney U-test was used for other variables. Statistical analysis was performed using StatView for Macintosh, version 5.0. $P<0.05$ was considered to be significant.

RESULTS

The overall survival of all patients and curatively-treated patients (Fig 1)

The overall PCS rates of all pateints (n=51) were 80.7% at one year, 40.6% at three years and 20.8% at five years. Five patients undergoing non-curative resection died within 17.0 months with a mean survival of 7.8 months. The overall PCS rates of 44 patients excluding in-hospital death and non-curative resection patients were 85.9% at one year, 44.9% at three years and 23.0% at five years. There was no significant difference in PCS curves and PCS rates between the two groups.

Analysis of prognostic factors

Time of diagnosis of liver metastasis (Fig 2)

Among these 44 patients, 52.3% belonged to the synchronous group and 47.7% belonged to the metachronous group. The PCS rate in the

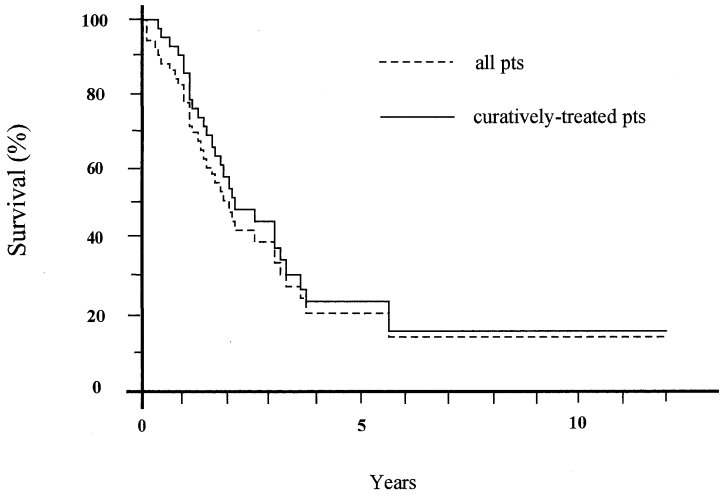

Fig 1. Cumulative survival of all 51 patients and 44 curatively-treated patients. The difference between the two groups was not significant (P=0.508). pts : patients

synchronous group was 90.9% at one year, 51.4% at three years and 26.4% at five years. The PCS rate in the metachronous group was 80.4% at one year, 37.6% at three years and 18.8% at five years. There was no significant difference in PCS curves and rates between the two groups.

Type of operation (Fig 3)

Among all 44 patients, 68.2% underwent minor resection and 31.8% underwent major resection. Among the 23 patients in the synchronous group, minor operations were performed on 19 (82.6%) and major operations on 4 (17.4%). Among the 21 patients in the metachronous

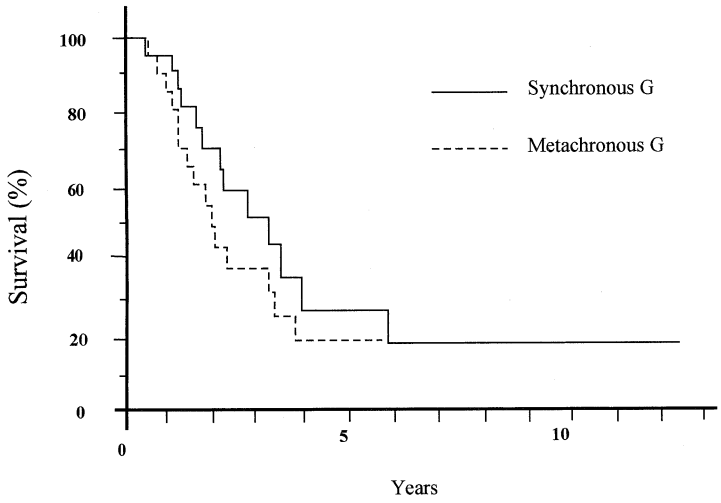

Fig 2. Cumulative survival after hepatic resection according to time of diagnosis of liver metastasis. There was no significant difference between the two groups (P=0.262).

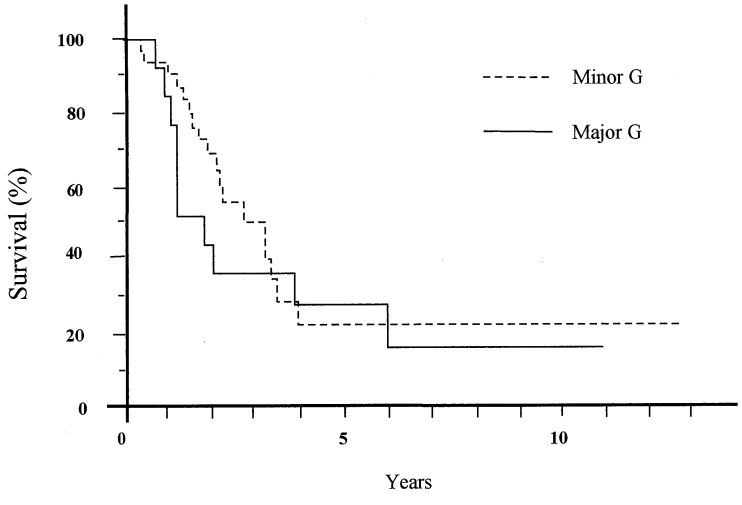

Fig 3. Cumulative survival after hepatic resection according to types of operation. No significant difference was observed between the two groups (P=0.448).

group, minor operations were performed on 10 (47.6%) and major operations on 11 (52.4%). The PCS retes in the group with minor operations were 90.0% at one year, 48.7% at three years and 19.5% at five years. The PCS rates in the major resection group were 75.5% at one year, 33.6% at three years and 25.2% at five years. There was no significant difference in PCS curves and rates between the two groups.

Number of liver metastases (Fig 4)

Among the 44 patients, 77.3% had a single metastasis while 22.7% had multiple metastases. The PCS rates of patients in the single group were 91.0% at one year, 50.3% at three years and 28.3% at five years. The PCS rates of those in the multiple group were 66.7% at one year, 20.0% at three years and 0.0% at five years. The difference in the PCS curves was statistically significant between the two groups.

Size of liver metastases (Fig 5)

The mean diameter of the liver metastasis in 43 patients using the largest size in the cases of multiple metastatic lesions was 3.3 cm, and ranged from 0.8 cm to 8.0 cm. One case was excluded from this analysis because the exact size was unknown. The PCS rates in the small group were 93.3% at one year, 63.6% at three years and 32.7% at five years. The PCS rates in large lesion group were 84.9% at one year, 33.4% at three years and 16.7% at five years. There was a statistically significant difference in the PCS curves between the two groups.

Location of primary colorectal cancer (Fig 6)

Regarding the location of the primary colorectal cancer, it was in the colon in 38.6% of the 44 patients and in the rectum in 61.4%. The PCS

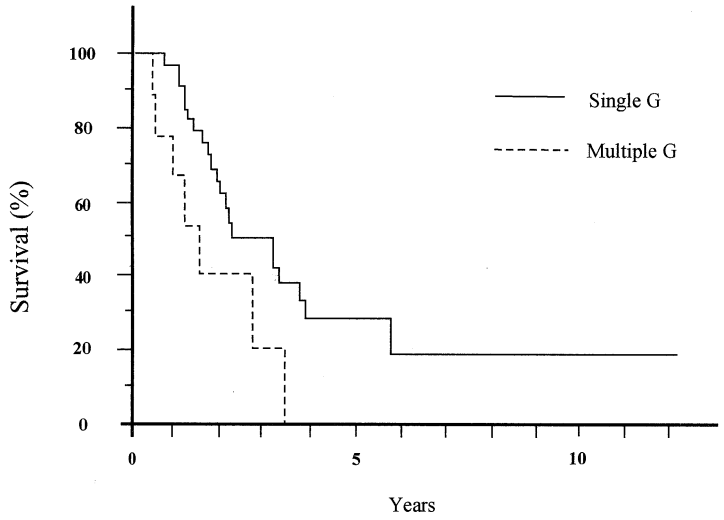

Fig 4. Cumulative survival after hepatic resection according to number of metastases. A significant survival advantage existed for the patients with a single lesion compared with those with multiple lesions (P=0.043).

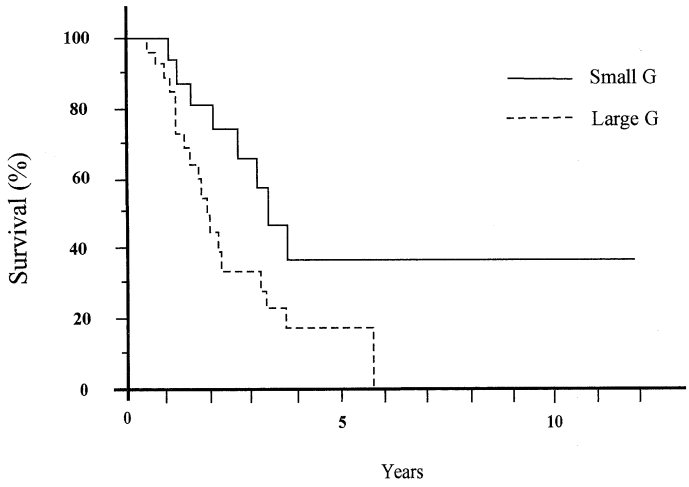

Fig 5. Cumulative survival after hepatic resection according to size of the liver metastasis. A significant survival advantage was noted for the patients with a small lesion compared with those with a large lesion (P=0.043).

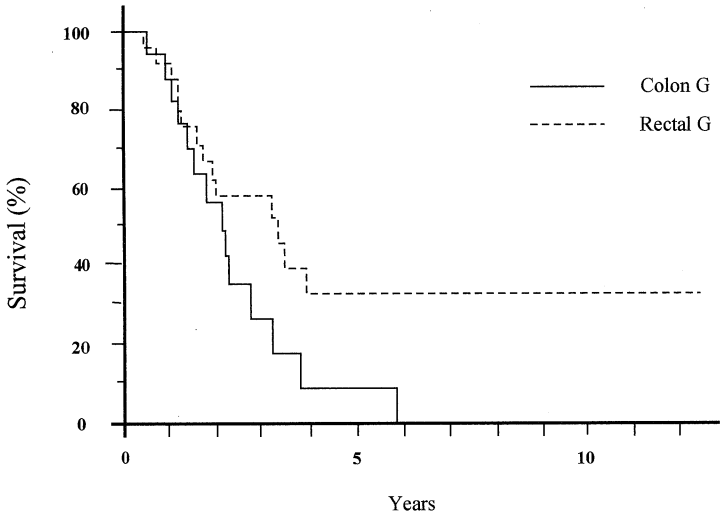

Fig 6. Cumulative survival after hepatic resection according to location of the primary colorectal cancer. There was no significant difference between the groups (P= 0.079).

rates in the colon group were 82.4% at one year, 26.6% at three years and 8.9% at five years. The PCS rates in the rectal group were 88.3% at one year, 57.9% at three years and 33.1% at five years. There was no statistically significant difference in PCS curves and rates between the two groups.

Histopathological differentiation of primary colorectal cancer (Fig 7)

Only one patient belonged to the poorly-differentiated group. The patient was then excluded from the analysis. Of the 43 remaining patients,

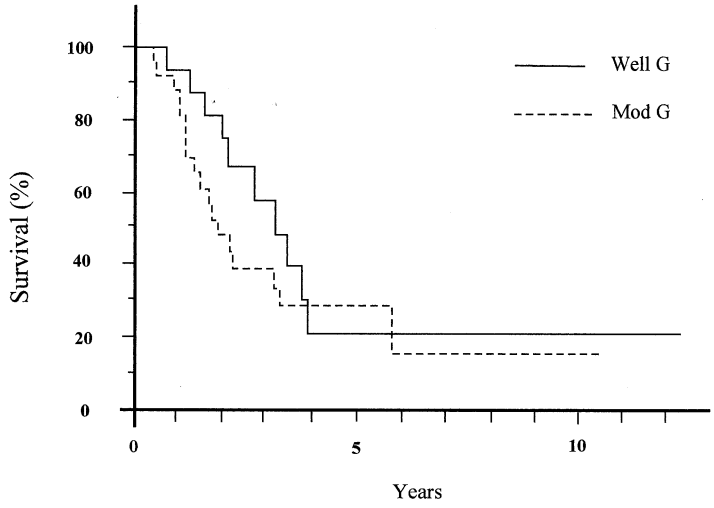

Fig 7. Cumulative survival after hepatic resection according to histopathological differentiation of colorectal cancer. There was no significant difference between the two groups (P=0.313).

37.2% were in the well-differentiated group and 65.1% were in the moderately-differentiated group. The PCS rates in the well-defferentiated group were 93.8% at one year, 56.4% at three years and 18.8% at five years. The PCS rates in the moderately-differentiated group were 80.3% at one year, 37.1% at three years and 26.5% at five years. No significant difference was observed in the PCS curves and rates between the two groups.

Nodal metastasis of primary colorectal cancer

Of the 44 patients, 40.9% belonged to the N(−) group and 59.1% to the N(+) group. The PCS rates in the N(−) group were 100.0% at one year, 65.7% at three years and 29.6% at five years. The PCS rates in the N(+) group were 76.0% at one year, 30.2% at three years and 18.1% at five years (Fig 8-1). There was a significant difference in the PCS curves (P=0.042). In the synchronous group, the number of N(−) patients was 10 (43.5%) and the number of N(+) patients was 13 (56.5%). The PCS rates for the N(−) patients of group were 100.0% at one year, 74.1% at three years and 39.5% at five years (Fig 8-2). The PCS rates for the N(+) group were 83.3% at one year, 28.8% at three years and 14.4% at five years. The N(−) group appeared to heve a significantly improved survival rate when compared to the N(+) group, though these differences were not statistically significant (P=0.073). In the metachronous group, the number of N(−) patients was eight (38.1%) and the number of N(+) patients was 13 (61.9%). The PCS rates for the N(−) group were 100.0% at one year, 51.4% at three years and 17.1% at five years (Fig 8-3). The PCS rates for the N(+) group were 69.2% at one year, 30.8% at three years and 20.5% at five years. There was no significant difference in the PCS curves, but there was one in the PCS rates at one year in the metachronous group.

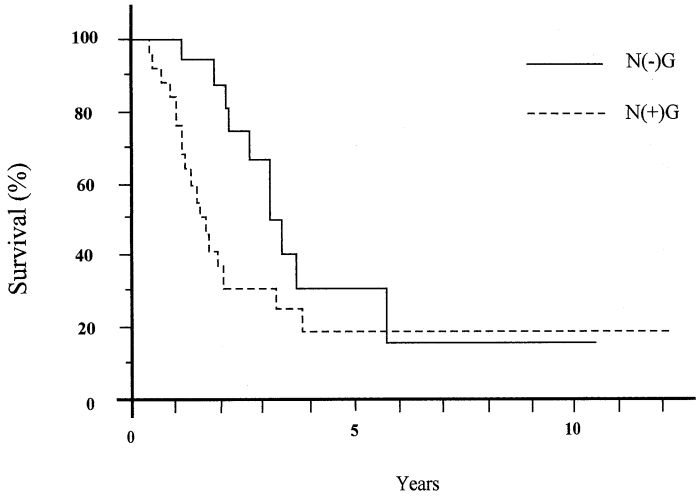

Fig 8-1. Cumulative survival after hepatic resection according to nodal metastases at the primary colorectal cancer operation. There was significant differnce between the PCS curves (P=0.042). N(−): nodal metastasis negative group, N(+): nodal metastasis positive group

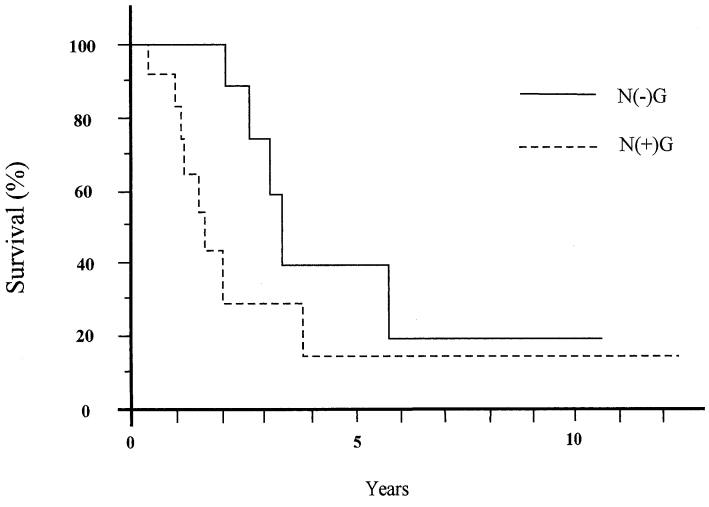

Fig 8-2. Cumulative survival after hepatic resection according to nodal metastases of the primary colorectal cancer in the synchronous group. The N(−) group appeared to have a significantly improved survival rate when compared to the N(+) group, though these difference was not statistically significant (P=0.073). N(−): nodal metastasis negative group, N(+): nodal metastasis positive group

Interval between primary colon cancer operation and liver metastasis resection in the metachronous group

The interval between the colorectal cancer operation and hepatic resection in the metachronous group ranged from 5 months to 110 months with a median interval of 17.0 months. With lymph node involvement, the median interval between the colorectal cancer operation and hepatic

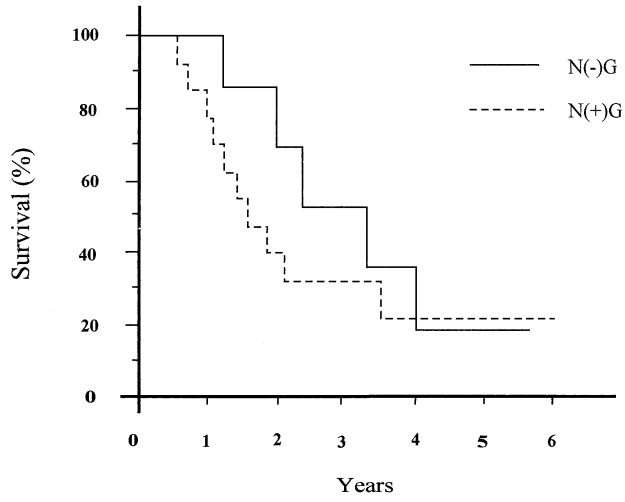

Fig 8-3. Cumulative survival after hepatic resection according to nodal metastases of the primary colorectal cancer in the metachronous group. There was not significant difference between the PCS curves (P=0.368), though there was a significant difference in the PCS rate at one year only (P=0.016). N(−) : nodal metastasis negative group, N(+) : nodal metastasis positive group

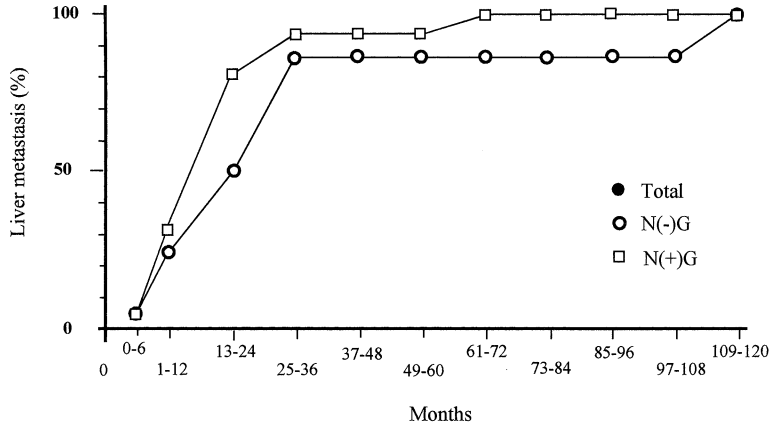

Fig 9. Accumulated percentage of liver metastasis in the metachronous group according to the interval between the primary colorectal cancer operation and liver metastasis resection. N(−) : nodal metastasis negative group, N(+) : nodal metastasis positive group

resection for liver metastasis was 37.7 months in the N(−) group and 15.7 months in the N(+) group. There was a statistical difference in the interval between the two groups. The accumulated percentage of liver metastases in the resected cases according to the interval between the primary coloretal cancer operation and hepatic metastasis resection is shown in Fig 9. Nineteen out of a total of 21 patients (90.5%) were operated on within the first three years for the treatment of hepatic metastasis.

DISCUSSION

It is natural to consider that complete removal of hepatic metastases is the goal of the treatment in patients with metastatic liver tumors. Many authors reported a five-year survival rate of 16-52.1% after hepatic resection in patients with colorectal hepatic metastasis.[1,9-14] The rate was 23% in our series of curatively resected patients. Table 2 shows a literature survey on a five-year survival rate of more than 30% in an individual institution or in personal experience during the last 20 years. The best survival rate of 52.1% was reported by Iwatsuki *et al*[12] in 1983. However, this report was based on the results for 24 very carefully selected patients. His colleagues, Gayowski *et al*,[15] reported a rate of 32% for 204 patients in 1994. In reported series of over 100 cases, the best survival rate of 38% was reported by Minagawa *et al*.[9] Their two selection criteria for surgery were removal of all gross diseases and preservation of at least 40% of the normal parenchyma of the liver. These favorable reports may encourage surgeons to treat this condition.

There is still controversy regarding which factors have a significant influence on a patient's prognosis after hepatic resection.[3,15] As for the hepatic lesion factors in our series, a better prognosis was obtained for patients with single lesions and small lesions (≦2 cm) on univariate analyses. As for the primary colorectal cancer factors in this study, a better prognosis was obtained in patients with no lymph node involvement and those with rectal cancer on univariate analyses. These factors excluding the location of the tumor indicate that the primary and/or metastatic hepatic tumor was at a less advanced atage.[15,16] The time of diagnosis of liver metastases, the type of liver resection, and the histopathological differentiation of colorectal cancer did not affect the prognosis of patients after hepatic resection. Our data demonstrate that less advanced hepatic metastasis in the liver and less advanced primary colorectal cancer, i.e. no nodal metastasis, are beneficial prognostically in treating patients with either synchronous or metachronous liver metastasis. Futhermore, our data also showed that hepatectomy for liver metastasis could be done without any increasing risks of surgery if it was thought to be technically feasible.[9]

In the present study, prognosis was not significantly different between

TABLE 2. Literature survey on a 5-year survival rate of more than 30%

Investigators	Publication	No. of patients	Survival rate		Operative Mortality
			3-year	5-year	
Iwatsuki S, *et al* [12]	1983	24	73*	52.1*	0
Butler J, *et al* [14]	1986	62	50**	34**	10
Doci R, *et al* [13]	1991	100		30*	5
Nakamura S, *et al* [11]	1992	31	44.7**	44.7**	0
Gayowski TJ, *et al* [15]	1994	204	43**	32**	0
Shirabe K, *et al* [3]	1997	31	42**	39**	
Minagawa M, *et al* [9]	2000	235	51**	38**	0
Seifert JK, *et al* [2]	2000	120		31**	5.8

* : actuarial survival, ** : cumulative survival

the synchronous and metachronous groups, and unlike other studies,[17,18] it was slightly better in the synchronous group than in the metachronous group. The mean diameter of metastatic lesions in the liver was 2.5 cm in the synchronous group and 4.5 cm in the metachronous group, the difference being significant ($p=0.0005$). The present study demonstrated that the prognosis of hepatic metastases of large diameters was poor, causing poor prognoses in the metachronous group. The presence of tumors with large diameters in the metachronous group might mean our failure of early detection of the recurrence of hepatic metastases, which is a problem we must reconsider. It is necessary to make steady efforts such as introducing regular follow-up imaging of colorectal cancer.

To detect resectable and curable samaller hepatic metastases effectively, the incidence and growth rate of metastatic hepatic tumors should be known. However, the detailed natural history of the colorectal cancer still remains unclear. In our series, 10.3% of the patients had synchronous hepatic metastasis and 5.3% developed hepatic metastases after resection of the primary tumor; that is, a total of 15.6% of the patients had liver metastasis. The reported incidence of the liver metastasis was 12%-25% in synchronously detected groups and 8%-16% in metachronously detected groups.[5,15,19-22] The distinction between the synchronousness and metachronousness of liver metastasis depends only on the detection time of this condition. A chronological analysis of the onset of liver metastasis showed the largest number of metastases to be present at the time of the primary colorectal cancer operation.[19,23] For preoperative assessment of hepatic metastasis, CT is the most often used and most reliable modality, but the tumor detection rate depends mainly on the size of the metastatic lesion, which leads to frequent non-detection of a lesion smaller than 1.0 cm in diameter.[19,24,25] At present, it is extremely difficult to identify lesions smaller than 0.5 cm in diameter by any modalities that are available.[26] Nomura *et al*[27] reported that the rumor doubling time of hepatic metastasis from colorectal cancer ranged from 45.5 days to 150.5 days, with a mean of 92.4 days ($\pm$29.4). On the basis of this growth rate, a 0.5 cm metastatic tumor in the liver would be calculated to grow to 1.24 cm at 12 months, 3.10 cm at 24 months and 7.73 cm at 36 months. The tumor size by this calculation suggests that an overlooked 0.5 cm lesion would be hard to detect within one year, but would be generally detected within 36 months.

In the metachronous group of our series, almost all of the patients had hepatic resections within three years after the primary colorectal cancer operation. A report by the American Society of Clinical Oncology stated that the majority of recurrences in patients who have undergone a complete resection of a colorectal cancer will occur within five years, and usually within three years of surgery.[28] Schoemaker *et al*[5] demonstrated that a yearly CT scan within five years after surgery resulted in earlier detection of metastatic nodules but did not increase the number of curative hepatecomies. Savio *et al*[29] reported that liver US performed intensively between 15 and 36 months after surgery was useful in the early detection of hepatic metastasis. Considering these reports and our data, the time between 12 and 36 months after the primary colorectal cancer operation should be focused on in order to detect curable and resectable hepatic

metastasis and to improve the cost-effectiveness of follow-up programs. In addition, we found that the median interval between the primary colorectal cancer operation and liver metastasis resection was 15.7 months in patients with lymph node involvement and 37.7 months in patients without lymph node involvement. Therefore, follow-up of the liver by imaging modalities should be begun intensively in the lymph node positive group at 12 months after surgery to indentify hepatic recurrences as early as possible.

In conclusion, it was considered that hepatic resection could be done safely, that earlier detection of hepatic metastasis could improve surgical results, and that intensive follow-up for liver metastasis should be done between 12 and 36 months after colorectal cancer surgery. However, the value of an intensive folllow-up system for liver metastasis has not yet been established in prospective studies.

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