World J. Surg. 28, 482–487, 2004
DOI: 10.1007/s00268-004-7214-x

WORLD
Journal of
SURGERY

Procedures of Choice for Resection of Primary and Recurrent Liver Metastases from Colorectal Cancer

Kuniya Tanaka, M.D., Ph.D., Hiroshi Shimada, M.D., Ph.D., Mitsuyoshi Ohta, M.D., Ph.D., Shinji Togo, M.D., Ph.D., Shuji Saitou, M.D., Shigeki Yamaguchi, M.D., Ph.D., Itaru Endo, M.D., Hitoshi Sekido, M.D., Ph.D.

Department of Surgery II, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, 236-0004 Yokohama, Japan

Published Online: April 19, 2004

Abstract. Although liver resection offers the only realistic chance of cure for patients with liver metastases from colorectal cancer, no consensus exists as to the procedure of choice for managing these tumors. Data from 193 patients who underwent hepatectomy for liver metastases from colorectal cancer and 26 of 193 patients who underwent repeat hepatectomy for recurrent metastases were collected. The suitability of resection was evaluated retrospectively based on known risk factors for recurrence and patterns of recurrence. On multivariate analysis, a positive surgical margin (SM+) was the only risk factor for recurrence after the initial resection ($p < 0.01$). SM+ ($p < 0.01$) and nonanatomic resection ($p < 0{\cdot}05$) that was less than a sectionectomy ($p < 0.05$) were risk factors for recurrence after repeat hepatectomy. Multiple tumors (four or more) was the most common pattern of recurrence after initial hepatectomy, and recurrence close to the line of resection was most common after repeat hepatectomy. Based on tumor doubling times, recurrence after initial hepatectomy seemed to originate from the primary colorectal lesion, whereas recurrence after repeat hepatectomy was derived from a hepatic metastasis. Retrospective analysis suggests that hepatectomy with clear surgical margins is more important than anatomic resection for initial hepatectomy, and at least sectionectomy is necessary for repeat hepatectomy.

Liver resection is the best available treatment for colorectal cancer metastases to the liver [1–5]. During the early days of hepatic surgery for colorectal metastases, only small, solitary unilobar lesions were resected. With the progress of surgical techniques and improved surgical skills, the indications for hepatectomy were extended to include large tumors, multiple unilateral metastases, and eventually multiple bilobar metastases when they could be removed entirely [6, 7]. Furthermore, several reports have now documented the benefit of repeat hepatectomy for recurrence in the liver remnant [8, 9]. Although general agreement has been reached that resection with a clear surgical margin is adequate for the initial resection, hepatectomy procedures still differ from facility to facility, and no uniform policy has been established. Standardization of procedures for repeat hepatectomy has not previously been attempted.

The current study was undertaken to develop guidelines for resecting primary and secondary liver metastases. We retrospectively analyzed risk factors for recurrence, patterns of recurrence, and estimates of tumor size at the time of colorectal resection based on tumor doubling times.

Correspondence to: Kuniya Tanaka, M.D., Ph.D.

Materials and Methods

Patients

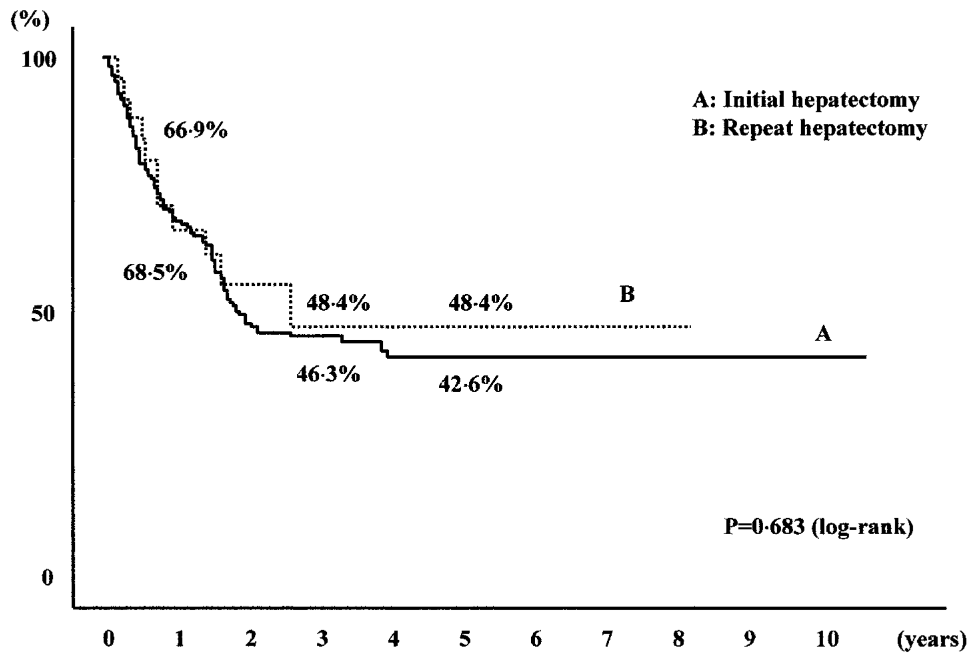
Between 1985 and 2000 a total of 193 patients underwent liver resection for colorectal cancer metastases. Among them, 26 patients underwent repeat liver resection for recurrent disease. Data from these patients were collected and reviewed. Operative feasibility and surgical outcome were compared between the initial and repeat hepatectomies. Risk factors for recurrence and patterns of recurrence after both the initial and repeat hepatectomies were compared.

Patterns of Recurrence

Patterns of recurrence were classified into three types, as described below. The pattern of multiple tumors was defined as four or more lesions. Near recurrence was defined as the development of fewer than four recurrent tumors near the original line of resection. Far recurrence was defined as the development of fewer than four recurrent tumors one segment or more distant from the original line of resection.

Calculation of Doubling Times of Tumors

The time course for determining the onset of recurrence was calculated using the doubling times (DTs) of the tumors. The tumor doubling time (T-DT) or carcinoembryonic antigen (CEA) doubling time (CEA-DT) was computed for each tumor. T-DT was calculated by the expression: log2/3 x [(T2 − T1)/(logD2 − logD1)], where T1 and T2 are the times, and D1 and D2 are the diameters at any two points in the clinical course before hepatectomy. CEA-DT was calculated by the expression: log2 x [(T2 − T1)/(logC2 − logC1)], where T is time, and C is the CEA level, as



No. at risk	0	1	2	3	4	5	6	7	8	9	10 (years)
A	189	103	60	40	31	23	12	7	4	4	1
B	26	14	9	6	4	3	2	1	1		

Fig. 1. Comparison of the cumulative disease-free survival rates after initial and repeat liver resection of hepatic metastases.

previously reported [10–14]. We also have shown that the T-DT of hepatic metastases is highly correlated with the CEA-DT in patients without extrahepatic metastases [13]. The T-DT does not correlate with the CEA-DT when extrahepatic metastases are present [14]. Therefore patients who had concomitant extrahepatic disease were excluded when only the CEA-DT was measurable. Consequently, data from 53 patients with liver recurrence after initial hepatectomy and from 9 patients with liver recurrence after repeat hepatectomy were collected to determine the onset of recurrence. When the tumor size was calculated to be less than 100 μm in diameter—the minimum implantable size [13, 15]—at the time of primary resection, we assumed that this recurrent tumor originated from the liver metastasis, not from the primary colorectal tumor.

Operative procedures

We treated patients with colorectal carcinoma metastatic to the liver according to the following principles. (1) Hepatic resection was attempted irrespective of the number or distribution of liver metastases so long as all of tumors could be resected and residual liver function was adequate. (2) The presence of extrahepatic metastases other than resectable lung metastases was a weak contraindication to surgery, and these decisions were made on a case-by-case basis. Hepatectomy may or may not have conformed to principles of anatomic resection. A hepatectomy that ensured tumor-free margins was the guiding principle. When it was believed that resection could not be tolerated because the amount of residual liver was unlikely to meet metabolic needs, portal embolization or a two-stage hepatectomy was performed. Intraoperative ultrasonography (IOUS) was used during all hepatic resections to determine if any occult tumors that had not been detected preoperatively were present and to confirm the relation between the tumor and vasculobiliary structures.

Operative procedures were defined following the terminology proposed by Strasberg [16], where segmentectomy is resection of a Couinaud segment [17], and sectionectomy is resection of one of Healey's segments [18]. Anatomic resections included segmentectomy, sectionectomy, hemihepatectomy, and trisectionectomy.

Calculation of Clinical Factors Affecting Hepatic Recurrence

Microscopic satellite lesions were defined as tumor cells invading the portal vein, hepatic vein, or intrahepatic bile duct irrespective of continuity or discontinuity with macroscopic liver tumors. Using Yasui's classification, liver tumors were classified into simple nodular (SN) or confluent nodular (CN) types depending on the characteristics of the cut surface of the resected tumor [19].

Patient Follow-up

After discharge, patients were followed monthly at our outpatient clinic. Complete radiologic evaluation, including conventional computed tomography, ultrasonography, and chest roentgenography, was performed every 3 months. CEA levels were monitored in all patients throughout the follow-up.

Statistical Analysis

Data on these patients were collected retrospectively from the physician, hospital charts, and the patients themselves. Statistical comparisons of baseline data were performed using the χ^2 test, Stu-

Table 1. Clinical characteristics and single-variable analysis in patients undergoing initial liver resection of hepatic metastasis from colorectal cancer.

Variables	Patients (no.)	Disease-free survival rate after initial liver resection: 3 Years	5 Years	p (log rank)
Primary lesion				
Site				
Colon	96	36.9	34.6	0.062
Rectum	93	55.8	50.7	
Duke's stage				
A	3	33.3	33.3	0.082
B	56	56.1	56.1	
C	124	43.0	37.3	
Liver metastases				
Type of metastases				
Synchronous	86	40.5	33.7	0.027
Metachronous	103	51.2	51.2	
Distribution				
Unilobar	119	51.6	47.7	0.049
Bilobar	70	37.1	33.4	
No. of metastases				
< 5	162	47.9	43.9	0.023
≥ 5	27	40.6	40.6	
Maximum diameter (cm)				
≤ 5	155	48.0	45.1	0.059
> 5	34	38.1	30.1	
Yasui's classification [19]				
Confluent nodular	46	44.5	44.5	0.102
Simple nodular	82	58.2	58.2	
Microscopic satellite lesions				
Yes	68	40.6	36.9	0.120
No	61	57.7	57.7	
Hepatectomy procedure				
Type				
Anatomic resection	73	52.9	49.6	0.507
Anatomic + wedge resection	41	55.4	47.5	
Wedge resection	75	38.5	36.0	
Range				
< 1 section	92	40.9	38.5	0.601
≥ 1 sections	97	53.4	48.2	
Portal embolization				
Yes	21	49.2	49.2	0.258
No	168	46.4	42.3	
Two-stage hepatectomy				
Yes	10	0.0	0.0	0.389
No	179	46.3	42.6	
Clear surgical margin (mm)				
< 5	60	24.9	16.6	< .001
≥ 5	83	68.3	68.3	
Postoperative intraarterial chemotherapy				
Yes	103	59.0	57.1	< .001
No	86	28.5	20.4	

The data for Duke's stages (6 patients) are unknown because the primary resections were performed in another hospital. Among those with Yasui's classification (61 patients), microscopic satellite lesions (60 patients), and clear surgical margins (46 patients) that were associated with the liver tumor are lacking because the cases were old.

dent's *t*-test, or the Mann-Whitney U-test. The Cox proportional hazard model was used to assess the independent effect of various risk factors on patients' disease-free survival. The disease-free survival rate was calculated by the Kaplan-Meier method. The significance of differences in the survival curves was determined by the log-rank test. A difference was considered significant at the level of $p < 0.05$.

Table 2. Multivariable analysis of prognostic factors for disease-free survival by the Cox proportional hazard model.

Factor	ARR	p
Metachronous metastases	0.60 (0.34–1.06)	0.078
Bilobar metastases	0.88 (0.43–1.82)	0.739
< 5 Metastatic nodules	0.80 (0.36–1.78)	0.589
Clear surgical margin of ≥ 5 mm	0.29 (0.15–0.56)	< 0.001
Postoperative intraarterial chemotherapy	0.64 (0.36–1.12)	0.118

Values in parentheses are 95% confidence intervals.
ARR: adjusted relative risk.

Results

Mortality, Morbidity, Feasibility

One patient died within 60 days of the initial hepatectomy (0.52%, 1/193). Postoperative bleeding occurred in this patient, and she died of sepsis and multiple organ failure 10 days after anterior sectionectomy. There were no operative deaths among patients who underwent repeat hepatectomy. The morbidity rates were 26.3% for initial hepatectomy versus 30.0% for repeat hepatectomy (p = 0.729). The duration of hepatectomy, total blood transfusion volume, and hospital stay after hepatectomy (mean ± SD) were 487.1 ± 136.4 minutes (median 475 minutes; range 186–865 minutes), 479.1 ± 575.3 ml (median 280 ml; range 0–3040 ml), and 22.0 ± 11.2 days (median 19 days; range 9–66 days) for the initial hepatectomy compared to 546.1 ± 155.5 minutes (median 569 minutes; range 301–850 minutes), 829.3 ± 352.6 ml (median 480 ml; range 0–2800 ml), and 25.7 ± 14.8 days (median 22 days; range 8–53 days) for the repeat hepatectomy ($p = 0.179$, $p = 0.184$, and $p = 0.384$, respectively).

Patient Outcome

Altogether, 4 of the 193 cases were not included in the evaluation (macroscopically noncurative hepatectomy in 2 and unknown outcome in 2). Of the remaining 189 patients, 128 (67.7%) developed recurrence (62 in the liver alone, 24 in the liver plus a distant site, 42 in a distant site alone) during a mean follow-up of 32 months (median 24 months; range 1–125 months). The 1-, 3-, and 5-year disease-free survival rates were 68.5%, 46.3%, and 42.6%, respectively. Of 62 patients (40.3%) who developed isolated hepatic recurrence, 25 underwent a second curative hepatectomy. One other patient in whom both liver recurrence and paraaortic lymph node metastases were present also underwent a second hepatectomy. Of these 26 patients, 18 (69.2%) had a second recurrence (9 in the liver alone, 2 in the liver plus a distant site, and 7 in a distant site alone) during a mean follow-up of 32.3 months (median 21 months; range 3–105 months). The 1-, 3-, and 5-year disease-free survival rates after repeat hepatectomy were 66.9%, 48.4%, and 48.4%, respectively ($p = 0.683$ vs. initial hepatectomy) (Fig. 1).

Risk Factors

A variety of factors affected hepatic recurrence after initial hepatectomy (Table 1). According to the univariate analysis, synchronous metastases ($p = 0.027$), bilobar metastases ($p = 0.049$), a large

Table 3. Clinical characteristics and single-variable analysis in patients undergoing repeat liver resection of hepatic metastasis from colorectal cancer.

Parameter	Patients (no.)	Disease-free survival rate after repeat liver resection			p (log-rank)
		1 Year	3 Years	5 Years	
Recurrence variables					
Disease-free interval					
≤ 1 Year	12	74.1	30.9	—	0.980
> 1 Year	14	61.9	54.2	54.2	
Distribution					
Unilobar	18	64.4	49.7	49.7	0.991
Bilobar	8	72.9	—	—	
Maximum diameter (cm)					
≤ 5	23	67.0	50.3	50.3	0.649
> 5	3	66.7	33.3	—	
Yasui's classification [19]					
Confluent nodular	12	91.7	69.8	69.8	0.270
Simple nodular	8	62.5	31.3	31.3	
Microscopic satellite lesions					
Yes	11	79.5	63.6	63.6	0.886
No	6	66.7	66.7	—	
Hepatectomy procedure					
Type					
Anatomic resection	7	85.7	85.7	85.7	0.025
Anatomic + wedge resection	8	83.3	55.6	55.6	
Wedge resection	11	45.5	—	—	
Range					
< 1 Section	10	50.0	—	—	0.016
≥ 1 Sections	16	77.1	67.5	67.5	
Clear surgical margin					
< 5 mm	12	54.0	16.2	16.2	0.006
≥ 5 mm	11	90.0	90.0	90.0	
Postoperative intraarterial chemotherapy					
Yes	12	73.3	61.1	61.1	0.604
No	13	61.5	40.4	40.4	

Data for Yasui's classification (6 patients), microscopic satellite lesions (9 patients), clear surgical margins (3 patients), and postoperative intraarterial chemotherapy are lacking because the cases are old.

number of tumors (≥ 5) ($p = 0.023$), a positive tumor margin ($p < 0.001$), and the absence of postoperative intraarterial chemotherapy ($p < 0.001$) were risk factors for recurrence. Multivariate analysis using these five factors in the Cox proportional hazard method revealed that a tumor-free margin was the only independent factor for recurrence after initial hepatectomy ($p < 0.001$) (Table 2). Among the 26 patients who underwent repeat hepatectomy, univariate analysis showed that a positive surgical margin ($p = 0.006$) and nonanatomic resection ($p = 0.025$) of less than a sectionectomy ($p = 0.016$) were risk factors for recurrence after a repeat hepatectomy (Table 3).

Liver Recurrence Patterns

Patterns of recurrence were analyzed. After an initial hepatectomy, multiple lesions were present in 43 patients (50.0%): near lesions in 24 (27.9%) and far lesions in 19 (22.1%). Hepatic recurrence developed in 11 patients after repeat hepatectomy, with multiple lesions in 3 (27.3%), near lesions in 6 (54.5%), a far lesion in 1 (9.1%), and other (near plus for lesions) in 1 ($p < 0.01$) (Table 4).

Calculating the Onset of Recurrence

The time of hepatic metastasis could be calculated for 135 lesions in 53 of 86 patients with recurrence after the initial hepatectomy and for 23 lesions in 9 of 11 patients with a second recurrence after the second hepatectomy. DTs were used to calculate the size of the metastasis when the primary colorectal carcinoma was resected. The calculated diameter at that time was < 100 μm in 10.4% of recurrent tumors after the initial hepatectomy, whereas it was that size in 69.6% in patients with recurrent tumors after the second hepatectomy ($p < 0.01$) (Table 5).

Table 4. Pattern of recurrence of hepatic metastasis from colorectal cancer.

Pattern of recurrence	After initial resection ($n = 86$)	After repeat resection ($n = 11$)	p (χ^2 test)
Multiple	50.0%	27.3%	
Near position	27.9%	54.5%	
Far position	22.1%	9.1%	
Near and far positions	0%	9.1%	< 0.01

Discussion

At present, 45% to 80% of patients who undergo hepatic resection of colorectal metastases to the liver develop recurrence [20–23]. Isolated liver recurrence initially develops in approximately 30% of patients [22], one-third of whom are potential candidates for further resection [23–26]. Moreover, one-third of the patients who suffer hepatic recurrence after a second hepatectomy underwent a

Table 5. Estimated size of recurrent hepatic metastasis at the time of colorectal resection based on the tumor doubling time.

Parameter	Recurrent tumor after initial resection (n = 135)	Recurrent tumor after initial resection (n = 23)	p
Estimated tumor size at the time of colorectal resection (mm)	3.29 ± 4.03 (range < 0.001–28.4; median 1.95)	0.99 ± 2.10 (range 0.002–6.06; median 0.056)	< 0.01 (Mann-Whitney U-test
Lesions whose diameter was determined to be ≤ 100 μm at the time of colorectal resection	10.4%	69.9%	< 0.01 (χ^2 test)

Data are mean ± SD.

third hepatectomy [27]. Although several reports have noted the benefit of repeat hepatectomy for liver recurrence [8, 9], the resectability rate is low. To improve both the disease-free interval and the overall survival rate, a surgical philosophy and technique must evolve.

It is reasonable to believe that most recurrences after hepatectomy are the result of occult tumors that are present at the time of resection [28]. It has been reported that microscopic satellite lesions are present in vessels and bile ducts around the macroscopic lesions [13]. These microscopic lesions are thought to originate from the primary colorectal tumor or from macroscopic metastases [13]. If the microscopic lesions represent intrahepatic spread similar to what occurs with hepatocellular carcinoma, anatomic resection with adequate surgical margins is essential. On the other hand, anatomic resection may not be necessary if the occult tumors originate from the primary colorectal tumor. Although distinguishing between these mechanisms is difficult, some means to do it must be developed to ensure that the most appropriate hepatectomy is performed in each case.

When a recurrence is derived from a metastatic lesion, one would expect the incidence of recurrence close to the line of resection to be high with the percentage of lesions < 100 μm in diameter at the time of colorectal resection also high. Recent reviews of the surgical procedures employed for initial resections concluded that the type of hepatectomy procedure (anatomic/major versus nonanatomic/limited) was not a prognostic factor [29–32]. However, an inadequate surgical margin does have an adverse effect on outcome, and many surgeons advocate that a margin of at least 1 cm be used [33–35]. The present study also failed to identify the type of initial hepatectomy as a predictor of disease-free survival by univariate analysis (Table 1), although the multivariate analysis revealed that a tumor-free margin predicted disease-free survival. In contrast, although multivariate analysis was not performed because the type of hepatectomy and the presence or absence of a tumor-free margin were interdependent, both nonanatomic liver resection of less than a sectionectomy and inadequate tumor-free margin were risk factors for recurrence after repeat hepatectomy.

Multiple recurrence was the most common pattern after initial hepatectomy. In contrast, recurrence close to the line of resection was most common after repeat hepatectomy. These findings suggest that intrahepatic spread is more common with a second hepatic recurrence than with the first recurrence after the initial resection. Recurrence close to the line of resection seems to be most common after repeat hepatectomy because the extent of the surgical margin was limited by the effort to preserve adequate residual liver tissue. However, major hepatectomy (Couinaud's three segments or more) was performed in only 2 of our 26 repeat hepatectomy cases at the initial resection. Therefore, if we performed major hepatectomy as the repeat hepatectomy in these patients, the estimated postoperative liver volume would be sufficient to avoid postoperative liver failure.

Furthermore, estimation of the time course indicated that the source of the recurrence after initial hepatectomy was the primary colorectal tumor but that the recurrences after repeat hepatectomy were derived from the original metastasis. These findings explain why a nonanatomic hepatectomy procedure was not a prognostic factor for the disease-free survival rate after the initial hepatectomy but was a predictor for recurrence after repeat hepatectomy.

Takahashi et al. [36] calculated that the minimum implantable size of a metastasis is 2^5 cells x 10 μm, the size of a single cancer cell [10]. In our previous study regarding microsatellite liver metastases [13–15], the minimum detectable size of microscopic lesions surrounding the macroscopic metastases was 100 μm. Therefore we assumed the minimum implantable size to be 100 μm the in present study.

In this series, the frequency of anatomic and anatomic + wedge resection for a repeat hepatectomy (57.6%, 15/26) (Table 3) was equivalent to that for initial hepatectomy (60.3%, 114/189) (Table 1) (p = 0.97). Consequently, operative feasibility was equivalent for initial and repeat hepatectomies. Although performing a second hepatic procedure is technically demanding, the complication rates and feasibility were comparable to those associated with primary hepatectomy. These results support a policy of performing radical hepatectomy for recurrence in the remnant liver. As we noted previously, only one-third of patients with an initial liver recurrence are potential candidates for repeat resection. Hence radical hepatectomy for an initial recurrence is indicated in only in a small number of patients. However, only one-third of the patients with recurrence after a second hepatectomy would undergo a third hepatectomy. Therefore to improve the outcome we believe that radical hepatectomy should be performed for the initial recurrence to reduce the possibility of a second recurrence after a second hepatectomy.

Liver recurrence after initial hepatectomy usually represents multiple metastatic foci from the primary disease rather than intrahepatic spread of existing metastases. Therefore most recurrences are not controllable, even by extensive hepatectomy. In contrast, it was presumed that recurrence after repeat hepatectomy predominantly represents intrahepatic spread. The results of this retrospective study suggest that resection with an adequate surgical margin, irrespective of hepatic anatomy, is all that is necessary for the initial hepatectomy. On the other hand, sectionectomy or a more extensive anatomic procedure should be performed when a second resection is indicated. The success reported in this series justifies a prospective randomized controlled study to define the role of hepatic resection for recurrence of hepatic metastases from colorectal carcinoma.

Résumé. Bien que la résection offre la seule chance de cure pour les patients porteurs de métastases d'origine colorectale, il n'existe aucun consensus quant au procédé de choix pour la prise en charge de ces tumeurs. Les

données provenant de 193 patients ayant eu une résection hépatique pour métastases d'origine colorectale et parmi ceux-ci, 26 patients qui ont eu une résection hépatique itérative pour récidive, ont été analysées. L'indication de résecabilité a été évaluée rétrospectivement, basée sur les facteurs de risque connus pour la récidive et pour leur mode de récidive. En analyse multivariée, une marge de résection chirurgicale positive (SM+) était le seul facteur de risque de récidive après résection initiale ($p < 0.01$). Une marge de résection (SM+) ($p < 0.01$) et une résection nonanatomique ($p < 0.05$) de moins d'une segmentectomie ($p < 0.05$) étaient des facteurs de risque de récidive après une résection hépatique itérative. Les tumeurs multiples (4) constituaient le mode le plus fréquent de récidive après résection initiale, alors que, la récidive près de la tranche de section était le mode de récidive le plus fréquent après résection itérative. Basé sur le temps de dédoublement tumoral, la récidive après résection hépatique initiale semble prendre son origine au niveau de la lésion colorectal primitive, alors que la récidive après résection itérative semble avoir comme origine la métastase hépatique. Une analyse rétrospective suggère que la résection hépatique avec une marge libre de tissu tumoral est plus importante qu'une résection anatomique lors de la résection initiale, alors qu'au moins une segmentectomie est nécessaire en cas de résection itérative.

Resumen. Aunque la resección hepática constituye la única posibilidad real de curación en pacientes con metástasis hepáticas de cáncer colorectal, aún no hay consenso sobre cual es el procedimiento de preferencia en el manejo de estas lesiones. Se recolectó la información de 193 pacientes sometidos a hepatectomía por metástasis hepáticas de cáncer colo-rectal y de 26 entre los 193 en quienes se practicaron hepatectomías repetidas por metástasis recurrentes. La adecuación de la resección fue evaluada retrospectivamente con base en factores de riesgo de recurrencia conocidos y en el patrón de recurrencia. En el análisis multivariado se encontró que un margen positivo en la resección (MR+) era el único factor de riesgo de recurrencia luego de la operación inicial ($p < 0.01$). El MR+ ($p < 0.01$) y una resección no anatómica ($p < 0.05$) aparecieron como factores de riesgo de recurrencia luego de hepatectomías repetidas. Tumores múltiples (4) apareció como el más importante patrón común de recurrencia luego de la hepatectomía inicial, en tanto que la recurrencia cerca de la línea de resección fue lo más común luego de hepatectomía repetida. Con base en los tiempos de doblaje del tumor, la recurrencia luego de la hepatectomía inicial pareció originarse a partir de la lesión colo-rectal primaria, pero la recurrencia luego de hepatectomía repetida se derivó de las metástasis hepáticas. El análisis retrospectivo sugiere que la hepatectomía con márgenes libres es más importante que la resección anatómica al practicar la operación inicial, pero por lo menos una seccionectomía es lo necesario en la hepatectomía repetida.

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