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ORIGINAL ARTICLE

Surgical strategy for colorectal cancer with synchronous liver and extrahepatic metastases: A scoring system and decision tree model

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Abstract

Background: The role of hepatectomy in a specific group of patients with synchronous colorectal cancer with liver metastases (SCRLM) and synchronous extrahepatic disease (SEHD) is still unclear. The aim of this study was to evaluate the efficacy of liver surgery and define the selection criteria for surgical candidates in patients with SCRLM + SEHD.

Methods: Between July 2007 and October 2018, 475 patients with colorectal cancer with liver metastases (CRLM) who underwent liver resection were retrospectively reviewed. Sixty-five patients with SCRLM + SEHD were identified and included in the study. Clinical pathological data of these patients were analyzed to evaluate the influence on survival. Important prognostic factors were identified by univariate and multivariate analyses. The risk score system and decision tree analysis were generated according to the important prognostic factors for better patient selection.

Results: The 5-year survival rate of patients with SCRLM + SEHD was 21.9%. The most important prognostic factors were SCRLM number of more than five, site of SEHD other than the lung only, inability to achieve SCRLM + SEHD R0 resection, and *BRAF* mutation of cancer cells. The proposed risk score system and decision tree model easily discriminated between patients with different survival rates and identified the profile of suitable surgical patients.

Conclusion: Liver surgery should not be a contraindication for patients with SCRLM + SEHD. Patients with complete SCRLM + SEHD R0 resection, SCRLM number less than or equal to five, SEHD confined to the lung only, and wild-type *BRAF* could have favorable survival outcomes. The proposed scoring system and decision tree model may be beneficial to patient selection in clinical use.

Keywords: Colorectal cancer with liver metastases; Extrahepatic metastases; Liver resection; Scoring system; Synchronous metastases

1. INTRODUCTION

Colon and rectal cancer (CRC) constitute the third most common cancer worldwide,[1] and approximately 26% to 30% of CRCs develop synchronous or metachronous liver metastases during the disease course.[2,3] Liver metastases are the main cause of death, and liver resection of colorectal cancer with liver metastases (CRLM) is the most effective treatment strategy, providing the chance of cure and long-term survival.[4,5] Under the modern oncosurgical approach, the 5-year survival rate after liver resection could reach approximately 50%.[6,7] The criteria of liver resection have been gradually expanded to initially unresectable CRLM, such as multiple bilobular liver disease or large metastatic liver tumors with major vascular invasion.[4,8] However, CRLM with synchronous extrahepatic disease (SEHD) remains a controversial issue due to the poor survival outcome after surgery in historical reports.[9]

In the past decade, several studies focusing on CRLM with SEHD have discovered that the complete resection of CRLM and SEHD could provide patients with a 5-year survival rate of approximately 26% to 32%.[10,11] Furthermore, in selected patients, the long-term survival may be equivalent to that in CRLM patients without SEHD.[11–14] Therefore, it has recently

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been proposed that the presence of SEHD should no longer be considered a contraindication to liver metastasectomy.[10,15] Although several selection criteria or risk score systems have been proposed to define patients who could possibly benefit from surgery, a consensus on the treatment strategy has not been well established, especially regarding the following specific group of patients: those with synchronous colorectal cancer with liver metastases and synchronous extrahepatic disease (SCRLM + SEHD). These patients have the most complicated clinical scenario, and the consideration of treatment should include the approaches to the primary tumor, liver metastasis, and extrahepatic lesions simultaneously. Very few studies have specifically addressed the surgical strategy of this group of patients, and the role of surgery is still unclear.

Therefore, the present study aimed to evaluate the long-term outcome of patients with SCRLM + SEHD after liver resection. Furthermore, we identified important prognostic factors associated with survival outcomes. Most importantly, we propose a risk score system and decision tree model that would be clinically useful tools to identify appropriate patients for liver surgery.

2. METHODS

2.1. Patients and follow-up

Between July 2007 and December 2018, 475 patients diagnosed with CRLM underwent initial liver and colorectal surgery at our tertiary referral medical center. Of these patients, 317 were diagnosed with SCRLM, including 65 patients with SEHD (Fig. 1). The data of these 65 patients were identified in our prospective database and retrospectively analyzed. The study was approved by the institutional review boards of the Taipei Veterans General Hospital.

The CRLM multidisciplinary team at our institution was founded in July 2007. Before treatment initiation, the strategies of simultaneous or staged liver-colorectal resection, treatment of extrahepatic disease (EHD), neoadjuvant chemotherapy administration, and subsequent adjuvant chemotherapy were discussed and decided upon by our multidisciplinary team comprising 4 hepatobiliary surgeons, 11 colorectal surgeons, 2 medical oncologists, 2 thoracic surgeons, 2 radiologists, and 1 pathologist. The liver tumor resectability and hepatectomy extent were evaluated by at least two of four hepatobiliary surgeons. All patients were followed up at our integrated outpatient clinic and received subsequent treatment.

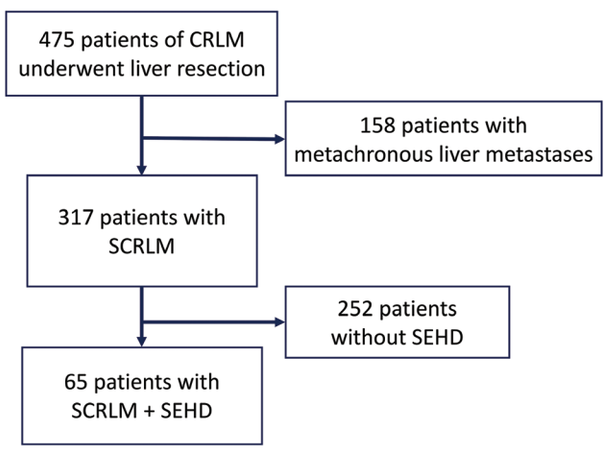

Fig. 1 Selection of the study group. Sixty-five of 475 patients were diagnosed with synchronous colorectal cancer with liver metastases and synchronous extrahepatic disease (SCRLM + SEHD).

2.2. Data collection

Patients' clinicopathological features and follow-up data were prospectively collected. Anatomical resection of fewer than three Couinaud segments or wedge resections was defined as minor hepatectomy and resection of three or more Couinaud segments was considered major hepatectomy. The diagnosis of EHD was based on the results of imaging studies, including CT, MRI, PET scans, bone scans, and pathology reports of EHD lesions. Clinicopathological features, surgical and medical treatment modalities, and oncological outcomes were reviewed for analysis. Overall survival (OS) was defined as the survival days after resection of the SCRLM.

2.3. Statistical analysis

The survival rates were estimated using the Kaplan–Meier method and were compared using the log-rank test; p values of <0.05 were considered significant. Risk factors associated with OS were determined by using the Cox proportional hazard model for multivariate survival analysis. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences version 25.0 for Windows, SPSS, Inc., Chicago, IL, USA).

2.4. Risk score system and decision tree analysis

SEHD risk score system was developed based on the results of multivariate analysis for independent prognostic factors of OS. Patients were assigned to different risk groups according to the sum of risk score points. To further develop the predictive algorithms for surgical treatment of SCRLM + SEHD, we used the decision tree model based on the chi-square automatic interaction detector (CHAID). Patients with OS greater than or equal to median survival were considered to have favorable survival outcomes after liver surgery. The significant prognostic factors for OS in multivariate analysis were used in the decision tree, and patients were divided into different survival groups according to the predictive oncological outcomes.

3. RESULTS

3.1. Patient demographics

Clinicopathological characteristics of the 65 patients are outlined in Table 1. The median age of these patients was 56.5 (range: 30-87) years, and more than half of the patients (56.9%) were male. The median body mass index observed in the study population was 22.84. A minority of the patients presented with hepatitis B surface antigen at 13.8%, anti-hepatitis C antibody at 4.6%, and cirrhosis accounting for 3% of the cases. The majority of the patients (86.2%) had poorly differentiated CRC tumor grade and local regional lymph node metastasis (92.3%). Half of the patients had multiple liver metastases, and the median number of CRLM was two. To surgically remove CRLM, nearly half of the patients required major liver resection, and two-thirds of the patients underwent simultaneous colorectal-liver resection for primary and liver metastatic lesions. Approximately two-thirds of patients received induction neoadjuvant chemotherapy before liver resection, and most patients (87.7%) received subsequent adjuvant chemotherapy. R0 resection for CRLM was achieved in most of the patients (86.2%); however, only one-third of patients (33.8%) received globally curative resection of all CRLM and EHD lesions.

The distribution of EHD locations is listed in Table 2. Patients were classified into five major categories: lung only, distant lymph node, peritoneal seeding, multiple sites, and others. The

Table 1

Patient characteristics

Characteristics	Patients (n = 65)
Gender	
Male/female (%)	37/28 (56.9/43.1)
Age	
Median (range), y	56.5 (30-87)
Body mass index	
Median (range), kg/m^2	22.84 (16.55-36.28)
Albumin	
Median (range), g/dL	3.9 (2.7-4.7)
Total bilirubin	
Median (range), mg/dL	0.51 (0.27-2.3)
Platelet count	
Median (range), /μL	200 500 (77 000-609 000)
Creatinine	
Median (range), mg/dL	0.72 (0.39-2.61)
Hepatitis B surface antigen positive	
Yes/no/NA (%)	9/46/10 (13.8/70.8/15.4)
Anti-hepatitis C antibody positive	
Yes/no/NA (%)	3/50/12 (4.6/76.9/18.5)
Cirrhosis	
Yes/no (%)	2/63 (3/97)
Primary CRC[a] T stage	
T1-T3/T4 (%)	43/22 (66.2/33.8)
Primary CRC N stage	
N0/N1-2 (%)	5/60 (7.7/92.3)
Primary CRC tumor grade	
Moderate/poor (%)	9/56 (13.8/86.2)
Primary CRC location	
Right/left/rectum (%)	13/30/22 (20/46/33)
CEA[b] level before hepatectomy	
Median (range), ng/mL	15.5 (0.8-1099)
CA 19-9[c] level before hepatectomy	
Median (range), U/mL	34.3 (0.7-4299)
Maximum diameter of the CRLM[d]	
Median (range), mm	31 (5-118)
Number of CRLM	
Median (range)	2 (1-16)
Multiple CRLM	
Single/multiple (%)	29/36 (44.6/55.4)
Type of liver resection	
Minor/major (%)	34/31 (52.3/47.7)
Simultaneous colorectal-liver resection	
Simultaneous/staged (%)	44/21 (67.7/32.3)
Neoadjuvant chemotherapy before liver resection	
Yes/no (%)	42/23 (64.6/35.4)
Adjuvant chemotherapy after liver resection	
Yes/no (%)	57/8 (87.7/12.3)
Surgical curability of CRLM	
R0/R1-2 (%)	56/9 (86.2/13.8)
Surgical curability of CRLM + EHD[e]	
R0/R1-2 (%)	22/43 (33.8/66.2)
BRAF mutation	
Wild type/mutation (%)	62/3 (95.4/4.6)
KRAS mutation	
Wild type/mutation (%)	42/23 (64.7/35.3)

[a]CRC = colorectal cancer.
[b]CEA = carcinoembryonic antigen.
[c]CA 19-9 = carbohydrate antigen 19-9.
[d]CRLM = colorectal cancer with liver metastasis.
[e]EHD = extrahepatic disease.

most frequent sites of extrahepatic involvement were the lungs only (n = 27, 41.4%), followed by multiple sites (n = 19, 26.2%).

3.2. Survival and prognostic factors

The OS after liver resection is presented in Fig. 2. The 3-year and 5-year OS rates were 39.6% and 21.9%, respectively (Fig. 2A), with a median survival after hepatectomy of 2.3 years. Patients who underwent complete R0 resection of all metastatic lesions had significantly better survival than patients who did not. The 3-year and 5-year OS rates were 63.6% vs 27.0% and 48.5% vs 8.3%, respectively ($p < 0.001$) (Fig. 2B).

The risk factors associated with OS after liver resection are summarized in Table 3. Seven factors were associated with worse OS in univariate analysis: poor CRC tumor grading, R1/R2 CRLM resection, CRLM number >5, multiple EHD sites, site of EHD other than the lung only, inability to achieve CRLM + EHD R0 resection, and *BRAF* mutation of cancer cells. Multivariate analysis was performed to identify independent prognostic factors of OS. Four factors were associated with an increased risk of mortality: CRLM number >5 (hazard ratio [HR], 6.799; 95% CI, 1.682-27.484), site of EHD other than lung only (HR, 2.836; 95% CI, 1.080-8.211), inability to achieve CRLM + EHD R0 resection (HR, 5.391; 95% CI, 1.679-17.307), and *BRAF* mutation of cancer cells (HR, 9.827; 95% CI, 1.947-49.610).

3.3. Risk score system

We developed a simple weighted scoring system. EHD other than lung site only, inability to achieve CRLM + EHD R0 resection, CRLM number more than five, and *BRAF* mutation of cancer cells were assigned weighted scores according to their hazard ratios. EHD other than lung site only was assigned one point, inability to achieve CRLM + EHD R0 resection and CRLM number more than five were assigned two points, and *BRAF* mutation of cancer cells was assigned three points. Total score points ranged from 0 to 6, and the median risk score was two. Patients were categorized into (1) low-risk group (score 0), (2) intermediate-risk group (score 1-2), (3) high-risk group (score 3-4), and (4) extremely high-risk group (score 5-6). The scoring system could significantly discriminate the OS after hepatectomy among different risk groups (Fig. 3, $p < 0.001$). Patients in the low-risk group had the best outcomes, with 3- and 5-year survival rates up to 87.5% and 75%, respectively, whereas patients in the extremely high-risk group had the worst prognosis, with a 0% 3-year OS. Although the low-risk group demonstrated excellent OS performance, the 3- and 5-year OS in the intermediate-risk group patients significantly dropped to 50% and 21.4%, respectively. In the high-risk group of patients, there was only a 3-year OS of 17.3% but no 5-year survival (Table 4.).

3.4. Decision tree model for surgical decision making

The decision tree model was generated by CHAID analysis to establish the predictive algorithms for surgical outcomes. Patients with OS ≥2.3 years (median survival) were considered to have favorable survival, and the key factors for favorable outcome prediction were R0 resection of CRLM + EHD, CRLM number less than or equal to five, and EHD site confined to the lung only (Fig. 4). In this decision tree model, the most decisive factor was R0 resection of CRLM + EHD. Patients with R0 resection of CRLM + EHD lesions would have >70% chance to survive >2.3 years and were considered in the good outcome group. Next, in patients without R0 resection of CRLM + EHD lesions, the second important decision factor was the CRLM number. Patients with CRLM number more than five would have no chance to survive >2.3 years and were considered to belong to the poor survival group. In patients without R0 resection of CRLM + EHD but with CRLM number less than or equal to five, the deciding factor of the third step would be the

Table 2

Location of extrahepatic disease

Extrahepatic tumor site	N	%	3-y OS (%)	5-y OS (%)	Median survival (mo)
Lung only	27	41.4	55.6	36.4	37.5
Distant lymph node	7	10.8	42.9	0	25.7
Peritoneum seeding	7	10.8	14.3	0	26.6
Others[a]	5	10.8	60.6	30.0	36.4
Total multiple sites	19	26.2	18.0	0	16.4
Lung + distant LN[b]	5	7.7	…	…	…
Lung + others	2	3.1	…	…	…
Lung + peritoneum seeding	1	1.5	…	…	…
Lung + bone	2	3.1	…	…	…
Other multiple sites[c]	9	10.8	…	…	…
Total	65	100	39.6	21.9	28.6

LN = lymphonde, OS = overall survival.

[a]Others: bladder, fallopian tube, seminal vesicle and prostate, small intestine, uterus, ovaries.

[b]Other multiple sites: peritoneal, appendix, small bowel mesentery, ovary, terminal ileum, uterus, kidney, chest wall, rib, distant lymph nodes.

site of EHD. If the EHD site was confined to the lung only, these patients could still have a >70% possibility of survival of >2.3 years and would belong to the good outcome group. If the EHD extended beyond the lung site only, the patients have only a one-third chance to survive for >2.3 years, and their survival would be a modest outcome.

4. DISCUSSION

Concomitant presentation of liver metastasis and extrahepatic metastatic lesions poses the most difficult challenge for multidisciplinary teams to provide healthcare to colorectal cancer patients. In the recent decade, CRLM with concomitant EHD has gradually been no longer considered a contraindication to liver resection due to advances in surgical techniques, chemotherapy regimens, and the oncosurgical approach.[10,11,13–16] Even in the selected patients with a fair survival rate similar to patients without EHD, it was also discovered that the specific group of patients with synchronous CRLM carried a worse prognosis, and the surgical strategy of these patients is still unclear. In our study, the 5-year survival rate of patients with SCRLM + SEHD after liver resection was 21.9%, providing evidence that liver metastasectomy could still provide long-term survival to these patients in the most complicated clinical situation. To further clarify the role of surgery and identify suitable surgical patients, four important prognostic factors were identified in our studies: inability to achieve CRLM + EHD R0 resection, CRLM number greater than five, EHD other than the lung site only, and *BRAF* mutation of cancer cells. Consistent with several previous reports, complete R0 resection of the CRLM and EHD seemed to have the greatest impact on survival outcomes.[10,17] Total removal of the CRLM and EHD lesions yielded a 5-year survival rate of 48.5%, whereas incomplete R0 metastasectomy of all lesions resulted in a poor 5-year survival rate of <10% in our study. Therefore, complete removal of all metastatic lesions should be the cornerstone of the whole surgical management strategy.

The presentation of EHD in different sites has been reported to have different survival outcomes in several studies. The lung site is the most favorable metastatic site, with the reported 5-year survival rate reaching 32% to 60%,[11,13,18] whereas lymph node metastasis and peritoneal carcinomatosis carry survival outcomes inferior to that with lung metastasis.[12,15,19] In a meta-analysis conducted by Hadden et al[10] that included 2308 patients with CRLM and EHD from 52 studies, lung metastasis had a survival outcome superior to those of peritoneal metastasis and lymph node metastasis. The reported median survival period for patients with lung, peritoneal, and lymph node metastases was 42, 29, and 25 months, respectively. The worst survival outcomes were exhibited in patients with multiple sites of EHD involvement, and the 5-year survival rates were <14%.[11,13,19] In the present study, lung site-only extrahepatic metastasis had the best 5-year survival rate of 36.4%. In addition, among the nine patients who survived >5 years, eight patients (88.9%) had lung-only metastasis. In a retrospective analysis of 150 patients with CRLM with lung metastasis after sequential resection of liver and lung metastatic lesions, 75 patients obtained survival of >5 years after the first metastasectomy. Among these 75 patients, 15 (20%) patients were considered to be cured due to disease-free survival of >5 years.[18] Even in patients with unresectable lung metastases, surgical removal of CRLM may still provide a potential benefit to patients. Albertsmeier et al[20] compared the survival outcome between patients with and without liver resection in the setting of CRLM with concomitant unresectable lung metastasis. Liver metastasectomy still provided a significantly longer median survival (2.6 vs 1.5 years, $p = 0.0182$), and liver resection was the most important prognostic factor to determine survival. Together with the collaborative evidence from the literature and the findings of our study, this may suggest that aggressive surgical treatment of CRLM with lung site-only metastasis should be a reasonable therapeutic strategy to provide patients long-term survival.

In addition to the traditional surgical-anatomical factors for survival risk assessment, evaluation of the biological behavior of the tumor by biomarker examination should be equally important. In several previous studies, *KRAS* mutation was discovered to have an important influence on the survival of CRLM patients who underwent liver resection.[21,22] The traditional clinical risk score (CRS) was proposed to be replaced by the new MD Anderson modified (mCRS) and Genetic and Morphological Evaluation scores, in which *KRAS* mutations were incorporated into the scoring systems to better predict survival outcomes.[23] However, in our study, *KRAS* mutation was not discovered to be a prognostic factor. Instead, *BRAF* mutation had a significant prognostic effect on patient survival. This finding is in concordance with the results of our previous research; the *BRAF* genotype was an independent prognostic biomarker in CRLM patients after liver metastasectomy, while *KRAS* mutation was not.[24] It was considered that *BRAF* mutation confers a distinct biological behavior to tumor cells and is usually refractory to standard chemotherapy regimen treatment.[25] For metastatic disease of CRC origin, perioperative neoadjuvant and adjuvant chemotherapy is almost mandatory even after curative metastasectomy surgery. The presence of *BRAF* mutation makes it

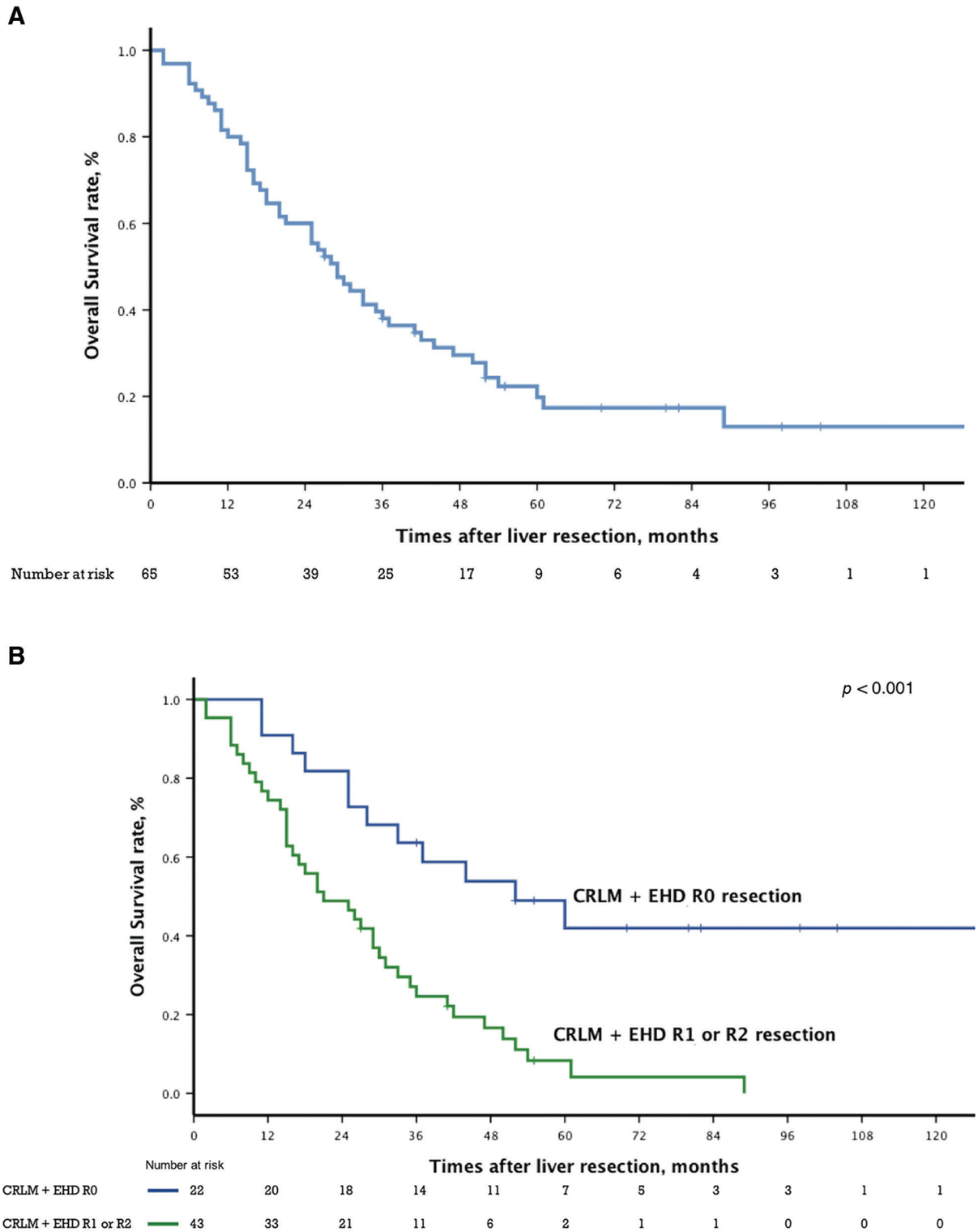

Fig. 2 Overall survival (OS) after hepatectomy of the patients. A, For all patients, the 3-y OS was 39.6%, and the 5-y OS was 21.9%. The median survival was 2.3 y. B, Survival curve of EHD R0 resection or not. Patients with complete R0 resection of all metastatic lesions had significantly better survival than patients without complete R0 resection, $p < 0.001$. EHD = extrahepatic disease.

challenging for multidisciplinary teams to provide optimal treatment. However, the prevalence of *BRAF* mutation among such patients seems not very high; our rate was 4.6%, and it was reported in the literature to be 2.1% to 6.1%.[24,26,27] Although

Table 3

Univariate and multivariate analyses for prognostic factors

	Reference		Univariate		Multivariate	
			HR (95% CI)	*p*	HR (95% CI)	*p*
Gender	Male	Female	1.078 (0.621-1.873)	0.789	…	…
Age	<65	≥65	1.485 (0.762-2.894)	0.762	…	…
Primary CRC location	Right	Left/rectum	0.909 (0.466-1.771)	0.779	…	…
Primary T	T2-3	T4	0.761 (0.428-1.353)	0.352	…	…
Primary N	N0	N1-2	3.762 (0.907-15.613)	0.068	1.495 (0.194-11.524)	0.7
Primary CRC tumor grade	Moderate	Poor	2.272 (1.101-4.687)	0.026	1.182 (0.657-4.997)	0.251
CRLM R0 resection	R0	R1-2	2.496 (1.158-5.380)	0.020	…	…
CRLM tumor size	<60 mm	≥60 mm	2.827 (0.852-9.382)	0.089	…	…
Number of CRLM tumor	≤5	>5	7.569 (2.762-20.741)	< 0.001	6.799 (1.682-27.484)	0.007
Multiple EHD sites	Single	Multiple	2.170 (1.182-3.984)	0.012	…	…
EHD in the lung only	Lung	Anywhere else	2.055 (1.137-3.714)	0.017	2.836 (1.080-8.211)	0.049
CRLM and EHD R0 resection	R0	R1-2	3.217 (1.689-6.334)	< 0.001	5.391 (1.679-17.307)	0.005
CA199 before hepatectomy	<70	≥70	1.640 (0.849-3.170)	0.141	…	…
CEA before hepatectomy	<10	≥10	1.089 (0.612-1.940)	0.772	…	…
Hepatitis B surface antigen	Negative	Positive	1.906 (0.875-4.150)	0.104	…	…
Anti-hepatitis C antibody	Negative	Positive	1.449 (0.441-4.759)	0.541	…	…
Cirrhosis	No	Yes	1.651 (0.395-6.897)	0.492	…	…
KRAS mutation	Wild type	Mutation	0.836 (0.454-1.540)	0.565	…	…
BRAF mutation	Wild type	Mutation	4.197 (1.234-14.282)	0.022	9.827 (1.947-49.610)	0.006

CEA = carcinoembryonic antigen; CRLM = colorectal cancer with liver metastases; CRC = Colon and rectal cancer; EHD = extrahepatic disease; HR = hazard ratio.

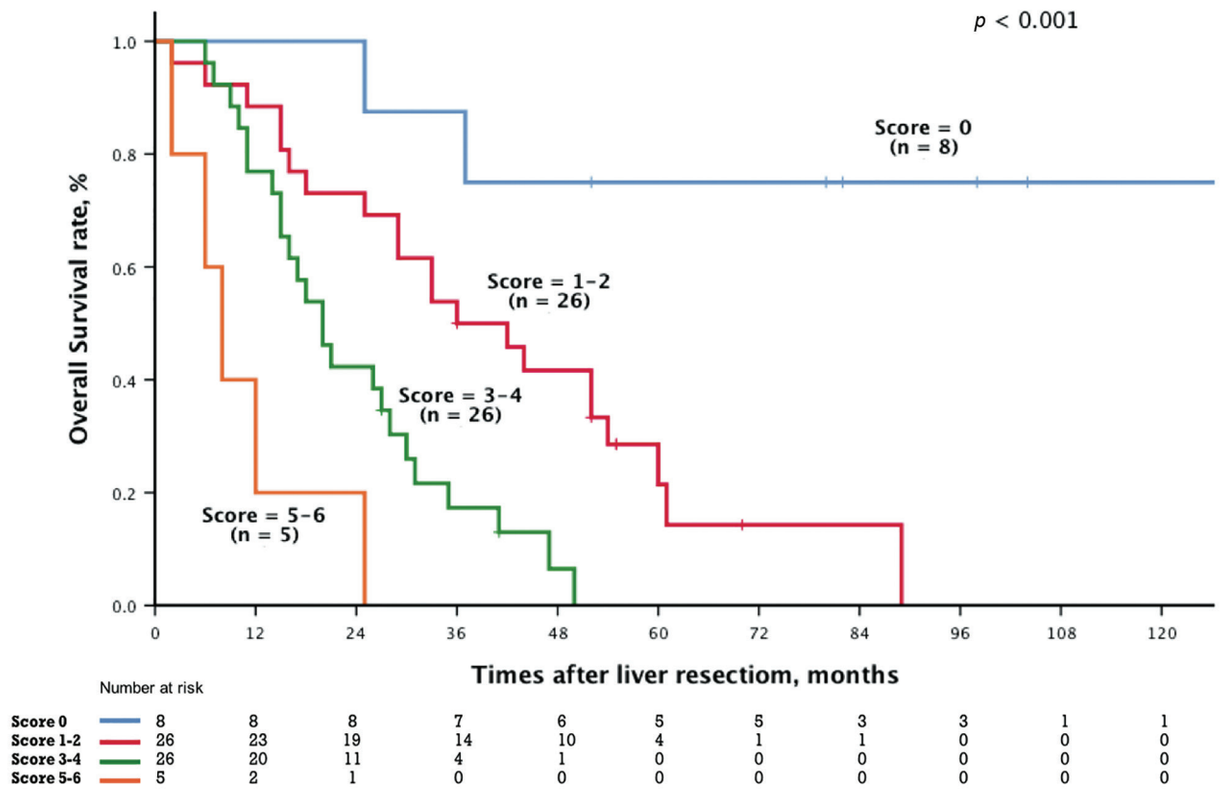

Fig. 3 Overall survival (OS) curves stratified by the risk score system. The survival amount in each group was significantly different ($p < 0.001$).

we recognize that *BRAF* mutation should be an important factor for treatment consideration, how this information should be incorporated into treatment strategy decisions needs to be further investigated.

To select appropriate patients for surgery, several risk score systems have been proposed in previous studies.[11–14,18] The patients in the low-risk groups, referred to as having no or very few risk points, achieved OS similar to that of patients without

Table 4

The overall survival of patients in different score groups

Score	No. of patients	3-y OS (%)	5-y OS (%)
0	8	85.7	75
1-2	26	50	21.4
3-4	26	17.3	0
5-6	5	0	0

OS = overall survival.

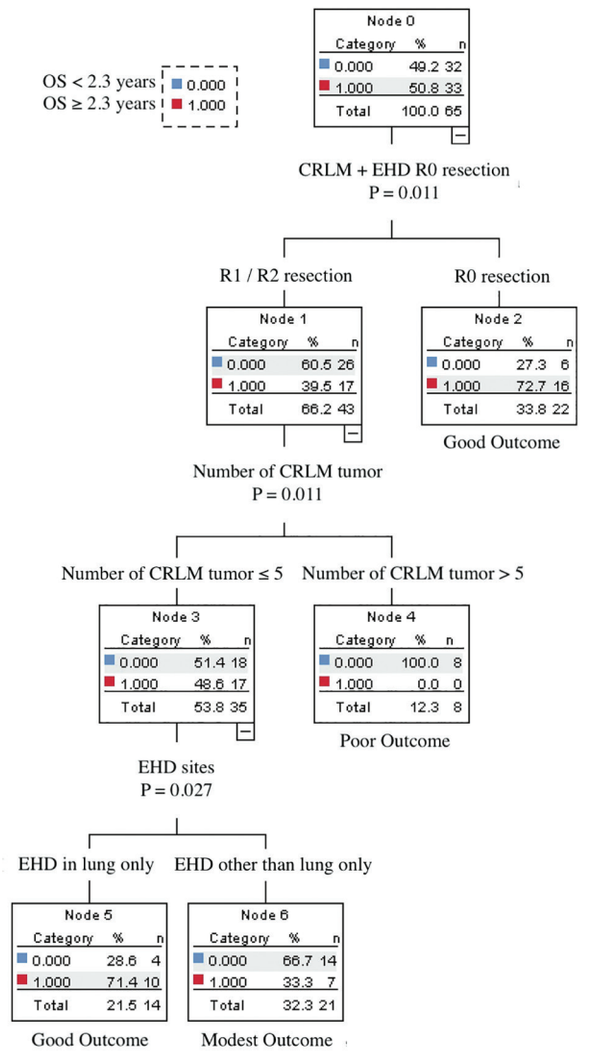

Fig. 4 Decision tree. Decision tree predicting survival under surgical intervention of SCRLM + SEHD according to the completeness of CRLM + EHD R0 resection, number of liver metastases, and site of EHD. EHD = extrahepatic disease; SCRLM = synchronous colorectal cancer with liver metastases; SEHD = synchronous extrahepatic disease.

EHD, whereas patients in the high-risk groups with multiple risk points had little chance of long-term survival. These scoring systems could be useful tools for clinicians to identify suitable surgical patients and decision making. Although the variables among these scoring systems are not unified, they mainly consist of anatomical-pathological factors, including the T stage of primary cancer, location of colorectal cancer, lymph node metastasis, number and size of CRLM, interval of CRLM and EHD developed from CRC diagnosis, site of EHD, number of EHD tumors, and complete resection of metastatic tumors. The risk score system in the present study not only consisted of anatomical factors, which were CRLM number less than or equal to five, EHD presented only in the lung site, and complete R0 resection of all metastatic lesions but also included a biological marker, *BRAF* mutation. This may also reflect the importance of the biological response to chemotherapy even in the selection of patients for surgery. Combining the four abovementioned factors, the scoring system easily discriminated good surgical-candidate patients (zero points) with a 5-year OS of 75% from poor candidate patients (five to six points) with no 5-year OS. To further facilitate clinical decisions, CHAID decision tree analysis was applied in this study. Whether CRLM and EHD tumors can be totally resected is the most important priority in surgical decisions. If R0 resection of CRLM and EHD cannot be completed, the liver tumor burden in terms of the liver tumor number and site of EHD may be the next important factor for decision making. Only patients with a low CRLM number and EHD in the lung site may still have good surgical outcomes. This algorithm flow chart may help to define the profile of patients with different possibilities of benefit from surgery and could, in addition to risk score systems, be a helpful tool for surgical patient selection. The decision tree model for predicting whether a patient's survival would surpass the median survival time was built using the CHAID method. Nonetheless, the decision tree does not incorporate *BRAF* mutations in its decision-making process, which can be attributed to the discrepancies in statistical methodologies employed. This may be associated with the rarity of *BRAF* mutation cases, constituting one of the limitations of the present study. Upon gathering a larger sample size, it is plausible that *BRAF* mutations may potentially play a significant role within the decision tree framework.

There were several limitations in the current study. First, this was a retrospective study with data retrieved from a prospectively collected database, and selection bias may exist. Second, in our research, the number of cases is relatively limited. This is primarily because patients with this particular condition are less likely to undergo surgical treatment. Nonetheless, even with a small sample size, sufficient statistical significance has been achieved, revealing unique characteristics that distinguish this population from other groups. Third, in identifying EHD, lymph node, and lung metastasis were mostly diagnosed by radiological imaging, including CT, MRI, or PET scan, instead of pathological confirmation. However, diagnosis and treatment decisions based on currently available information also reflect our daily practice in the real world. Fourth, although *BRAF* mutation was identified as an important risk factor in our study, the limited number of patients with *BRAF* mutation may have resulted in a potential statistical bias. Fifth, the developed scoring system resulted from a single institution series with a limited number of cases. The efficacy of the scoring system may be further validated by an external cohort in a subsequent study.

In conclusion, in selected patients, liver resection for cases of SCRCLM + SEHD can still yield long-term survival. Key factors for a favorable outcome are complete CRLM + EHD R0 resection, CRLM number less than or equal to five, EHD sites limited to the lung only, and wild-type *BRAF* in cancer cells. In patients with these favorable factors, survival outcomes similar to those for CRLM without EHD may be expected. The proposed risk score system and decision tree model may be useful tools to identify patients who could truly benefit from liver surgery, and these systems can be easily incorporated into our daily practice for surgical decision making.

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