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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Reconsideration of the Indications for Adjuvant Chemotherapy for Liver Metastases from Colorectal Cancer After Initial Hepatectomy

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ABSTRACT

Background. The effectiveness of perioperative adjuvant chemotherapy for colorectal cancer liver metastasis (CRLM) remains a matter of debate. Despite the lack of clear evidence supporting its effectiveness after curative hepatectomy, adjuvant chemotherapy has been widely used clinically. The purpose of this study was to clarify the indications for adjuvant chemotherapy in order to develop an appropriate treatment strategy for CRLM.

Methods. The clinicopathological factors of 110 patients who underwent initial hepatectomy for CRLM between April 2000 and March 2010 were retrospectively analyzed. The prognostic factors of CRLM were identified and then CRLM was stratified according to the number of prognostic factors into the high-score group (H-group: score 2 or 3) and the low-score group (L-group: score 0 or 1), and the effectiveness of adjuvant chemotherapy was analyzed in each group.

Results. Multivariate analysis identified pT4 ($p = 0.0047$), lymph node metastasis in colorectal cancer (CRC) ($p = 0.0165$), and H2-classification ($p = 0.0051$) as factors related to a poor prognosis. The overall 5-year survival rate was markedly higher in the L-group (68 %) than in the H-group (26 %, $p < 0.0001$). Moreover, in the L-group, patients who did not receive adjuvant chemotherapy had the same prognosis as those who received adjuvant chemotherapy. As for recurrence, tumor relapse more often was treated by resection in the L-group than in the H-group ($p = 0.0339$).

Conclusions. Adjuvant chemotherapy did not improve overall survival and disease-free survival in patients with no more than two factors of the H2-classification, invasion depth pT4, and lymph node metastasis in CRC.

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Colorectal cancer (CRC) is the second most common malignancy in Japan. The liver is the most common metastatic site, followed by the lung, in patients with advanced CRC. Hepatectomy has become accepted as the optimal and potentially curative treatment for patients with colorectal liver metastasis (CRLM). The 5-year survival rate after hepatectomy has been reported to range from 45 to 58 % in recent years.[1,2] However, the risk of postoperative recurrence, especially in the remnant liver, remains high, occurring in ~75 % of patients.[1] On the other hand, combinations of 5-fluorouracil/folinic acid with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) plus molecular target agents have improved the tumor response to more than 50 % and the median survival time to over 20 months for unresectable or advanced recurrent CRLM in a recent report.[2] It is anticipated that hepatectomy combined with chemotherapy will become the mainstream approach for CRLM in the future. However, at present, it remains a matter of debate whether all patients with CRLM would benefit from adjuvant chemotherapy. The purpose of this study was to clarify the indications for adjuvant chemotherapy in order to develop an appropriate treatment strategy for CRLM.

PATIENTS AND METHODS

Patients

From April 2000 to March 2010, 117 initial hepatectomies for CRLM were performed at Osaka Medical College

Hospital. Seven patients were excluded for the following reasons: four had extrahepatic metastasis; three were lost to follow-up after discharge. As a result, 110 patients were included in this study. No perioperative mortality was observed.

Surgical Indications and Procedure

In this series, hepatectomy was indicated for CRLM when the following three conditions were met: (1) the primary CRC was curatively resected; (2) metastases were located only in the liver; (3) exclusion of both number of metastasis $\geq$5 and the size of the largest tumor >5 cm. All patients underwent potentially curative hepatectomy with removal of gross tumor and showed negative macroscopic margins. With respect to hepatic hilar lymph nodes, lymph node dissection was not routinely performed, because node-positive cases in this region were strongly associated with extremely poor survival in our previous experience.[3] Synchronous (as opposed to metachronous) CRLM was defined as simultaneous presentation of liver metastasis at the time of CRC operation and was detected in 39 patients (35 %). These patients underwent either synchronous or metachronous hepatectomy, based mainly on the condition of the individual patient and on emergency needs. Non-anatomical hepatectomy was performed in principal, with anatomical hepatectomy preferred in cases when this procedure suggested advantages in terms of operative time, blood loss, safety, and invasiveness. Hepatic resection was performed following the standard technique, as previously reported.[4] During the resection procedure, surgical margins were confirmed carefully by using intraoperative ultrasonography to obtain margins of 5–10 mm. In 80 % of cases, the hepatic surgical margin was $\geq$5 mm.

Patient Follow-Up

Patients were examined for CRCLM recurrence by ultrasonography and contrast-enhanced computed tomography (CT) every 4–6 months and blood tests, including tumor markers, such as carcinoembryonic antigen (CEA) every 2–3 months after discharge. When recurrence was suspected, magnetic resonance imaging (MRI) was performed to check for new lesions in the remnant liver, whereas systemic recurrence was checked by fluorodeoxyglucose-positron emission tomography or gallium scintigraphy. Chest and pelvic CT was also performed every 6 months for local and pulmonary metastases or recurrence. Recurrence was diagnosed when at least two imaging studies confirmed new lesions showing typical features of CRC/CRLM, compared with the previous images. Recurrent CRLM was treated by repeat resection when applicable ($n = 39$).

Chemotherapy

Patients themselves decided whether they took adjuvant chemotherapy after having been told that the efficacy of adjuvant chemotherapy for CRLM was controversial. After discharge, most patients (77 patients: 70 %) received adjuvant chemotherapy, such as 5-fluorouracil $\pm$ levofolinate calcium, tegafur/uracil $\pm$ calcium folinate, oteracil (TS-1), and so on. 25 patients received potent adjuvant chemotherapy, such as FOLFOX, FOLFIRI, and hepatic arterial infusion (HAI) with 5-FU/cisplatin.

H-Classification

The H-classification by the *Japanese Classification of Colorectal Carcinoma* is based on the maximum size and the number of tumors in the General Rules for Clinical and Pathologic Studies on Cancer of the Colon, Rectum and Anus, 7th Japanese edition of 2006: H0: no liver metastasis; H1: number of metastases $\leq$4 and size of largest tumor $\leq$5 cm; H2: other than H1, H3; H3: number of metastases $\geq$5 and size of largest tumor >5 cm.[5]

Clinicopathological Analysis

Patient demographics, laboratory test results, including levels of tumor markers, tumor characteristics, treatment, recurrence, and survival data, were analyzed to identify prognostic factors in terms of the survival rate at 5 years after initial curative hepatectomy for CRLM. Surgically resected specimens were studied macro- and microscopically to determine various tumor characteristics, including size of the largest tumor, number, morphology, extent of the tumor, and surgical margins. For microscopic analysis, resected specimens were fixed in 10 % formaldehyde and sliced into 5-mm-thick sections. After each section was sliced into 5-μm-thick tissue sections and stained with hematoxylin and eosin, two pathologists performed reviews for histological confirmation of the pathological diagnosis. In this study, surgical margin status was defined based on the distance to the lesion(s) closest to the cut surface of the liver and macroscopically classified into two categories of surgical margins ($\geq$1 and 0 mm). Moreover, patients with CRLM were stratified into two subgroups according to the prognostic factors.

Statistical Analysis

The tumor-node-metastasis (TNM) stage according to the latest edition of the International Union against Cancer TNM classification was used.[6] Actuarial survival rates were calculated using the Kaplan–Meier method. Univariate analyses were performed using the log-rank test. Multivariate analyses were performed by Cox proportional

TABLE 1 Clinicopathological factors for DFS and OS in 330 patients undergoing curative resection for macroscopically small (≤5.0 cm) solitary HCC without macroscopic vascular invasion

Factors	Categorization	Number (*n*)	5-year survival rate (%)	Univariate analysis	Multivariate analysis	Odds ratio	CI
Patients background characteristics							
Gender							
	Male	42	53	0.6105			
	Female	58	59				
Age (years)							
	≥65	78	54	0.6232			
	<65	32	58				
Viral infection							
	Yes	12	46	0.3182			
	No	98	47				
Diabetes mellitus							
	Yes	8	25	0.0207	0.0513		
	No	102	45				
Tumor-related factors: colorectal							
Location							
	Rectum	36	47	0.2406			
	Colon	74	58				
CEA							
	Positive	36	62	0.3552			
	Negative	32	65				
CA19-9							
	Positive	21	64	0.6951			
	Negative	48	63				
T factor							
	pT4	26	29	0.0002	0.0047	2.72	1.37–5.31
	≤pT3	84	64				
N factor							
	pN0	68	43	0.0017	0.0165	2.32	1.16–4.99
	≥pN1	42	70				
Venous invasion							
	Positive	16	49	0.9073			
	Negative	85	85				
Lymphatic invasion							
	Positive	15	61	0.3912			
	Negative	85	55				
Tumor-related factors: liver							
CEA							
	Positive	79	52	0.1111			
	Negative	31	71				
CA19-9							
	Positive	21	55	0.4551			
	Negative	48	58				
Timing of CRCLM							
	Synchronous	39	65	0.4136			
	Metachronous	71	49				

TABLE 1 continued

Factors	Categorization	Number (*n*)	5-year survival rate (%)	Univariate analysis	Multivariate analysis	Odds ratio	CI
Tumor size (cm)							
	≥5	17	31	0.0169	0.4001		
	<5	93	59				
Tumor number							
	Single	64	58	0.3843			
	Multiple	46	50				
H-classification							
	H1	87	60	0.0053	0.0051	4.13	1.56–10.2
	H2	23	37				
Surgical factors							
Anatomical resection							
	Yes	34	44	0.1626			
	No	76	60				
Major hepatectomy							
	Yes	26	41	0.1486			
	No	84	59				
Surgical time (min)							
	≥300	50	49	0.2054			
	<300	60	60				
Surgical bleeding (ml)							
	≥600	34	51	0.9323			
	<600	76	57				
Blood transfusion							
	Yes	17	40	0.2149			
	No	93	58				
Surgical margin (mm)							
	=0	8	43	0.5165			
	≥1	102	51				
Others							
Adjuvant chemotherapy							
	Yes	77	56	0.3649			
	No	33	53				
Time to recurrence (years)							
	≤1	49	11	<0.0001			
	>1	61	83				

CRC colorectal cancer, *CRLM* colorectal liver metastasis, *CEA* carcinoembryonic antigen

hazards regression. Statistical comparisons were made by Fisher's exact probability test. All analyses were performed using the JMP version 9.0 software package (SAS Institute, Cary, NC, USA) on Mac OS X. Values of $p < 0.05$ were considered significant.

RESULTS

The overall 5-year survival rate after initial hepatectomy was 55 %, and the median survival was 42 months. The 5-year disease-free survival rate (DFS) was 30 %, and the recurrence rate was 69 % (76/110). Of the 76 cases with recurrence, 93 % (71/76) occurred within 2 years after the initial hepatectomy.

Factors Affecting Overall Survival

On univariate analysis, significant differences in the overall survival rate (OS) were seen with diabetes mellitus (comorbidity vs. not, $p = 0.0207$), depth of invasion in CRC (≤pT3 vs. pT4, $p = 0.0002$), lymph node metastasis in CRC (pN0 vs. pN1/2, $p = 0.0017$), tumor size of CRLM

(≥5 vs. <5 cm, $p = 0.0169$), H-classification (H1 vs. H2, $p = 0.0053$), and time to recurrence (≤1 vs. >1 year, $p < 0.0001$). On multivariate analysis, pT4 ($p = 0.0047$), lymph node metastasis in CRC ($p = 0.0165$), and H2-classification ($p = 0.0051$) were significant independent prognostic factors (Table 1).

Effect of Adjuvant Chemotherapy on OS by Subgroup

CRLM patients were stratified according to the number of above-mentioned independent risk factors for OS into a high-score group (H-group: score 2 or 3) and a low-score group (L-group: score 0 or 1).

Overall 1-, 3-, 5-, and 7-year survival rates in the L-group were 97, 81, 68, and 59 %, respectively, markedly better than the corresponding survival rates of 85, 37, 26, and 18 % in the H-group (Fig. 1, $p < 0.0001$).

Figure 2a shows OS curves of patients with adjuvant chemotherapy in the L-group. The 1-, 3-, and 5-year OS rates in patients administered adjuvant chemotherapy ($n = 52$) were similar to those without adjuvant chemotherapy ($n = 24$). Moreover, DFS curves from both groups were similar to each other group within 1 year after initial hepatectomy (Fig. 2b). In contrast, in the H-group, the 1-, 3-, and 5-year OS rates were significantly better in patients with adjuvant chemotherapy ($n = 25$) than in those without adjuvant chemotherapy ($n = 9$; 96, 51, and 36 vs. 56, 0, and 0 %, respectively), and patients who did not receive adjuvant chemotherapy were not alive more than 3 years after hepatectomy ($p < 0.0001$, Fig. 3).

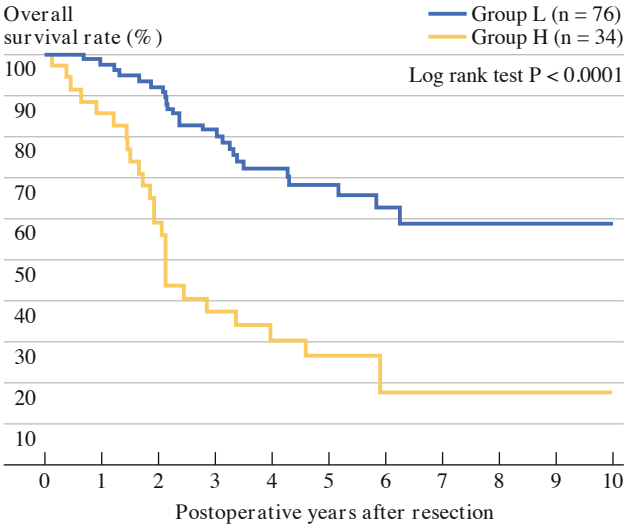

FIG. 1 The OS data after hepatectomy for colorectal liver metastasis in the low-score group (L-group, *blue line*, $n = 76$) and the high-score group (H-group, *yellow line*, $n = 34$). The 1-, 3-, 5-, and 7-year OS rates were 97, 81, 68, and 59 %, respectively, in the L-group and 85, 37, 26, and 18, respectively, in the H-group. The OS rate was significantly better in the L-group than in the H-group ($p < 0.0001$)

Table 2 compares the outcomes after the initial hepatectomy between the L-group and the H-group. Time to recurrence and site of recurrence were similar between the two groups. However, first recurrent tumors were more often treated by resection in the L-group than in the H-group ($p = 0.0339$).

DISCUSSION

In the present study, the H2-classification of CRLM, invasion depth pT4, and lymph node metastasis in CRC were identified as predictors for OS in CRLM. CRLM was stratified according to the three above-mentioned factors into a high-score group (H-group) and a low-score group (L-group). Whereas significant improvement in survival was observed following chemotherapy in the H-group, no improvements in survival and DFS were observed in the L-group.

Unlike the Japanese guideline, the guideline of the National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) (recommended perioperative adjuvant chemotherapy for CRLM.[7,8] However, postoperative adjuvant chemotherapy clearly prolonged DFS but did not improve OS in all patients with CRLM. Thus, the efficacy of adjuvant chemotherapy for CRLM remains a matter of debate. Portier et al.[9] reported a randomized phase III trial that evaluated the efficacy of adjuvant 5-FU/LV for patients after curative hepatectomy compared with surgery alone. This trial showed that the 5-year DFS was significantly better in the 5-FU/LV group than in the surgery alone group, but the 5-year OS did not differ significantly between these groups. As for preoperative adjuvant chemotherapy, Nordlinger et al.[10] reported a phase III trial (EORTC 40983) that randomly assigned 364 patients with resectable liver metastasis to perioperative FOLFOX4 or surgery alone. Although the 3-year, progression-free survival was significantly better in the FOLFOX group than in the surgery alone group among eligible patients, it was not significantly better in the intention-to-treat analysis (35 vs. 28 %, $p = 0.058$). Furthermore, they reported that OS was not better in the FOLFOX group than in the surgery alone group [hazard ratio (HR) = 0.87, 95 % confidence interval (CI) 0.66–1.14, $p = 0.303$] at the American society of Clinical Oncology meeting in 2012.[11] Despite the lack of clear evidence supporting its effectiveness after curative hepatectomy, adjuvant chemotherapy has been widely used clinically.

Why did adjuvant chemotherapy not improve OS for resectable CRLM? This was thought to be because hepatectomy exerts a major effect in cases of CRLM, thus the

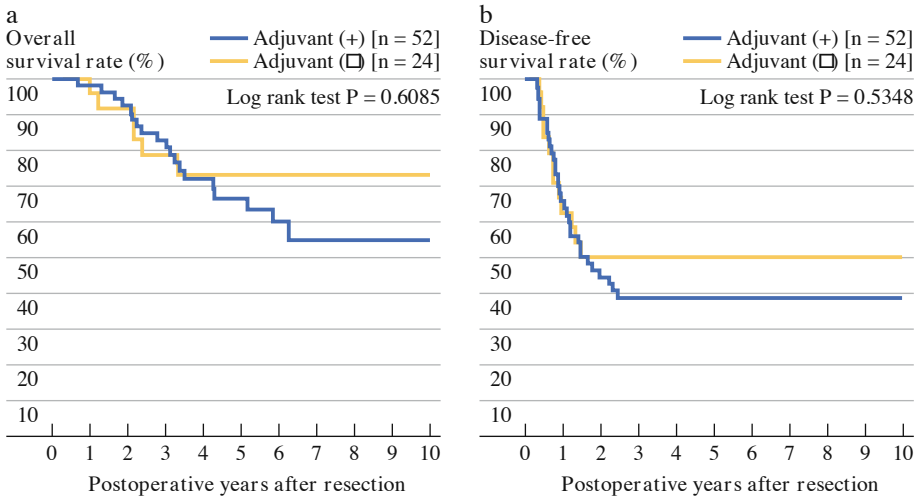

FIG. 2 The OS and DFS after hepatectomy for colorectal liver metastasis by adjuvant chemotherapy in the low-score group. Data for adjuvant (+) ($n = 52$) are shown by a *blue line*, and data for adjuvant (−) ($n = 24$) are shown by a *yellow line*. **a** There was no significant difference in survival rate when comparing the two groups. **b** The DFS curves were closely similar for each group within 1 year after initial hepatectomy and were not different between both group

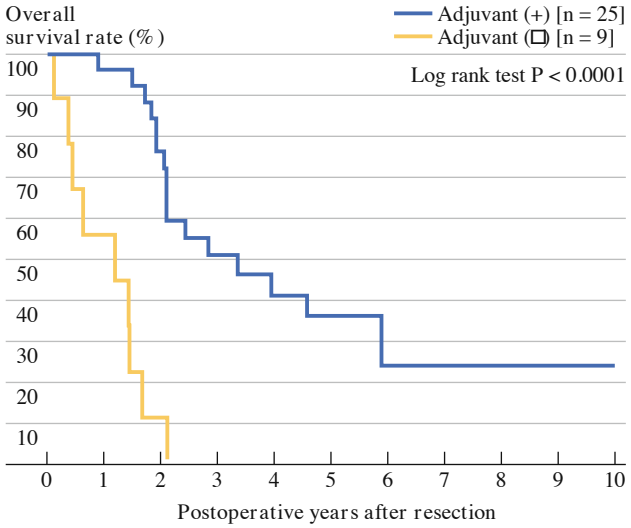

FIG. 3 The OS after hepatectomy for colorectal liver metastasis by adjuvant chemotherapy in high-score group. Data for adjuvant (+) ($n = 25$) are shown by a *blue line*, and data for adjuvant (−) ($n = 9$) are shown by a *yellow line*. Patients who did not receive adjuvant chemotherapy were not alive more than 3 years after hepatectomy. The 1-, 3-, and 5-year OS rates were significantly better in patients given adjuvant chemotherapy ($n = 25$) than in those not given adjuvant chemotherapy ($n = 9$) (96, 51, and 36, vs. 56, 0, and 0, respectively, $p < 0.0001$)

majority of cases can be radically cured with hepatectomy alone. In other words, adjuvant chemotherapy is being given to patients who do not need it.

This present study found that the H2-classification of CRLM, pT4, and lymph node metastasis in CRC were the factors predicting a poor prognosis in CRLM. With respect

TABLE 2 Comparison of outcomes between the H-group and the L-group

Factors	L-group ($n = 76$)	H-group ($n = 34$)	p value
Recurrence	44 (58 %)	32 (94 %)	<0.0001
Time to recurrence			
≤1 year after operation	28 (64 %)	21 (66 %)	1.0000
>1 year after operation	16 (36 %)	11 (34 %)	
Site of recurrence			0.3565
Liver	17 (39 %)	16 (50 %)	
Lung	12 (27 %)	3 (9 %)	
Others	2 (5 %)	3 (9 %)	
Multiple	13 (29 %)	10 (32 %)	
Treatment of recurrence			0.0339
Resection	27 (61 %)	12 (37 %)	
Except resection	17 (39 %)	20 (63 %)	

to the H-classification of CRLM, in 1994, the Japanese Society for Cancer of the Colon and Rectum proposed a classification system for liver metastasis known as the H-classification.[5] This H-classification was widely applied by Japanese physicians to evaluate patient prognosis. On the other hand, with respect to the significance of pT4 and lymph node metastasis, numerous studies have proposed these as predictors of tumor recurrence and prognosis in CRCLM patients who have undergone curative hepatectomy.[1,3,12–15]

In the present study, OS was compared between the two groups stratified according to prognostic factors. In the L-group, the overall 5-year survival rate was good (65 %), similar to previous reports, but in the H-group, it was poor

(25 %).[16,17] Moreover, there was no significant difference between adjuvant chemotherapy and nonadjuvant chemotherapy in the L-group. In particular, the DFS curves were very similar for adjuvant chemotherapy and no adjuvant chemotherapy within 1 year after initial hepatectomy, i.e., adjuvant chemotherapy did not contribute to improving OS and DFS in the L-group. On the other hand, adjuvant chemotherapy in the H-group improved OS compared with no adjuvant chemotherapy, and patients who did not receive adjuvant chemotherapy were not alive more than 3 years after initial hepatectomy.

However, the 5-year survival rate of patients given chemotherapy was unsatisfactory at 36 %. Given that the anticancer agents used were outdated, the 5-year survival rate may have been slightly higher had novel regimens, such as FOLFOX, been used.

As for recurrence after initial hepatectomy, early recurrence within 1 year after curative hepatectomy for CRLM correlates with poor prognosis, as reported by Yamashita et al..[18] Although time to recurrence after initial hepatectomy and site of recurrence were not different between the two groups in the present study, the rate of re-resection for recurrent lesions was significantly higher in the L-group than in the H-group. de Jong et al.[19] reported that repeat hepatectomy can offer the chance of long-term survival, with 5-year survival of 47.1, 32.6, and 23.8 % following the first, second, and third hepatectomy, respectively. Welter et al.[20] reported that patients with repeat pulmonary metastases secondary to CRC can have long-term survival, with median survival of 72.6 months and 5-year survival of 53.8 %, within 4 metastases. It is important that the recurrent lesion be resectable and is removed surgically to improve the prognosis.

As for the timing of adjuvant chemotherapy, preoperative chemotherapy has several theoretical advantages compared with postoperative chemotherapy, including the ability to downsize unresectable disease, reduce the extent of liver resections, eliminate possible micrometastases that diagnostic tools cannot detect, and assess response to chemotherapy.[21,22] Preoperative chemotherapy has been shown to be a useful approach for initially borderline or unresectable CRLM; Tanaka et al.[23] showed that neoadjuvant chemotherapy for CRCLM patients with bilateral multiple ($\geq$5) tumors was associated with improved survival, enabling complete resection. However, the benefit of preoperative chemotherapy for resectable CRLM with respect to OS has not been established. More agreement exists on a link between chemotherapy-associated changes and poor postoperative outcomes (), and the rate of progressive disease on preoperative chemotherapy was reported to be 5–7 %.[10,24–26] In our view, preoperative chemotherapy can be recommended for downsizing borderline or unresectable liver metastasis, but not for resectable lesions, for which adjuvant chemotherapy is preferred at present. At our facility, postoperative adjuvant chemotherapy was considered unnecessary for patients who did not meet more than one of the following criteria: H2, pT4, or LN metastasis. However, adjuvant chemotherapy was thought to improve outcomes in patients who met two or more of the above criteria.

Finally, we propose that adjuvant chemotherapy should be undertaken with caution until the results of ongoing, randomized, controlled trial regarding adjuvant chemotherapy become available.

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