

# Early Recurrence After Initial Hepatectomy for Colorectal Liver Metastases

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**Objective:** This study investigated the frequency of early recurrence in patients who had undergone hepatectomy for colorectal cancer liver metastasis (CRLM) and assessed the indications for adjuvant chemotherapy in these patients.

**Methods:** This retrospective analysis included 133 consecutive patients who underwent initial hepatectomy for CRLM between April 2000 and May 2010 and have been followed more than 5 years.

**Results:** Of the 133 patients, 83 (62%) experienced tumor recurrence, with 14 of the 83 recurrences within 6 months after initial hepatectomy. Overall survival was significantly poorer in patients with recurrences within 6 months than those without any recurrence ( $P = 0.015$ ). The frequency of adjuvant chemotherapy was significantly lower in patients with recurrences within 6 months than those without recurrences within 6 months. Multivariate analysis showed that H-2 classification was the only independent risk factor for recurrence within 6 months after hepatectomy ( $P = 0.002$ ). Adjuvant chemotherapy improved prognosis in patients classified as H2.

**Conclusions:** Patients who experienced tumor recurrence within 6 months after initial hepatectomy for CRLM had a poorer prognosis than patients who experienced recurrence after 6 months. Patients with H2-classification of CRLM should receive preoperative adjuvant chemotherapy.

**Key words:** Early recurrence – Colorectal liver metastasis – Adjuvant chemotherapy – H classification

Colorectal cancer (CRC) is the second most common malignancy in Japan, with 50% of these patients developing liver metastases. Hepatectomy is currently the only potentially curative

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treatment for patients with colorectal liver metastasis (CRLM).<sup>1–6</sup> The 5-year survival rate after hepatectomy has been reported to range from 45% to 58%,<sup>5,7</sup> with recurrences observed in 80%–85% of patients with CRLM.<sup>6</sup> Although shorter time to recurrence has been found to correlate with poorer prognosis in patients who undergo resection for colorectal cancer,<sup>2,3</sup> hepatocellular carcinoma,<sup>8</sup> and renal cell carcinoma,<sup>9</sup> the relationship between time to recurrence after resection and prognosis in patients with CRLM is unclear, because many recurrent tumors can be resected, and resection may enhance long-term survival.<sup>2,10,11</sup>

Recently developed chemotherapy regimens for advanced recurrent CRLM, such as FOLFOX and FOLFIRI, have improved tumor response rates to over 50% and median survival times to over 20 months.<sup>7</sup> However, it remains unclear whether all patients with CRLM would benefit from adjuvant chemotherapy after hepatectomy. To develop an appropriate treatment strategy for CRLM, this study analyzed the impact of early recurrence on recurrence sites/patterns and survival, as well as clarifying the indications for adjuvant chemotherapy.

## Patients and Design

### *Patients*

This retrospective analysis included 133 patients who underwent initial hepatectomies for CRLM at Osaka Medical College Hospital between April 2000 and May 2010 and were followed-up for at least 5 years. None of these patients received preoperative neoadjuvant chemotherapy or died perioperatively.

### *Surgical indications and procedure*

Hepatectomy for CRLM was performed when (1) the primary CRC was curatively resected; (2) metastases were located only in the liver; and (3) there were <5 metastases, with the largest-sized tumor being ≤5 cm in diameter. All patients underwent potentially curative hepatectomy with removal of the gross tumor and showed negative macroscopic margins. Dissection of hepatic hilar lymph nodes was not routinely performed, since positive nodes in this region were strongly associated with extremely poor survival.<sup>8</sup> Synchronous (as opposed to metachronous) CRLM was defined as simultaneous presentation of liver metastasis at the time of CRC operation and was detected in 42 of the 133 patients (32%). These patients underwent either synchronous or metachronous hepatectomy, based

mainly on the condition of the individual patient and on emergency needs. Nonanatomic hepatectomy was performed in principal, with anatomic hepatectomy preferred when advantages were suggested, in operation time, blood loss, safety, and invasiveness. Hepatic resection was performed using the standard technique, as previously reported.<sup>12</sup> During the resection, surgical margins of 5 to 10 mm were confirmed by intraoperative ultrasonography.

### *Patient follow-up*

Patients were examined for CRLM recurrence by ultrasonography and contrast-enhanced computed tomography (CT) every 4 to 6 months and blood tests, including tumor markers such as carcinoembryonic antigen (CEA), every 2 to 3 months after discharge. Patients suspected of recurrence were examined by magnetic resonance imaging (MRI) to check for new lesions in the remnant liver, or by fluorodeoxyglucose-positron emission tomography or gallium scintigraphy to check for systemic recurrence. Chest and pelvic CT were also performed every 6 months to check for local and pulmonary metastases or recurrence. Recurrence was diagnosed when at least 2 imaging methods confirmed new lesions showing typical features of CRC/CRLM, when compared with the previous images. Recurrent CRLM was treated by repeat resection when applicable (n = 46).

### *Chemotherapy*

Patients themselves decided whether to undergo adjuvant chemotherapy after having been informed that its efficacy in treating CRLM was unclear. After discharge, most patients (78 patients; 59%) received adjuvant chemotherapy, such as 5-fluorouracil ± levofolinate calcium, tegafur/uracil ± calcium folinate, or oteracil (TS-1). A total of 28 patients received potent adjuvant chemotherapy, such as FOLFOX, FOLFIRI, or hepatic arterial infusion (HAI) with 5-FU/cisplatin.

### *H-classification*

The H-classification of the *Japanese Classification of Colorectal Carcinoma* is based on the maximum size and number of tumors, as determined by the “General Rules for Clinical and Pathologic Studies on Cancer of the Colon, Rectum and Anus,” 7th Japanese edition of 2006.<sup>13</sup> According to this

classification system, H0 indicates no liver metastases, H1 indicates  $\leq 4$  metastases and largest tumor size  $\leq 5$  cm, H3 indicates  $\geq 5$  metastases and largest tumor size  $> 5$  cm, and H2 indicates non-H1 and non-H3.

### Clinicopathological analysis

Patient demographics, laboratory test results including levels of tumor markers, tumor characteristics, treatment, recurrence, and survival data were analyzed to identify factors prognostic of 5-year survival rate after initial curative hepatectomy for CRLM. Surgically resected specimens were studied maybe macro- and microscopically to determine various tumor characteristics, including size of the largest tumor, and tumor number, morphology, extent, and surgical margins. For microscopic analysis, resected specimens were fixed in 10% formaldehyde and sliced into 5-mm-thick sections. Sections were sliced into 5- $\mu$ m-thick tissue sections, stained with hematoxylin and eosin, and examined by 2 pathologists to histologically confirm the pathologic diagnosis. In this study, surgical margin status was based on the distance to the lesion(s) closest to the cut surface of the liver and macroscopically classified as  $\geq 1$  mm and 0 mm.

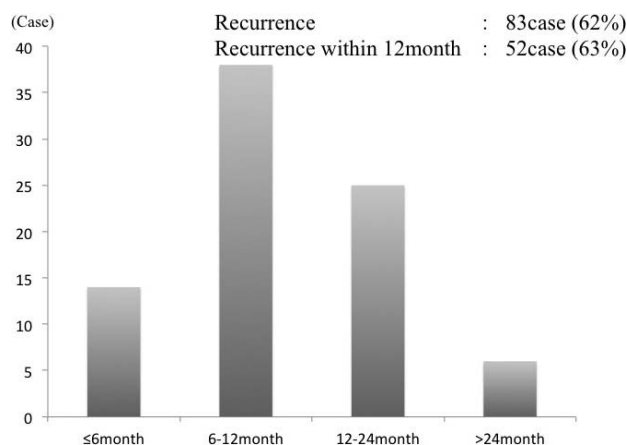
Moreover, patients with CRLM were stratified into 2 subgroups according to prognostic factors.

### Statistical analysis

The tumor-node-metastasis (TNM) stage of each tumor was determined based on the latest edition of the International Union Against Cancer TNM classification.<sup>14</sup> Actuarial survival rates were calculated using the Kaplan-Meier method. Univariate analyses were performed using the Wilcoxon test. Multivariate analyses were performed by Cox proportional 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, with values of  $P < 0.05$  considered statistically significant.

## Results

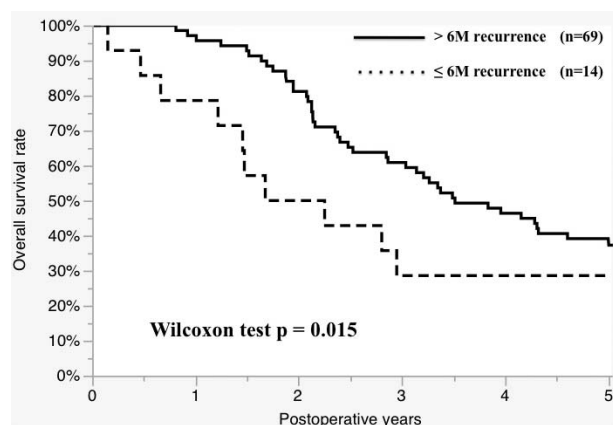
The overall 5-year survival rate after initial hepatectomy was 59%, and the median survival was 60 months. The recurrence rate was 62% (83/133); of the 83 patients with recurrence, 14 (17%) experi-



**Fig. 1** Recurrences after initial hepatectomy for colorectal liver metastasis. The recurrence rate was 62% (83/133). Of the 83 patients who experienced tumor recurrence, most did so within 2 years of initial hepatectomy with 14 (17%) experiencing recurrence within 6 months.

enced recurrence within 6 months, and most within 2 years, after initial hepatectomy (Fig. 1).

Fig. 2 shows overall survival (OS) curves after initial hepatectomy according to time to recurrence in patients who developed recurrences. Overall 3- and 5-year survival rates in patients with recurrence within 6 months were 29% respectively, markedly lower than the corresponding survival rates, 61% and 39%, respectively, in patients with recurrence after 6 months (Fig. 2;  $P = 0.001$ ). Median OS was significantly shorter in patients with recurrence within 6 months (20 months; range 2–124 months) than in patients with recurrence after 6 months (42 months; range: 21–184 months).



**Fig. 2** OS curves after initial hepatectomy in patients with recurrence within 6 months and after 6 months. The OS of the 2 groups differed significantly ( $P = 0.015$ ).

Table 1 Comparison of clinical characteristics between recurrence within 6 months and no recurrence within 6 months after curative hepatectomy in CRLM patients<sup>a</sup>

Factors	≤6 mo recurrence (n = 14)	6 mo recurrence free (n = 119)	Uni <i>P</i> value	Multi <i>P</i> value
Background characteristics				
Sex (n), male/female <sup>b</sup>	11/3	72/47	0.249	
Age, y (range)	71 (28–83)	67 (38–89)	0.242	
Age ≥ 70, n (%)	8(57)	46 (39)		0.251
Diabetes mellitus, n (%)	3 (21)	10 (8)	0.141	
Tumor-related factors: colorectal				
Location, colon/rectum <sup>b</sup>	10/4	76/43	0.770	
pT4, n (%)	4 (29)	21 (18)	0.299	
pN1, n (%)	11 (79)	67 (56)	0.153	
Tumor-related factors: liver				
Synchronous metastasis, n (%)	6 (43)	36 (30)	0.370	
H-classification (H2), n (%)	7 (50)	15 (13)	0.002	0.032
CEA ≥ 5 (ng/ml), n (%)	11 (79)	83 (70)	0.757	
CA19-9	≥ 37(ng/ml)	6 (43)	47 (40)	1.000
Tumor size ≥ 3(cm), n (%)	13 (93)	61 (51)	0.003	0.059
Tumor number (single), n (%)	6 (43)	76 (64)	0.152	
Surgical factors				
Major hepatectomy, n (%)	4 (29)	25 (21)	0.504	
Laparoscopy/open	4/10	37/82	1.000	
Surgical time, min (range)	300 (120–700)	285 (60–829)	0.976	
Surgical bleeding, mL (range)	315 (20–8690)	310 (10–2920)	0.976	
Blood transfusion, n (%)	3 (21)	15 (13)	0.404	
Surgical margin ≥1 mm, n (%)	14 (100)	110 (92)	0.597	

≤6 mo, recurrence within 6 months after surgery; CEA; carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; H-classification; H1, number of metastases ≤4 and size of largest tumor ≤5 cm; H3, number of metastases ≥5 and size of largest tumor >5 cm; H2, Other than H1, H3.

<sup>a</sup>Median with range, unless otherwise specified.

<sup>b</sup>Number of patients.

The clinical characteristics of the patients with recurrence within 6 months, and without recurrence within 6 months are summarized in Table 1. The recurrence within 6 months was significantly associated with higher rates of CRLM size ≥3 cm ( $P = 0.003$ ) and H2-classification ( $P = 0.002$ ). Multivariate analysis showed that the only independent risk factor for recurrence within 6 months after initial hepatectomy was H2-classification ( $P = 0.032$ ).

Figure 3 shows disease-free survival (DFS) and OS curves of patients classified as H1 who did or did not receive adjuvant chemotherapy. The 1-, 3-, and 5-year DFS and OS rates were similar in the 64 patients who were and the 47 who were not administered adjuvant chemotherapy.

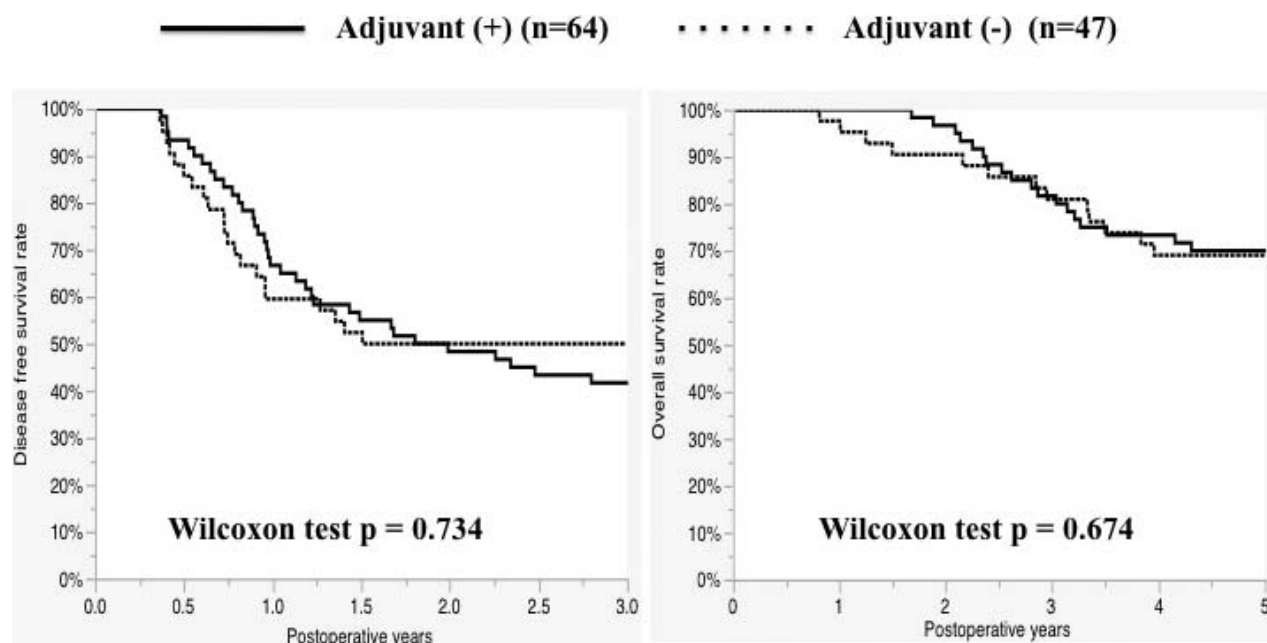
In contrast, the DFS in patients classified as H2 was markedly better in the 14 patients who received adjuvant chemotherapy (18 months) than in the eight patients who did not receive adjuvant chemotherapy (8 months), and in all patients who did not receive adjuvant chemotherapy but experienced recurrence within 2 years after initial hepatectomy ( $P = 0.001$ ; Fig. 4). In addition, the 1-, 3-, and 5-year

OS rates were significantly higher in the 14 H2 patients who received adjuvant chemotherapy (93%, 79%, and 57%, respectively) than in the eight patients who did not (75%, 13%, and 13%, respectively;  $P = 0.004$ ; Fig. 4).

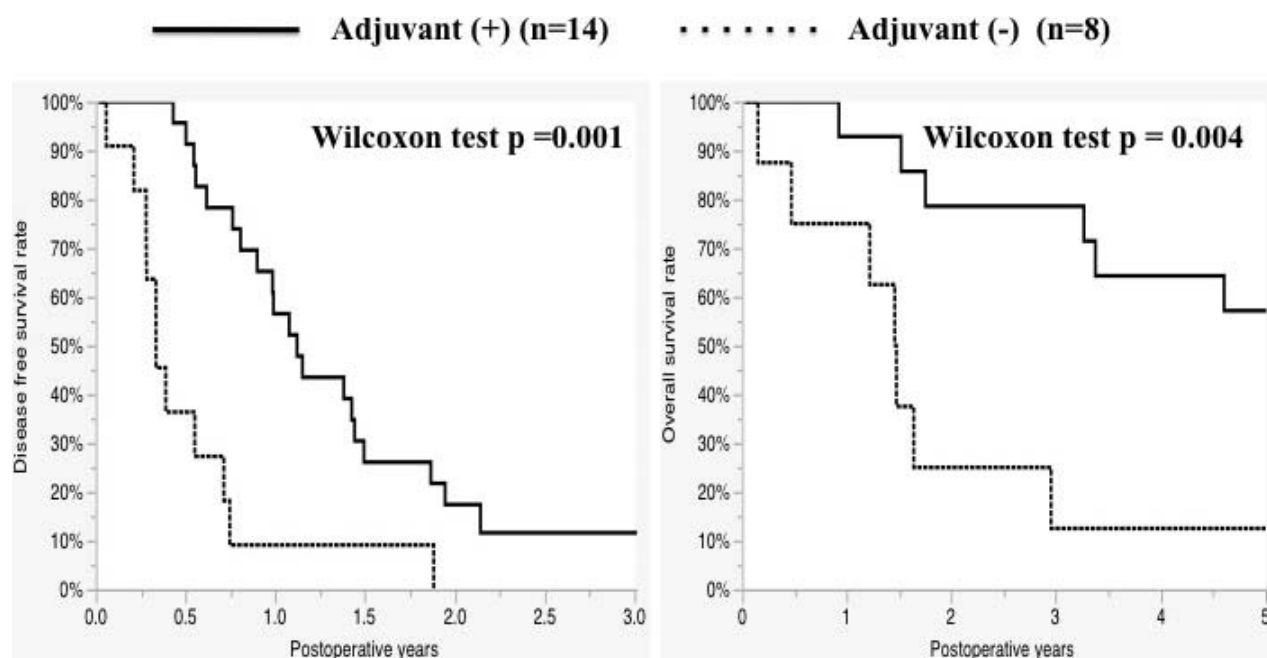
Table 2 compares the outcomes after initial hepatectomy among patients who experienced recurrence within 6 months, at 6 to 12 months, and at >12 months. Liver recurrence was more frequent in patients who experienced recurrence within 6 months (9/14; 64%) than in those who experienced recurrence at 6 to 12 (14/38; 37%) and >12 (12/31; 38%) months. First recurrent tumors were rarely treated by resection in patients who experienced recurrence within 6 months (5/14; 36%) than in patients who experienced recurrence at 6 to 12 (20/38; 53%) and >12 months (21/31; 68%;  $P = 0.044$ ).

## Discussion

This study showed that patients with tumor recurrence within 6 months after initial hepatectomy for colorectal liver metastasis (CRLM) had a poorer



**Fig. 3** OS and DFS after hepatectomy for colorectal liver metastasis in patients classified as H1 who did and did not receive adjuvant chemotherapy. Disease-free and OS curves were similar in patients who did (n = 64, solid lines) and did not (n = 47, dotted lines) receive adjuvant chemotherapy. There was no significant difference in disease-free and OS rate when comparing the 2 groups.



**Fig. 4** OS and DFS after hepatectomy for colorectal liver metastasis in patients classified as H2 who did and did not receive adjuvant chemotherapy. All patients who did not receive adjuvant chemotherapy experienced recurrence within 2 years after hepatectomy. The 3- (79% versus 13%) and 5-year (57% versus 13%) OS rates were significantly higher in patients who did (n = 14; solid lines) than did not (n = 8, dotted lines) receive adjuvant chemotherapy ( $P = 0.004$ ).

Table 2 Comparison of recurrence site and treatment according to the time to recurrence after curative hepatectomy in CRLM patients

Factors	≤6M (n = 14)	6-12M (n = 38)	>12M (n = 31)	P value
Site of recurrence, n (%)				NS
Liver only	9 (64)	14 (37)	12 (38)	
Lung only	3 (21)	6 (16)	8 (26)	
Other site	0 (0)	4 (10)	3 (10)	
Multiple	2 (14)	14 (37)	8 (26)	
Treatment for recurrence, n (%)				0.044
Resection	5 (36) <sup>a</sup>	20 (53)	21 (68)	
Chemotherapy	5 (36)	14 (37)	8 (26)	
None	4 (28)	4 (10)	2 (6)	

6-12 mo, 6-12 months recurrence after surgery; >12 mo, recurrence more than 12 months after surgery.

<sup>a</sup> ≤6 months versus >12 months.

prognosis than patients who experienced recurrence after 6 months. H2-classification of CRLM was the only independent risk factor for recurrence within 6 months after initial hepatectomy, suggesting that these patients receive neoadjuvant chemotherapy.

The time of recurrence after initial hepatectomy for CRLM is often correlated with the malignant potential of the tumor, with early recurrence associated with poorer prognosis. For example, the prognosis of patients with recurrence within 6 months was significantly poorer than that of patients with recurrence after >6 months.<sup>15</sup> Similarly recurrence within 1 or 2 years after hepatectomy was associated with poorer prognosis than later recurrence.<sup>16,17</sup>

We found that 17% of patients undergoing curative hepatectomy for CRLM developed recurrence within 6 months, and that those with recurrence within 6 months had a poorer prognosis than patients with recurrence after 6 months. The risk factors for early recurrence previously reported, such as tumor doubling time, CEA level, tumor size, multiple metastasis, positive surgical margin, lymph node metastasis, histology of the primary tumor, and clinical risk score, were not observed in these patients.<sup>2,5,6,18-23</sup> The H2-classification of CRLM was a risk factor for recurrence within 6 months after hepatectomy in this study.

We also found no clear evidence showing that perioperative chemotherapy was effective in improving OS. Although the 5-year DFS rate was shown to be significantly higher in patients who received 5-FU/LV plus surgery than in patients who received surgery alone, their 5-year OS rates did not differ significantly.<sup>24</sup> Moreover, assessments of preoperative neoadjuvant chemotherapy showed that the 3-year progression-free survival rate was significantly higher in patients who received preoperative FOLFOX followed by surgery than in

patients who received surgery alone (10), but that OS rates were similar (HR = 0.87, 95% CI: 0.66-1.14,  $P = 0.303$ ).<sup>11</sup>

The inability of adjuvant chemotherapy to improve OS in patients with resectable CRLM may have been due to the curative ability of hepatectomy in most patients. Adjuvant chemotherapy, however, may have considerable impact on outcomes after curative hepatectomy in selected patients.

Most patients who experience tumor recurrence within 6 months after hepatectomy are not administered sufficient chemotherapy. Unlike in Europe and the United States, most patients in Japan receive adjuvant chemotherapy after surgery. Our study found that the H2-classification of CRLM was a risk factor for recurrence within 6 months after hepatectomy. A comparison of DFS and OS in patients stratified by H-classification showed that the 5-year OS rates were 62% to 64% in the H1-group, similar to previous reports.<sup>25,26</sup> Moreover, the DFS and OS curves were very similar in H1 patients who did and did not receive adjuvant chemotherapy. In contrast, adjuvant chemotherapy improved OS in patients classified as H2-group, with most patients who did not receive adjuvant chemotherapy experiencing tumor recurrence within 2 years after initial hepatectomy. These findings suggest the need for adjuvant chemotherapy in patients with tumors classified as H2.

The liver has been reported to be the most common site of recurrence (43%) after hepatectomy for CRLM.<sup>27</sup> We found that the recurrence rates in the remnant liver after curative hepatectomy for CRLM in patients with recurrences at ≤6, 6 to 12, and >12 months were 64%, 37%, and 38%, respectively. However, patients who experienced recurrence within 6 months had a reduced opportunity to undergo resection therapy than patients in the other groups. Repeat hepatectomy can enhance

long-term survival, with 5-year survival rates of 47.1%, 32.6%, and 23.8% after the first, second, and third hepatectomies, respectively.<sup>28</sup> Patients with repeat pulmonary metastases secondary to CRC and  $\leq 4$  metastases had a median survival of 72.6 months and a 5-year OS rate of 53.8%.<sup>29</sup> Patient prognosis can be improved if the recurrent lesion is resectable and is removed surgically.

Finally, laparoscopic hepatectomy has spread worldwide rapidly recently, and it is reported that laparoscopic hepatectomy can be superior to open hepatectomy in elderly patients in particular in the point of respiratory related complications.<sup>30</sup> However, there were around 40% of  $\geq 70$  years old, and laparoscopic hepatectomy was performed as few as 30% in this study. As a result, they didn't have an effect on early recurrence.

## Conclusion

These findings suggest that eligible patients should receive adjuvant chemotherapy, and that patients classified as H2 should receive preoperative adjuvant chemotherapy.

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