Maximal Debulking Liver Resection as a Beneficial Treatment Strategy for Advanced and Aggressive Colorectal Liver Metastases

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Abstract. *Background: A survival benefit is generally considered unobtainable following incomplete hepatic resection in patients with colorectal liver metastases. However, this question should be readdressed considering recent chemotherapy, often combining a monoclonal antibody directed against colorectal cancer with various classic and improved strategies. We examined whether a survival benefit could be obtained from maximal reduction surgery for colorectal liver metastases. Patients and Methods: We retrospectively analyzed data from 165 patients with liver recurrence after hepatectomy for colorectal metastases. Results: We hypothesized that recurrence soon after surgery, frequently involved metastases left behind during liver resection, resembling the situation after debulking hepatectomy. When patients were divided according to time of liver recurrence, patients with early recurrence had significantly poorer overall survival than those with later recurrence (p<0.01). However, patients with multiple bilobar metastases (n=77), having a greater likelihood of metastases left behind at hepatectomy, had similar survival whether recurrence was early or late (p=0.13). Response to chemotherapy before first hepatectomy was prognostically important (relative risk of 0.107; p=0.02) for patients with early liver recurrence, as were number of recurrent tumors and status of extrahepatic disease. Conclusion: Debulking surgery for multiple bilobar metastases may represent a treatment strategy with potential survival benefit, especially when initial metastases respond well to pre-hepatectomy chemotherapy.*

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Liver resections are increasingly performed for metastatic colon cancer, owing to improvements such as pre-hepatectomy portal vein embolization (PVE), planned 2-stage hepatectomy, and refined vascular resection and reconstruction techniques. Even so, curative resection is not always possible initially. For such patients, preoperative chemotherapy is increasingly used to reduce tumor size and control any micrometastases not detected pre- or intraoperatively. However, most patients never undergo hepatectomy, although increasing numbers of patients with colorectal liver metastases undergo effective chemotherapy.

Several studies of hepatocellular carcinoma (HCC) patients are instructive concerning patients with colorectal liver metastases. These HCC reports describe long-term survivors after reduction surgery (1-3). Curative surgical resection represents the best hope of long-term survival, but most HCCs are not amenable to operative resection because of either extent of disease or cirrhosis-related liver dysfunction (4, 5). However, reduction surgery followed by transcatheter arterial chemoembolization (6), arterial infusion chemotherapy (7), or percutaneous isolated hepatic perfusion (3) has been reported to obtain favorable results for patients harboring HCC with multiple intrahepatic metastases.

A general consensus has been long maintained that no survival benefit can be obtained from incomplete hepatic resection in patients with multiple colorectal liver metastases (8). However, current studies in the era of effective chemotherapy have demonstrated effectiveness of strategies combining ablation with hepatectomy (9, 10); success of hepatectomy leaving behind sites of metastases that disappeared during chemotherapy (11, 12); and diminished impact of surgical margin status on operative outcome (13, 14). Therefore, the question of survival benefit from maximal reduction surgery for advanced colorectal liver metastases should be reopened, as it has for advanced HCC.

As for stratification of patients, according to the European Society for Medical Oncology (ESMO) consensus guidelines,

(15) patients with potentially resectable metastases after down-sizing chemotherapy are assigned to group 1. Patients whose metastases where secondary surgery is not possible, but with imminent or present symptoms are assigned to group 2. For group 2 patients, very active chemotherapy is recommended. Group 3 patients without imminent symptoms and limited risk of rapid deterioration, minimal treatment burden for prevention of tumor progression with symptom disappearance and prolongation of life is recommended. The strategy of reduction hepatectomy proposed in this study mainly intends to convert the group 2 patients with dismal prognosis into group 3, whereby they could obtain prolongation of life with sequential chemotherapy.

In the present study, we hypothesized that liver recurrence involving small numbers of tumors occurring shortly after resection of bilobar multiple metastases represents a status similar to that after maximum debulking surgery. We retrospectively analyzed patients treated at our Institution to estimate survival benefit from reductive hepatectomy to remove colorectal cancer metastases.

Patients and Methods

Patients. Between 1992 and 2011, members of our Department of Gastroenterological Surgery at the Yokohama City University treated 431 patients in whom colorectal liver metastases were diagnosed at liver resection with curative intent. Among 431 patients, 26 were excluded because R0 or R1 resection status could not be undertaken. All the remaining 405 patients were followed-up for six months or more after the operation. Among these patients, 270 had unilobar or fewer than four metastases and 135 had four or more metastases including lesions in both major lobes. Of all 405 patients, 165 have had liver recurrence at the time of writing (88 patients in the unilobar/few metastases group and 77 in the bilobar/multiple metastases group). Data from these 165 patients were subjected to analysis (Figure 1). The median follow-up duration for the 165 patients was 31 (range=6 - 239) months. We hypothesized that liver recurrence shortly after surgery, especially if detected at the time of the first follow-up imaging, frequently involved metastases left behind during liver resection. Therefore, patients were divided into two groups; those with either early liver recurrence (n=35) or with later liver recurrence (n=130). All early remnant liver recurrences were detected on the first computed tomography (CT) evaluation. At our Institution, follow-up CT is performed every three to four months, therefore all early liver recurrences were detected within four months after liver resection.

Preoperative staging. Preoperative staging included physical examination, measurement of serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9, colonoscopy, barium enema, abdominal imaging by ultrasonography and CT, CT arterioportography, and chest imaging by routine radiography or CT. Since 2002, positron-emission tomography has been used for preoperative staging.

Prehepatectomy chemotherapy. As a rule, patients initially deemed to have unresectable liver involvement or patients with marginally resectable metastases (four or more metastases including lesions in both major lobes, a massive tumor 80 mm or more in diameter, or unfavorable tumor location with invasion of major vascular structures) underwent prehepatectomy chemotherapy.

Of the 165 patients with liver recurrence, 55 received pre-hepatectomy chemotherapy. Response to chemotherapy was evaluated using CT, according to the Response Evaluation Criteria in Solid Tumors criteria (RECIST criteria) (16).

Hepatectomy procedures. Hepatectomy was not necessarily performed according to anatomic principles of resection; the guiding aim was attainment of tumor-free margins. Resectability was established usually based on remnant liver (25% to 30% or more) or excessive risk of surgery considering tumor location, liver function, patient age, and resected volume as defined using a prediction score system introduced by Yamanaka *et al*. (17). Intraoperative ultrasonography was used to identify any occult tumors not detected preoperatively. Any extrahepatic metastases were resected whenever possible, as decided on a case-by-case basis.

Adjuvant therapy. After resection for liver metastases or extrahepatic metastases, adjuvant chemotherapy was carried out *via* hepatic artery infusion or intravenous infusion, generally with 5-fluorouracil and folinic acid with or without addition of oxaliplatin or irinotecan.

Patient follow-up. Patients underwent follow-up evaluation monthly at our outpatient clinic. Serum CEA, CA19-9, and p53 was measured every month, CT was performed every three to four months, and a chest roentgenogram was obtained every six months for five years after the most recent operation.

Statistical analysis. Statistical comparisons of baseline data were performed by the Mann–Whitney *U*-test, the χ^2 test, or Fisher's exact test. Survival rates were calculated by the Kaplan–Meier method. Univariate and multivariate analyses for continuous variables were performed using a receiver-operating characteristic curve for analysis. Multivariable regression analysis was carried out by a proportional hazard method using a Cox model. Differences between survival curves were analyzed by the log-rank test. A difference was considered significant when the two-sided *p*-value was below 0.05.

Results

Rates for 1-, 3- and 5-year overall survival after hepatectomy in all 165 patients with liver recurrence were 87.2%, 54.8%, and 36.7%, respectively.

Patient outcome: early vs. later recurrence. Perioperative characteristics of patients with early recurrence and of those with later recurrence were compared (Table I). The proportion of bilobar metastases (p=0.033), number of metastases (p=0.008), maximum size of metastases (p=0.018), and serum CEA (p<0.001) were greater in the early-recurrence group than in the later-recurrence group. A greater proportion of patients in the early-recurrence group had hepatectomy with PVE (p=0.002) or 2-stage hepatectomy (p=0.027), while relatively fewer patients in this group underwent repeat hepatectomy for liver recurrence (p=0.026). When survival

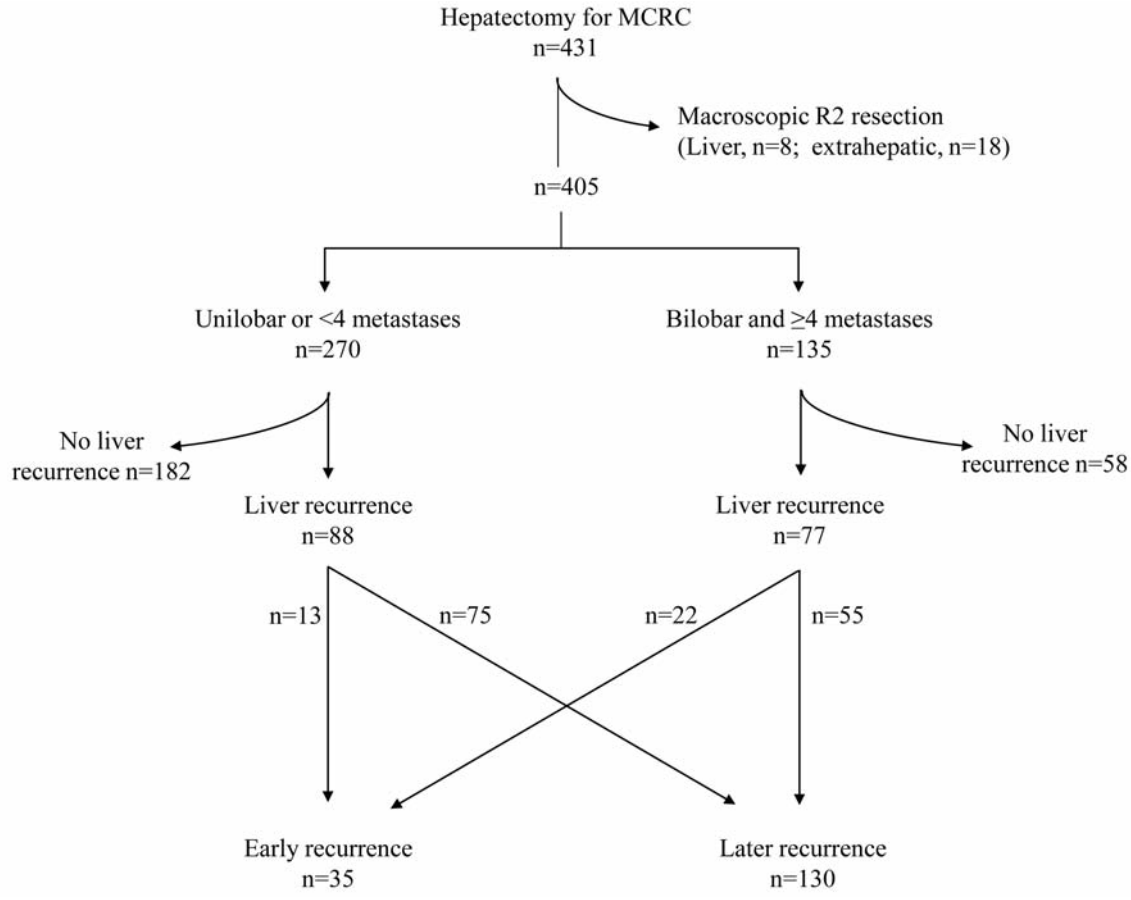

Figure 1. *Patient disposition. MCRC, Metastatic colorectal cancer.*

was compared between groups, 1-, 3-, and 5-year overall survivals in the early-recurrence group were 64.8%, 32.0%, and 27.4%, respectively, which was significantly poorer than those in the later-recurrence group (93.1%, 60.8, and 39.4%, respectively; $p<0.001$).

Outcome for early vs. later recurrence in patients with unilobar or fewer than four metastases and in patients with multiple, bilobar metastases. Patients were divided into two categories according to the number and distribution of metastases: unilobar/fewer than four metastases (n=270) and four or more metastases including lesions in both major lobes (n=135). Impact of the time of liver recurrence on outcome was compared within each category. Among 270 patients with unilobar or fewer than four metastases, 88 had liver recurrence: early in 13, and later in 75. Among 135 patients with bilobar metastases or at least four metastases, 77 had liver recurrence: early in 22, and later in 55 (Figure 1).

In the group with unilobar or fewer than four metastases, no significant difference in patient characteristics was evident between patients with early recurrence and patients with later recurrence. When survival was compared between the early-recurrence group and the later-recurrence group for patients with unilobar or fewer than four metastases, overall survival was significantly poorer in the early group than in the later group ($p<0.001$, Figure 2). In the group with bilobar and at least four metastases-group, no significant differences in patient characteristics were observed except for a higher serum CEA concentration in the early-recurrence group (334±484 ng/ml) than the later-recurrence group (212±686 ng/ml, $p<0.001$). The overall survival rate did not differ between early- and the later-recurrence groups for patients with bilobar and at least four metastases ($p=0.129$, Figure 3).

When overall survival was compared among these four groups, patients with early recurrence in the unilobar/few metastases group had significantly poorer survival than patients with early recurrence in the bilobar/multiple metastases group, and patients with later recurrence and either bilobar/multiple or unilobar/few metastases ($p<0.001$). Survival of patients with early recurrence in the

Table I. *Demographic and clinical characteristics in patient groups defined by time of liver recurrence.*

Variable		Early recurrence (n=35)	Later recurrence (n=130)	*p*-Value
Age, years		61.6±12.0 (63, 35-83)	62.7±9.2 (63, 30-83)	0.800
Gender	Male	18 (51%)	79 (61%)	0.339
	Female	17 (49%)	51 (39%)	
Primary tumor				
Site	Colon	23 (66%)	89 (68%)	0.839
	Rectum	12 (34%)	41 (32%)	
Dukes stage	A	0	3 (2%)	0.552
	B	10 (29%)	30 (23%)	
	C	25 (71%)	97 (75%)	
Histology	Well	7 (20%)	37 (28%)	0.468
	Moderate	24 (69%)	84 (65%)	
	Other	4 (11%)	9 (7%)	
Liver metastases				
Timing	Synchronous	26 (74%)	74 (57%)	0.095
	Metachronous	9 (26%)	56 (43%)	
Distribution	Unilobar	9 (26%)	61 (47%)	0.033
	Bilobar	26 (74%)	69 (53%)	
Number		7.0±6.4 (5, 1-27)	4.7±5.6 (3, 1-38)	0.008
Maximum size, mm		52.2±41.8 (45, 8-185)	35.4±23.8 (30, 8-150)	0.018
Serum CEA, ng/ml		235.3±402.4 (56.8, 1-1729)	117.4±468.4 (8.1, 1.2-4498)	<0.001
Extrahepatic disease	Present	5 (14%)	20 (15%)	>0.999
Number of liver recurrences	<4	16 (46%)	80 (63%)	0.081
	≥4	19 (54%)	47 (37%)	
	Unknown	0	3	
Treatment related				
Tumor-free margin, mm	>0	23 (66%)	89 (68%)	0.839
	0	12 (34%)	41 (32%)	
PVE	Performed	13 (37%)	17 (13%)	0.002
Staged hepatectomy	Performed	8 (23%)	10 (8%)	0.027
Prehepatectomy chemotherapy				
	Performed	12 (34%)	44 (34%)	>0.999
Response to chemotherapy	PR	4	25	0.264
	SD	4	11	
	PD	4	7	
Adjuvant chemotherapy	Performed	24 (69%)	107 (82%)	0.098
Repeat hepatectomy for liver recurrence				
	Performed	6 (17%)	50 (38%)	0.026

Values of continuous variables are mean±SD. Medians and ranges are shown in parentheses. Well, Well-differentiated adenocarcinoma; Moderate, moderately-differentiated adenocarcinoma; CEA, carcinoembryonic antigen; PVE, portal vein embolization; PR, partial response; SD, stable disease; PD, progressive disease.

bilobar/multiple group was similar to that of patients with later recurrence in either the bilobar/multiple or unilobar/few group.

Prognostic factors for patients with early recurrence. Univariate analysis identified the presence of concomitant extrahepatic metastases (p=0.05), number of recurrent tumors (p<0.001), repeat hepatectomy for recurrent tumors (p=0.001), and response to pre-hepatectomy chemotherapy (p=0.025) as significant prognosticators among the 35 patients with early recurrence (Table II). Multivariate analysis using factors identified by univariate analysis selected three factors as being independently associated with prognosis: favorable response (stable disease or better) to chemotherapy [relative risk (RR)=0.107; 95% confidence intervals (CI)=0.016 to 0.704; p=0.0200]; absence of extrahepatic metastases (RR=0.141; 95% CI=0.034 to 0.593; p=0.0075); and fewer than four recurrent tumors (RR=0.205; 95% CI=0.072 to 0.582; p=0.0029).

When patients with early recurrence in both the unilobar/few and the bilobar/multiple groups were divided according to number of recurrent tumors (which was selected as a prognosticator in patients with early recurrence), no

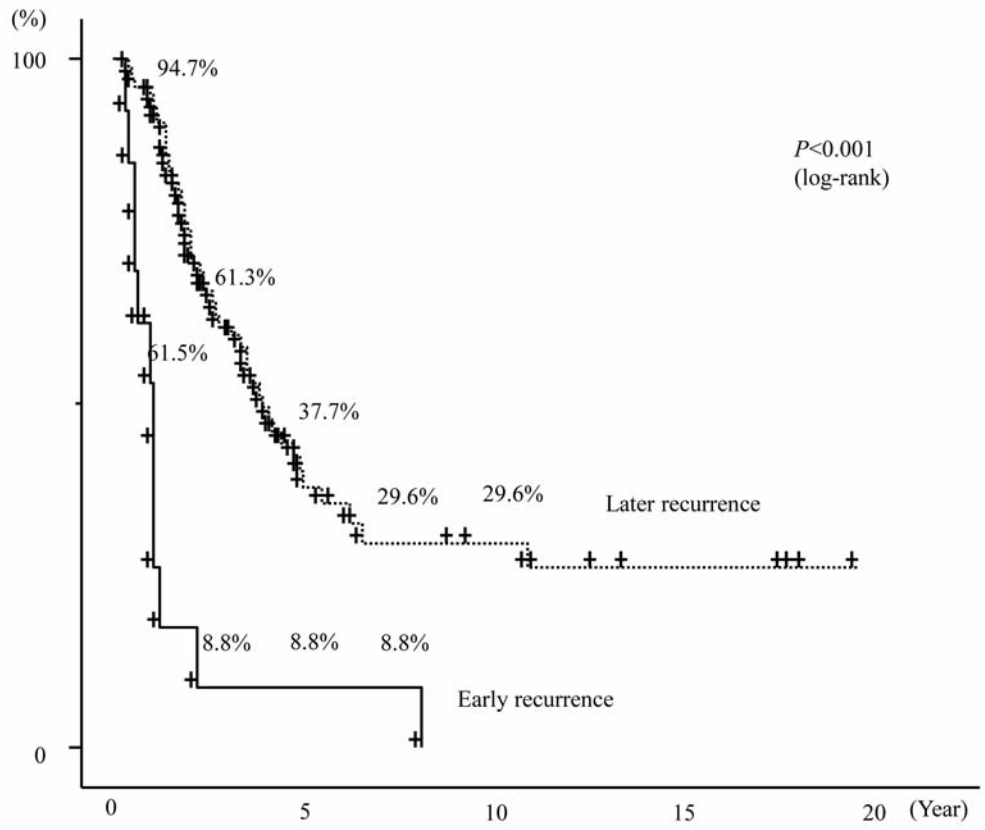

Figure 2. *Comparison of cumulative overall survival rates after liver resection in patients with unilobar or fewer than four metastases at diagnosis between those with early (continuous line, n=13) and those with later (broken line, n=75) recurrences. Overall survival was better in the later-recurrence group than in the early-recurrence group (p<0.001).*

significant difference of overall survival was evident between patients with a small number (<4) of recurrent tumors (median survival=13.1 months) and those with large number (≥4) of recurrent tumors in the group of patients with unilobar or fewer than four metastases (7.6 months, p=0.154). On the other hand, overall survival of patients with small numbers of recurrent tumors in the bilobar/multiple group were significantly better than for patients with large numbers of recurrent tumors (96.1 months *vs*. 8.1 months, p<0.001).

Discussion

We hypothesized that recurrences detected soon after surgery, especially those detected in the first follow-up imaging, frequently may represent metastases left behind during liver resection. Furthermore, a small number of recurrences detected shortly after resection of multiple bilobar liver metastases seem particularly likely to be metastases left behind during initial liver resection. Such status could be considered equivalent to that following maximal debulking surgery for advanced and aggressive liver metastases.

We observed that patients with early recurrence had greater liver tumor bulk at initial hepatectomy, whether measured directly or estimated according to number, size, extent, distribution, and preoperative CEA (18), than did patients with later recurrence. Furthermore, patients with early recurrence were frequently treated with advanced surgical strategies as staged procedures and hepatectomy with PVE, while having fewer repeat resections for recurrence than patients with later recurrence, which could contribute to poor prognosis in the early-recurrence group. When patients were divided according to initial status of their liver metastases, no significant difference in patient characteristics was observed between patients with early recurrence and those with later recurrence in the unilobar/few-metastases group. However, patients with early recurrence had poorer survival than those with later recurrence. On the other hand, among patients in the bilobar/multiple-metastases group, prognosis after hepatectomy was similar between the early- and later-recurrence groups. Furthermore, when patients with early recurrence were compared between those with recurrence from unilobar/few metastases and from bilobar/multiple

Table II. *Univariate analysis for prognostic factors in patients with early recurrence.*

Variable		No.	% Survival			*p*-Value
			1 Year	3 Years	5 Years	
Patient-related						
Age, years	<63	19	60.3	31.3	23.4	0.697
	≥63	16	68.4	33.3	33.3	
Gender	Male	18	59.0	31.5	21.0	0.718
	Female	17	70.6	33.6	33.6	
Primary-related						
Site	Colon	23	69.6	44.5	37.1	0.122
	Rectum	12	55.0	9.2	9.2	
Histology	Moderate	24	69.6	40.6	32.5	0.460
	Other	11	54.5	18.2	18.2	
Dukes stage	B	10	55.6	29.6	29.6	0.771
	C	25	68.0	32.8	26.2	
Liver-related						
Timing	Synchronous	26	64.2	31.2	23.4	0.546
	Metachronous	9	66.7	33.3	33.3	
Distribution	Unilobar	9	66.7	-	-	0.108
	Bilobar	26	64.2	42.7	36.6	
Number	<5	16	68.8	33.0	24.8	0.924
	≥5	19	61.5	29.8	29.8	
Maximum tumor size, mm	<45	17	64.7	39.2	39.2	0.270
	≥45	18	64.9	26.0	17.3	
Prehepatectomy CEA, ng/ml						
	<57	17	64.7	31.1	31.1	0.805
	≥57	18	64.9	33.7	25.3	
Extrahepatic metastases	Present	5	40.0	-	-	0.050
	Absent	30	69.0	38.2	32.7	
Liver recurrence						
Number of recurrences	<4	16	93.8	65.5	65.5	<0.001
	≥4	19	39.1	5.6	-	
Repeat hepatectomy	Performed	6	100	100	100	0.001
	Not performed	29	57.3	17.3	-	
Treatment-related						
Tumor-free margin, mm	>0	23	65.2	27.2	20.4	0.445
	0	12	64.2	38.5	38.5	
PVE	Performed	13	50.3	31.5	31.5	0.618
	Not performed	22	72.7	31.8	23.9	
Staged procedure	Performed	8	43.8	29.2	29.2	0.254
	Not performed	27	70.4	33.6	28.0	
Hepatectomy with ablation	Performed	7	34.3	-	-	0.084
	Not performed	28	71.4	36.5	31.2	
Prehepatectomy chemotherapy						
	Given	12	64.2	41.3	-	0.457
	Not given	23	65.2	28.0	23.3	
Response to chemotherapy	≥SD	8	100	64.3	-	0.025
	PD or not given	27	55.6	23.8	19.8	
Adjuvant chemotherapy	Given	24	69.7	31.1	31.1	0.300
	Not given	11	54.5	32.7	21.8	

Moderate, Moderately-differentiated adenocarcinoma; CEA, carcinoembryonic antigen; PVE, portal vein embolization; SD, stable disease; PD, progressive disease.

metastases, overall survival of patients who initially had unilobar/few metastases was significantly poorer than survival for those with bilobar/multiple metastases, even though the initial status of metastases was aggressive and surgical procedures were invasive in the bilobar/multiple metastases group. These results suggest that early recurrences from bilobar, multiple metastases might be biologically less aggressive than those from unilobar/few metastases. Liver

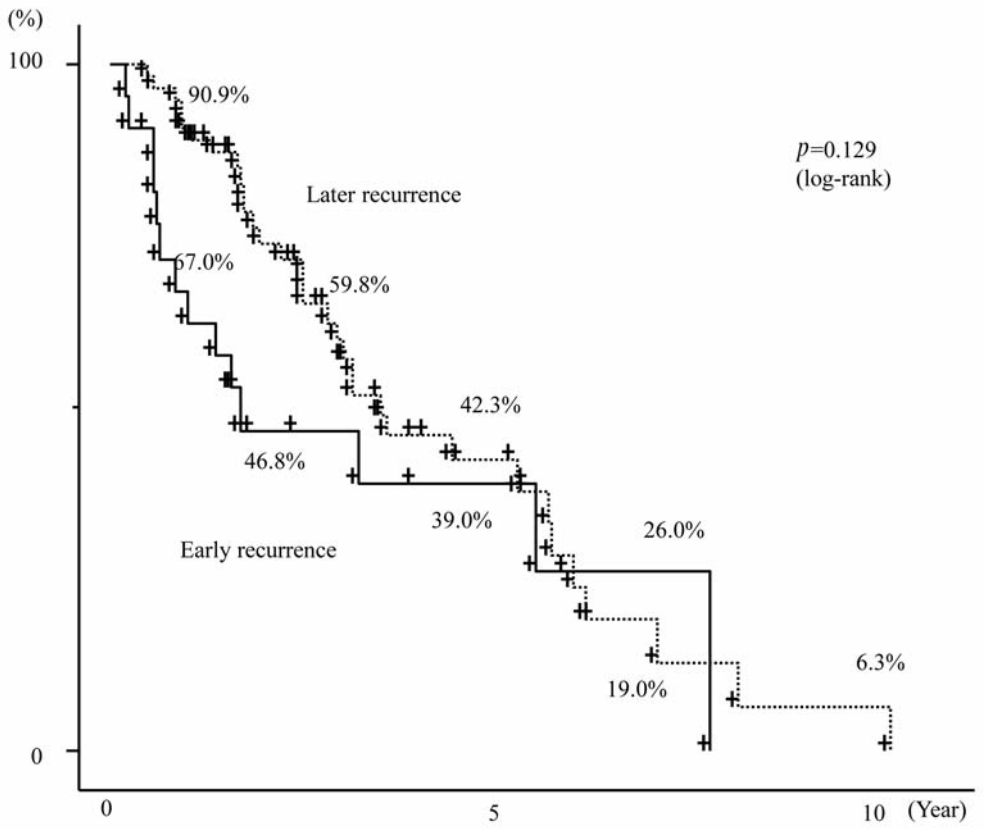

Figure 3. *Comparison of cumulative overall survival rates after liver resection in patients with bilobar metastases numbering four or more at diagnosis. No significant difference between patients with early recurrence (continuous line, n=22) and those with later recurrence (broken line, n=55) was observed (p=0.129).*

recurrences from metastases with non-aggressive behavior usually occur in small numbers and later after surgery, and are more likely to qualify for repeat hepatectomy, which improves outcomes. However, in our patients with early liver recurrence, while there were no differences in the number of recurrent nodules or frequency of repeat liver resection between those initially having bilobar/multiple metastases and those having unilobar/few metastases, prognosis for those with early recurrence from bilobar/multiple metastases was significantly better than that for patients with early recurrence from unilobar/few metastases. This suggests that the biological behavior differed between these two types of early recurrence. As already described, early recurrence from bilobar multiple metastases resembles that after maximal debulking surgery, hence prolonged survival may be attainable by debulking surgery.

With respect to prognostic factors among patients having liver recurrence soon after hepatectomy, the number of recurrent tumors, response to chemotherapy before the first hepatectomy, and status of extrahepatic disease at first hepatectomy were selected as prognosticators. Therefore, a small number of liver recurrences after resection of metastases limited to the liver after a favorable response to pre-hepatectomy chemotherapy may be associated with a favorable prognosis despite recurrence soon after hepatectomy. When patients with early recurrence were further divided according to number of recurrent tumors, survival of patients with fewer than four recurrent nodules was significantly greater than that of those with four or more recurrent nodules in the bilobar multiple metastases group. As already described, we suspected that small numbers of recurrent tumors appearing early after hepatectomy for bilobar/multiple metastases are likely to represent metastases left behind during initial liver resection. Relatively favorable outcome from such recurrences may justify debulking surgery.

Biological advantages for cytoreductive surgery are multiple. Small residual tumors are apt to be more sensitive to chemotherapy than large tumors with a relatively poor blood supply (19). Removal of large tumors also reduces the likelihood that drug-resistant clones will appear as a result of spontaneous mutations (20). Moreover, small tumors require fewer cycles of chemotherapy, thus reducing the

probability of drug-induced resistance. Each 10% increase in achievement of maximal cytoreductive surgery was associated with a 5.5% increase in the median survival time, while maximal cytoreduction is among the most powerful determinants for survival among patients with advanced ovarian cancer (21).

From our present results concerning colorectal liver metastases, strategy of conversion of ESMO group 2 patients into group 3 by reduction hepatectomy might become an optimal treatment. Debulking surgery for multiple bilobar metastases might still offer survival benefit, especially when the initial metastases respond favorably to prehepatectomy chemotherapy.

Competing Interests

The Authors declare that they have no competing interests.

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