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Repeat Hepatectomy for Recurrent Colorectal Metastases

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Abstract. Recurrence rates after hepatic resection in patients with colorectal metastases are reported to range from 47% to 80%. Hepatic recurrence is seen in 35% to 50% of patients. Aggressive surgical resection appears to be a worthwhile treatment in patients with recurrent hepatic metastases to promote longer patient survival because surgical resection remains the only curative therapy available. This is a retrospective review of our experience with 15 patients undergoing repeat hepatic resection culled from 67 patients undergoing initial hepatectomy for metastatic colorectal cancer. Of 67 patients who underwent hepatectomy for colorectal hepatic metastases, 33 developed hepatic recurrence at a median interval of 23 months (range 1–176 months) after the first hepatectomy. The second hepatectomy was performed in 15 patients 5 to 29 months after the first hepatectomy, with no mortality. The mean operating time and blood loss at the second hepatectomy were similar to those at the first hepatectomy. The mean hospital stay at the second hepatectomy was significantly shorter than that at the first hepatectomy. The cumulative survival rate for the 15 patients was 42.4% at 3 years and 21.2% at 5 years, respectively, which compared favorably with the survival rate of the 67 patients who underwent initial hepatectomy. Patients who underwent the second hepatectomy had significantly higher survival rates from the first hepatectomy than the 18 patients with unresectable hepatic recurrence. Repeat hepatectomy can be performed safely and provides long-term survival rates similar to those of first hepatectomies. In appropriately selected patients, repeat hepatectomy for colorectal metastases is a worthwhile treatment.

Hepatic metastasis from colorectal cancer carries a poor prognosis without surgical intervention. Although hepatectomy is generally considered the only mode of curative treatment available for patients with colorectal liver metastases, recurrence occurs in more than 60% of the patients, the liver being the most common location [1]. A further attempt at repeat hepatic resection seems justified in these patients because surgical resection remains the only form of treatment that can extirpate all the cancer lesions detected.

Since the late 1980s, several articles have been published on the subject of repeat hepatectomy for recurrent colorectal hepatic metastases [2–8]. Most of these articles, however, were based on the experience of only small numbers of patients, and so it is difficult to evaluate these studies in terms of the risk of the procedure and the expected benefit of long-term survival. We have reviewed our institutional experience to assess the survival benefits of patients undergoing repeat hepatectomy for colorectal metastases.

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Patients and Methods

From April 1985 to February 1997 a total of 69 patients underwent hepatic resection for colorectal hepatic metastases at the First Department of Surgery, Nara Medical University. There were two postoperative hospital deaths at the time of the first hepatectomy. Of the remaining 67 patients who were discharged from the hospital, 33 developed hepatic recurrence, detected 1 to 176 months (median 23 months) after the first hepatectomy. Of the 33 patients, 15 underwent repeat hepatectomy for recurrence and were enrolled in this retrospective study.

The eight women and seven men ranged in age from 43 to 78 years (median 63 years) at the time of the second hepatectomy. A summary of these patients is presented in Table 1. The location of the primary tumors was the rectum in eight patients and colon in seven patients. Original Dukes' stage was B in 4 patients and C in 11 patients. The first liver metastases were synchronous with the primary tumor in nine patients and metachronous in six patients. Seven patients had a solitary liver metastasis, and eight had multiple hepatic metastases. Resection of the primary and metastatic liver tumors had been considered curative in all cases.

After hepatic resection, all patients were followed closely using ultrasonography, computed tomography scanning, magnetic resonance imaging, and measurement of the serum levels of carcinoembryonic antigen and carbohydrate antigen. If metastatic liver tumors were detected after the first hepatectomy, the patient was carefully examined and found to be free of extrahepatic disease. Whenever it was considered that the recurrent tumors might be resectable, clinical status and liver function were deemed adequate measures.

In each patient the clinical and pathologic data were analyzed retrospectively. The data included operating time, blood loss, duration of hospital stay, site and stage of the primary lesion, nature and treatment of the first and recurrent hepatic metastases, and cumulative survival rate.

Another group of 18 patients with unresectable recurrent hepatic tumors comprised the historical control group for comparison of the survival rate. These patients had either multifocal

Table 1. Characteristics of patients and their initial hepatic resection.

Patient no.	Age/sex	Location of primary	Dukes' stage	Initial resection timing	Liver nodules	Initial resection type	Margins (mm)
1	63/M	Rectum	B	Synchronous	2	Wedge	<10
2	67/F	Rectum	C	Synchronous	1	Wedge	<10
3	66/F	Colon	C	Metachronous	1	Anatomic	12
4	67/M	Rectum	C	Metachronous	1	Anatomic	15
5	46/F	Rectum	C	Synchronous	2	Wedge	12
6	45/M	Rectum	C	Metachronous	1	Anatomic	15
7	56/F	Colon	C	Metachronous	2	Wedge	<10
8	48/F	Rectum	C	Synchronous	7	Wedge	<10
9	68/F	Colon	C	Metachronous	1	Wedge	<10
10	69/M	Colon	B	Synchronous	2	Wedge	<10
11	44/F	Rectum	C	Synchronous	2	Wedge	15
12	78/M	Colon	C	Synchronous	1	Anatomic	10
13	43/M	Rectum	B	Synchronous	3	Wedge	<10
14	69/M	Colon	C	Synchronous	8	Wedge	<10
15	53/F	Colon	B	Metachronous	1	Wedge	<10

Table 2. Operating time, blood loss, and hospital stay.

Parameter	Second hepatectomy ($n = 15$)	Initial hepatectomy for metachronous tumors ($n = 24$)	p
Operating time (min)	229.8 ± 76.8	268.8 ± 72.1	NS
Blood loss (ml)	1331.4 ± 785.2	1678.4 ± 1410	NS
Duration of hospital stay (days)	53.3 ± 18.5	80.0 ± 24.4	0.029

hepatic metastases or associated unresectable extrahepatic disease.

Furthermore, for a comparison of the operating time, blood loss, and duration of hospital stay, we selected a group of 24 patients who underwent an initial hepatectomy without simultaneous resection of the primary lesion. Patients who underwent synchronous resection of the primary lesion and metastases were excluded from this group because synchronous resection of the primary lesion and metastases were excluded from this group because synchronous resection affects operating time, blood loss, and duration of hospital stay. In this group, anatomic resection was carried out in 16 patients, and wedge resection was performed at eight hepatectomies. Twelve complications (50%) occurred at the first hepatectomy in 12 patients of this group.

Data were expressed as the mean ± SD. Values for operating time, blood loss, and duration of hospital stay were analyzed by Student's *t*-test. Survival curves after hepatic resection were obtained by the Kaplan-Meier method. Survival curves were compared by the log-rank test. A value of $p < 0.05$ was considered significant.

Results

There were no 30-day operative mortality or postoperative hospital deaths in 15 patients. Reversible complications occurred in three patients, consisting of two superficial wound infections and a subphrenic abscess. Operating time, blood loss, and hospital stay are summarized in Table 2. The mean operating time and blood loss at the second hepatectomy were 229.8 ± 76.8 minutes and 1331.4 ± 785.2 ml, respectively. These values were not significantly different from those at the first hepatectomy. The mean hospital stay at the second hepatectomy was significantly shorter than that at the first hepatectomy.

The anatomic resection was performed in 2 patients and wedge resection in 13 patients (Table 3). Ten patients had a solitary hepatic deposit resected; Of these, one patient had a concomitant lung metastasis removed simultaneously. Three patients had two and one patient had three hepatic nodules resected. The mean diameter of the largest tumor was 26 mm (range 15–65 mm). The redo hepatic resection margins were less than 10 mm in 13 patients.

The interval between the first and second hepatectomy was 15 ± 8 months (median 15 months). The follow-up period after the second hepatectomy ranged from 2 to 66 months (median 16 months). During the follow-up period, 8 of 15 patients were noted to have another recurrence after the second hepatectomy. The extrahepatic metastatic site included lung, bone, and intraperitoneal lymph nodes. Two patients underwent partial lung resection and are alive without disease at 66 and 39 months, respectively, after the second hepatectomy. Intrahepatic recurrence after the second hepatectomy was observed in six cases. Of these, one patient underwent the third hepatectomy for hepatic recurrence 10 months after the second hepatectomy.

The median survival time from the second hepatectomy was 16 months, and the 3- and 5-year survival rates were 42.4% and 21.2%, respectively. On the other hand, the overall 3- and 5-year survival rates from the first hepatic resection for 67 patients were 52.7% and 31.7%, respectively. There was no difference between the survival curves for these two groups (Fig. 1).

The overall 1-, 3-, and 5-year survival rates as calculated from the time of the first hepatectomy for 15 patients were 100%, 65.0%, and 37.1%, respectively. In patients with unresectable hepatic recurrence, the 1-, 3-, and 5-year survival rates, calculated from the time of the first hepatectomy, were 77.8%, 32.4% and 0%, respectively. The survival rates were significantly better in the resectable group compared with those of the unresectable group ($p < 0.05$) (Fig. 2).

Discussion

Numerous reports have confirmed that hepatic resection for colorectal metastases has resulted in prolonged survival [9–11].

Table 3. Data for second hepatic resection.

Patient no.	Liver nodules	Resection type	Size of the largest tumor (mm)	Margin (mm)	Interval between liver resections (months)	Outcome after second liver resection/months	Comments
1	2	Anatomic	55	50	16	DOD/15	
2	1	Wedge	20	<10	6	DOD/59	
3	1	Wedge	35	<10	29	DOD/28	
4	1	Wedge	20	25	10	ADF/66	PRL after 2nd hepatectomy
5	1	Wedge	35	<10	12	DOD/23	3rd Hepatectomy 10 months after 2nd hepatectomy
6	1	Wedge	35	<10	12	ADF/39	PRL before and after 2nd hepatectomy
7	1	Anatomic	20	<10	22	ADF/33	
8	2	Wedge	32	<10	20	DOD/16	
9	1	Wedge[a]	27	<10	24	DOD/14	
10	2	Wedge	15	<10	5	DOD/10	
11	1	Wedge	30	<10	25	ADF/18	
12	1	Wedge	65	<10	18	AWD/6	
13	1	Wedge	18	<10	5	ADF/6	
14	3	Wedge	21	<10	13	ADF/5	
15	1	Wedge	35	<10	15	ADF/2	

[a]Combined with partial lung resection.
DOD: dead of disease; ADF: alive, disease-free; AWD: alive with disease; PRL: partial lung resection.

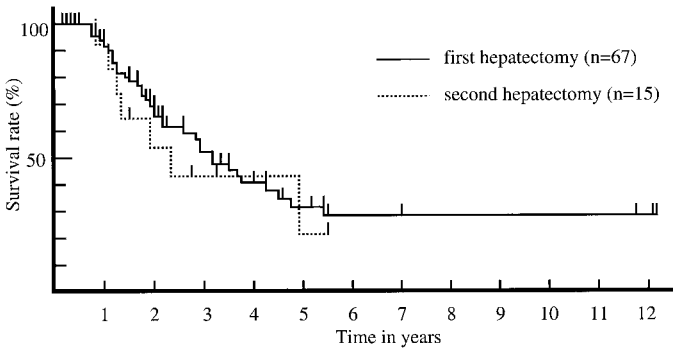

Fig. 1. Survival as measured from the time of the initial hepatectomy for 67 patients who underwent an initial hepatectomy (solid line) and from the time of the second hepatectomy for 15 patients who underwent a second hepatectomy (dashed line). There was no difference between the two groups.

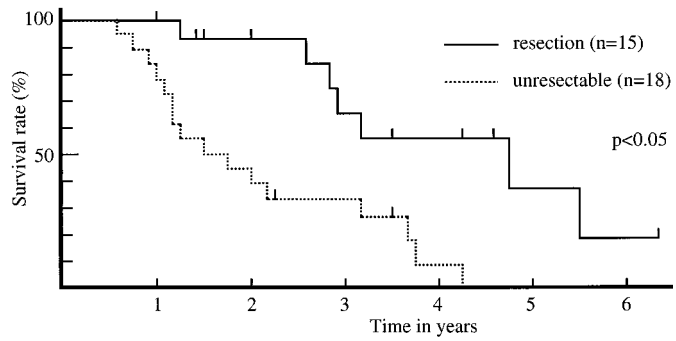

Fig. 2. Cumulative survival curves for recurrent colorectal hepatic metastases after initial hepatectomy of patients with resectable hepatic recurrences (solid line, $n = 15$) or unresectable recurrences (dashed line, $n = 18$). There was a significant difference between the two groups ($p < 0.05$, log rank).

The long-term survival in as many as 38% of patients after hepatectomy was obtained. Unfortunately, the recurrence rates after hepatic resection in patients with colorectal metastases are reported to range from 47% to 80%. Hepatic recurrence occurs in 35% to 50% of patients. An attempt at a second hepatic resection seems justified in patients with hepatic metastases to improve the long-term prognosis.

A number of reports have demonstrated that repeat hepatectomy for colorectal metastases is a safe, effective mode of treatment in selected patients [2–8]. Morbidity, mortality, and survival rates seem to be comparable with those after the initial hepatic resection.

Some may think that intraoperative bleeding increases with repeat hepatectomy compared with primary resection. Indeed, some authors reported an increased risk of bleeding after repeat hepatectomy [12, 13]. It is difficult to expose the operative field because of the adhesions on the raw surface of the previous hepatectomy. In our present series, the amount of blood loss at the second hepatectomy was not markedly different from that at the first hepatectomy. Furthermore, the operating time at the second hepatectomy was similar to that at the first hepatectomy. It must be taken into account that more wedge resections versus anatomic resections were performed at the second hepatectomy in our series.

In respect to the hospital stay, some authors have reported that the mean hospital stay at the second hepatectomy was similar to that at the first hepatectomy. It is obvious that the mean hospital stay in our series was longer than that in other published data from Western countries. However, a comparison of the hospital stay at the first and second hepatectomy in our series showed a clear advantage of the second hepatectomy. Postoperative complications were seen less frequently at the second hepatectomy than at the first hepatectomy (20% versus 50%). It was considered that a low incidence of postoperative complications was attributable to the shorter hospital stay at the second hepatectomy.

Regular follow-up using a combination of diagnostic methods

after hepatectomy plays a significant role in detecting recurrent tumors that may be resectable. If the second hepatectomy is planned, a thorough investigation to rule out extrahepatic recurrence is essential. Intraoperative evaluation is also necessary to detect occult metastatic deposits. All the patients who had repeat hepatectomy in our series had undergone intraoperative ultrasonography.

The results of the current study compared favorably with those from previously published reports. The overall 3- and 5-year survival rates for our 15 patients after the second hepatectomy were 42.4% and 21.2%, respectively. Others have reported figures of 30% to 60% and 11% to 41%, respectively [14–17]. In our series the survival curve after the second hepatectomy was not significantly different from that after the first hepatectomy. Other published series also showed equivalent survival results when comparing initial and second hepatectomies for isolated colorectal metastases. These results suggest that in selected patients recurrent hepatic metastases can still be treated efficaciously by means of repeat hepatectomy, just as they benefited from the first hepatectomy for the initial hepatic metastases.

It is difficult to conduct a randomized controlled study comparing surgical resection and no treatment for resectable recurrent colorectal hepatic metastases. In our series, although the background of the patients treated with repeat hepatectomy was not identical to that of the patients who did not undergo surgical treatment, the survival rate after the first hepatectomy was significantly better in the former group than in the latter.

Our criteria for selecting patients for repeat hepatectomy were basically the same as those used to select the first-time candidate. Some authors believe that the number of metastases should be limited [6, 12]. This conflicts with our opinion. We consider that patients who have multiple metastases are candidates for repeat resection if the lesions are technically resectable. In a series of 170 patients Fernández-Trigo et al. [14] reported there was no significant difference in survival according to the number of liver metastases at the second hepatectomy. Adam et al. [15], in a series of 64 patients, found that the number of tumors was not significant on multivariate analysis for survival after the second resection. In our experience, patients presenting with synchronous extrahepatic disease are not good candidates for repeat hepatectomy. Of the 15 patients in our series, 3 underwent pulmonary resection for lung metastases. One patient who had concomitant lung metastases died from recurrent disease 10 months from the time of the second operation. The other two patients who underwent pulmonary resection are alive and have been disease-free for 66 and 39 months, respectively, after the second hepatectomy. The patients who presented with extrahepatic disease remain a challenge.

Conclusions

Fifteen patients underwent repeat hepatectomy for recurrent colorectal hepatic metastases with no operative mortality, minimal morbidity, and long-term survival. We concluded that repeat hepatectomy is a safe, effective treatment in selected patients.

Résumé

La fréquence globale des récidives après résection hépatique pour métastases colorectales varie de 47 à 80%. La récidive de métastases hépatiques est notée chez 35% à 50% des patients. La résection chirurgicale est indiquée chez le patient ayant une récidive de métastase hépatique chaque fois que possible car la chirurgie agressive reste le seul geste thérapeutique à visée curatrice actuellement disponible. Cette revue rétrospective concerne 15 patients ayant eu une résection itérative de métastase(s) hépatique(s) parmi 67 patients ayant eu une hépatectomie pour métastase(s) d'origine colorectale. Parmi ces 67 patients, 33 ont développé une récidive hépatique après un délai médian de 23 (extrêmes 1–176) mois après la première résection hépatique. La deuxième résection hépatique a été réalisée entre 5 et 29 mois après la première sans aucune mortalité. La durée moyenne de l'intervention et les pertes sanguines lors de la deuxième hépatectomie étaient similaires à celles de la première résection. La durée moyenne du séjour à l'hôpital de la deuxième résection était significativement plus courte qu'après la première. La survie cumulative des 15 patients étaient, respectivement, de 42.4% à 3 ans et de 21.2% à 5 ans, ce qui compare favorablement avec la survie des 67 patients qui ont eu leur résection de première intention. La survie des patients qui ont eu une deuxième résection était significativement plus élevée que celle des 18 patients dont la récidive n'étaient pas resécable. L'hépatectomie itérative peut être effectué avec sécurité et donne une survie à distance comparable à la première résection. La résection hépatique itérative pour métastase(s) hépatique des cancers colorectaux est une thérapeutique valable dans des cas sélectionnés.

Resumen

Las tasas de recurrencia luego de resección hepática en pacientes con metástasis colorrectales oscilan entre 47% y 80%. La recurrencia hepática ocurre entre 35% y 50% de los casos. La resección quirúrgica agresiva parece ser una modalidad terapéutica de valor para el logro de mayor sobrevida en pacientes con metástasis hepáticas recurrentes, por cuanto la resección quirúrgica sigue siendo la única forma disponible de terapia curativa. Este es un estudio retrospectivo de nuestra experiencia con 15 pacientes sometidos a resección hepática repetida, dentro de un grupo de 67 casos que recibieron hepatectomía por cáncer colorrectal metastásico. De estos 67 casos, 33 desarrollaron recurrencia hepática en un intervalo promedio de 23 meses (rango 1–176), luego de la hepatectomía inicial. La segunda hepatectomía fue practicada en 15 pacientes a los 5 y 29 meses después de la primera, sin mortalidad. El tiempo operatorio promedio y la pérdida de sangre en la segunda hepatectomía fueron similares a los de la primera, pero el promedio de la hospitalización fue menor en la segunda. La tasa acumulativa de supervivencia de los 15 pacientes fue 42.4% a 3 años y 21.2% a 5 años, lo cual se compara favorablemente con la tasa de supervivencia de los 67 pacientes que recibieron la hepatectomía inicial. Los pacientes sometidos a la segunda hepatectomía exhibieron tasas de sobrevida significativamente superiores luego de la primera hepatectomía, en comparación con los 18 pacientes con recurrencia no resecable. La hepatectomía repetida puede ser practicada en forma segura y resulta en tasas de sobrevida a largo plazo similares a las de las hepatectomías primarias. En pacientes debidamente seleccionados, la hepatectomía repetida por metástasis de cáncer colorrectal constituye una modalidad valiosa de tratamiento.

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Invited Commentary

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Kin and associates report a retrospective review of 15 patients who underwent repeat hepatic surgery for metastatic colorectal cancer to the liver. Their patients came from an initial group of 67 patients who had undergone liver resection for metastatic colorectal cancer. Thirty-three patients developed a hepatic recurrence after the first hepatic resection; fifteen of these patients underwent a successful repeat hepatic resection with a survival rate of 21.2% at 5 years. Their results confirm the findings of other surgeons' experience that repeat hepatic operation for recurrent colorectal liver metastases gives comparable results to first hepatic operations in terms of operative mortality, morbidity, survival, disease-free survival, and patterns of recurrence [1].

In our experience with hepatic resection for colorectal metastases, a successful outcome depends on two key factors: extrahepatic disease and the ability to obtain at least a 1-cm margin around the hepatic tumor. The authors report that 9 of their 15 patients had less than a 1-cm margin after a wedge resection for their initial hepatic resection. Was this a cause for the recurrent tumor that required a second liver resection?

Evaluation of extrahepatic disease may be difficult. The addition of positron-emission tomography (PET) scanning is helpful for evaluating intra- and extrahepatic recurrence. The difference between PET scans and computed tomography (CT) portography, which has high sensitivity, is the improved specificity of the PET scan [2]. Results of PET scanning changed our management in one-fourth of patients considered for a repeat hepatectomy.

The authors do not mention the use of cryoablation. This technique has been useful in conjunction with surgical resection for advanced hepatic tumors and to achieve a more than 1-cm tumor-free margin when standard surgical margins are close [3].

The coeditors of the *Journal of Gastrointestinal Surgery*, Drs. Cameron and Kelly, recently published an editorial on "The Value of Consensus," which referred to a consensus statement on the "Treatment of Hepatic Metastases from Colorectal Cancer." The panel agreed that "given the current state of knowledge, a single, accessible, metachronous metastasis in a good-risk patient with adequate control of the primary lesion and no evidence of extrahepatic disease should be treated with local hepatic resection, whether or not it is symptomatic" [4]. Other patients with hepatic metastasis should be managed by controlled clinical trials based on uniform standards of staging.

Repeat hepatic surgery for colorectal cancer metastasis to the liver has benefited carefully selected patients and may be performed with low mortality and morbidity in centers staffed with experienced hepatic surgeons. A second hepatic resection provides long-term survival results comparable to results of the first hepatic operation. Hopefully, trials can be undertaken as recommended by the consensus panel. I predict that the results will confirm the authors' conclusions regarding repeat hepatectomy for recurrent colorectal metastasis.

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