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ORIGINAL ARTICLE

Aggressive Surgical Resection of the Primary Tumor without Metastasectomy First in Stage IV Colon Cancer with Unresectable Synchronous Liver-only-metastases Patients Cannot Provide the Survival Benefits Compared with Chemotherapy First

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Background: Controversy exists over whether aggressive surgical resection of the primary tumor without metastasectomy first or chemotherapy first in stage IV colon cancer with unresectable synchronous liver-only-metastases (CLM) improves patients. **Materials and Methods:** We retrospectively reviewed the outcome of 156 patients initially diagnosed with unresectable synchronous CLM who were under treatment in our institution from January 2004 to December 2012. Patients with extrahepatic diseases or previous hepatic resection were excluded. All patients with a follow-up of at least 3 months were included. Progression-free survival (PFS) and 5-year overall survival (OS) curves were calculated using the Kaplan–Meier method. **Results:** Among the 156 patients with CLM, 43 (27.56%) received aggressive surgical resection of the primary tumor without metastasectomy first, 113 (72.43%) received systemic chemotherapy first. At 5 years, the adjusted PFS and OS in stage IV colon cancer with inoperable metastases were 24.2% and 20.4%, respectively, in the surgical resection of the primary tumor first group and 46.0% and 16.9% in the chemotherapy first group ($P = 0.515$ and $P = 0.742$, respectively). In multivariate analysis, there was no statistical difference in the PFS and 5-year OS between the surgical resection of the primary tumor first group and chemotherapy first. **Conclusion:** Surgical resection of the primary tumor without metastasectomy first in CLM is not associated with improved survival as compared with chemotherapy first. Additional research is necessary to determine which patients may benefit from this intervention.

Key words: Stage IV colon cancer with liver-only metastases, simultaneous surgical resection of primary tumor and metastasectomy, progression-free survival, 5-year overall survival

INTRODUCTION

Colon cancer, the most common metastases arising in the liver, affect 15–20% of patients at the time of diagnosis and develop in 60% of patients as the disease progresses.[1] Notably, only 20% of patients with stage IV colon cancer with unresectable synchronous liver-only-metastases (CLM) present with resectable lesions at diagnosis.[2] For resectable cases, primarily simultaneous colon tumor resection and liver metastasectomy (R0 resection) followed by adjuvant chemotherapy is the sole potentially curative treatment, yielding a 5-year overall survival (OS) rate of up to 50%.[3] Then, optimizing the aggressive primary tumor without metastasectomy first or chemotherapy first is extremely crucial for achieving an optimal R0 resection rate for patients with stage IV CLM with primarily unresectable metastatic tumors.

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Currently, in a substantial number of patients initially diagnosed with unresectable CLM. Conversion chemotherapy can render initially unresectable liver metastasis to secondary resectability using modern chemotherapy regimens that include folinic acid, fluorouracil, and oxaliplatin (FOLFOX) and folinic acid, fluorouracil, and irinotecan (FOLFIRI).[4-6] In addition, chemotherapy efficacy can be increased using monoclonal antibodies, such as cetuximab and bevacizumab.[7,8] Combining chemotherapy with an aggressive repeat surgical resection, radiofrequency ablation (RFA), and transcatheter arterial chemoembolization may yield a potentially curative treatment and a high long-term survival rate for patients with unresectable CLM.[9]

The surgical resection of a liver metastatic lesion provides survival benefits to patients. Prognostic impacts of simultaneous colon and metastatic liver tumor resections on patients with CLM with primarily resectable liver metastasis have been proven.[9] However, for treating colon cancer with unresectable liver metastasis, whether receiving surgical resection of the primary tumor without metastasectomy first or chemotherapy first in stage IV colon cancer with inoperable liver metastases is optimal remains controversial. The purpose of this study was to investigate the survival outcome whether resection of the primary tumor without metastasectomy first in patients with unresectable synchronous CLM is associated with improved OS compared with patients undergoing chemotherapy first.

MATERIALS AND METHODS

Patient selection

From January 2004 to December 2012, 156 patients diagnosed initially with colon cancer with synchronous liver-only metastases (CLM) who were under treatment in our institution (Tri-Service General Hospital, Taiwan) were recruited for this study. All treatment strategies were decided during our multidisciplinary team meetings. Clinical data were extracted from the retrospectively collected Cancer Registry Group, Tri-Service General Hospital. All patients with initial CLM who underwent a rescue surgery and with at least a 3-month follow-up were included. The progression-free survival (PFS) and 5-year OS curves were calculated using the Kaplan–Meier method.

According to the American Joint Committee on Cancer Staging System Manual (sixth and seventh editions) and on the basis of the radiology and pathology reports, 289 patients were diagnosed with stage IV colorectal cancer (CRC) with liver-only metastases in our hospital. These patients underwent a curative surgery or chemotherapy and were enrolled in the study. All operations were performed by colorectal surgeons. Both treatments were relatively well tolerated and associated with manageable toxicities. Patients meeting all of the following criteria were excluded from this study: Patients (1) with known simultaneous surgical resection of primary colon and metastatic liver tumor (R0 resection), (2) with rectal cancer, (3) with concomitant extrahepatic metastatic disease, (4) with a history of malignancy, (5) who had not completed the entire treatment course in our hospital, (6) who lacked follow-up data, (7) with a history of hepatic resection, and (8) who had not received a chemotherapy or palliative treatment. Patients were included from our prospectively maintained institutional database after reviewing individual medical charts.

A total of 156 patients for stage IV colon cancer with inoperable synchronous liver-only metastases included in this retrospective analysis were not randomized and were divided into two groups: (1) Patients with surgical resection of the primary tumor with metastasectomy first and (2) patients with chemotherapy first. After a definitive diagnosis, the decision of recommending a surgery first or chemotherapy first was dependent on the clinical judgment of the attending physicians and that of our multidisciplinary team; these decisions reflected the general performance of the patients and their unresectable liver metastasis stages. In the primary tumor resection with metastasectomy first group, we included all patients who had undergone at least the first stage of the primary colon tumor resection for advanced CLM because of severe bleeding, a symptomatic sign, and an emergent condition in CLM. In the chemotherapy-treated group, we included patients whose performance was similar to those of the surgically treated patients.

Among these patients, 43 (27.56%) received surgical resection of the primary colon tumor without metastasectomy followed by adjuvant chemotherapy, and 113 (54.3%) received chemotherapy with a regimen of infusional FOLFOX/FOFIRI on a 2-weekly 3-day course.

All patients were preoperatively examined using thoracoabdominal imaging (ultrasonography, computed tomography [CT]), routine blood tests, serum tumor marker levels, and colonoscopy. The database included (1) patient demographics, namely name, gender, age, family history, levels of tumor markers (including carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA 19-9]), (2) characteristics of the tumor, namely location, gross appearance, and the critical pathological prognostic features of the tumor, and invasion pattern of the cancer tissue.

A preoperative chemotherapy was planned when liver metastases were primarily unresectable (i.e., when completely removing all CLM results in insufficient remnant liver volume),

and chemotherapy was considered for cases with synchronous metastases (diagnosed before, during, or within 3 months of the primary colon resection). The chemotherapy response was monitored every 2 months through CT imaging according to the treatment guidelines of the Comprehensive Cancer Network[10] by using the Response Evaluation Criteria in Solid Tumors during the final period.[11] Patients who would have an extremely low remnant liver volume (<30% or <40%) after the complete removal of all lesions were considered to have technically unresectable CLM.[9] Resection of all detectable lesions with tumor-free margins was the objective of the surgery in all patients. When chemotherapy was insufficient to downsize the metastases and act as a curative treatment, a surgery, which included three techniques, was recommended to increase the resectability: Colorectal resection, liver resection, and portal vein embolization and RFA followed by resection.

Patients responding to chemotherapy were reconsidered for a surgery when the overall strategy could completely eliminate CLM through R0 resection. The preoperative examination included CT of the chest, abdomen, and pelvis to evaluate liver and extrahepatic diseases and colonoscopy to assess local recurrence of the primary tumor.

Postoperative management

Follow-up after the hepatectomy included physical examination, blood chemistry panels (such as the complete blood cell count and CEA, CA 19-9 levels, and liver function tests), and abdominal sonogram 1 month after surgery and every 4 months thereafter. CT of the chest, abdomen, and pelvis were performed every 8 months, and a colonoscopy was performed annually. As a routine policy, chemotherapy was recommended postoperatively for six to twelve cycles to decrease the risk of disease recurrence. A cure was defined as a disease-free interval of 5 years or more after the latest hepatectomy and colectomy, with the patients being free of disease at the latest follow-up. Patients who died of curatively resected metastases or disease recurrence were defined as the "noncured." If recurrence was suspected, additional examinations, such as chest CT, whole body bone scan, and even whole body positron emission tomography, were performed to clarify the recurrence site.

The 5-year OS time was calculated from the date of the definite operation to the date of the latest follow-up or death. PFS was determined from the date of the definite operation to the date of the confirmation of recurrence.

Statistical analysis

The primary endpoint was to determine whether the addition of chemotherapy to curative surgical resection conferred a PFS and 5-year OS to patients with stage IV colon cancer with inoperable metastases. The analyzed factors were age (≤70 years and >70 years), sex (male and female), location of the primary tumor (right-side colon or left-side colon), histopathological classification (nonpoorly differentiated–well or moderately, and poorly differentiated), tumor size (≤49 mm and >49 mm), CEA (≤5 ng/mL and >5 ng/mL), and CA 19-9 (≤2 5 U/mL and >25 U/mL).

SPSS version 22 (IBM Corp., Armonk, NY, USA) was used for data entry and statistical analyses. Each variable factor of the 5-year OS and DFS rates was estimated using the Kaplan–Meier method. The significance of the differences between the subgroups was calculated using the log-rank test. $P < 0.05$ was considered significant for multivariate analyses, which were performed using the Cox proportional hazard model. All statistical tests were two-tailed, and $P < 0.05$ was considered significant.

Ethics statement

This retrospective study was approved by the Institutional Review Board of Tri-Service General Hospital (appropriate in Taiwan). No informed consent was obtained because the data were analyzed anonymously.

RESULTS

After excluding 133 patients, 156 patients with stage IV colon cancer with inoperable synchronous liver metastases were enrolled in our study. Most patients with liver metastases presented with unresectable disease because of the tumor size and location and limited liver reserve. On the basis of the date of treatment, the patients were divided into two groups: (1) 43 (27.56%) received surgical resection of the primary colon tumor without metastasectomy followed by adjuvant chemotherapy first and (2) 113 (54.3%) received chemotherapy first.

Among all patients, forty-three patients with primarily unresectable liver metastases underwent the primary colon tumor resection first followed by chemotherapy; subsequently, then planned to metastatic tumor resection. Among these patients, 51.1% (22/43) of patients did not respond to adjuvant chemotherapy. Furthermore, 113 patients with primarily unresectable liver metastases either did not undergo a surgical tumor resection or underwent only a diversion or bypass surgery. Of the 113 patients who received chemotherapy first, only 21.2% (24/113) exhibited responsiveness to chemotherapy and underwent simultaneous surgical resection of colon tumor with liver metastasectomy. Figure 1 shows a flowchart of the study population.

The mean age of the study patients was 61.28 ± 12.58 years (24–90 years), and most patients were

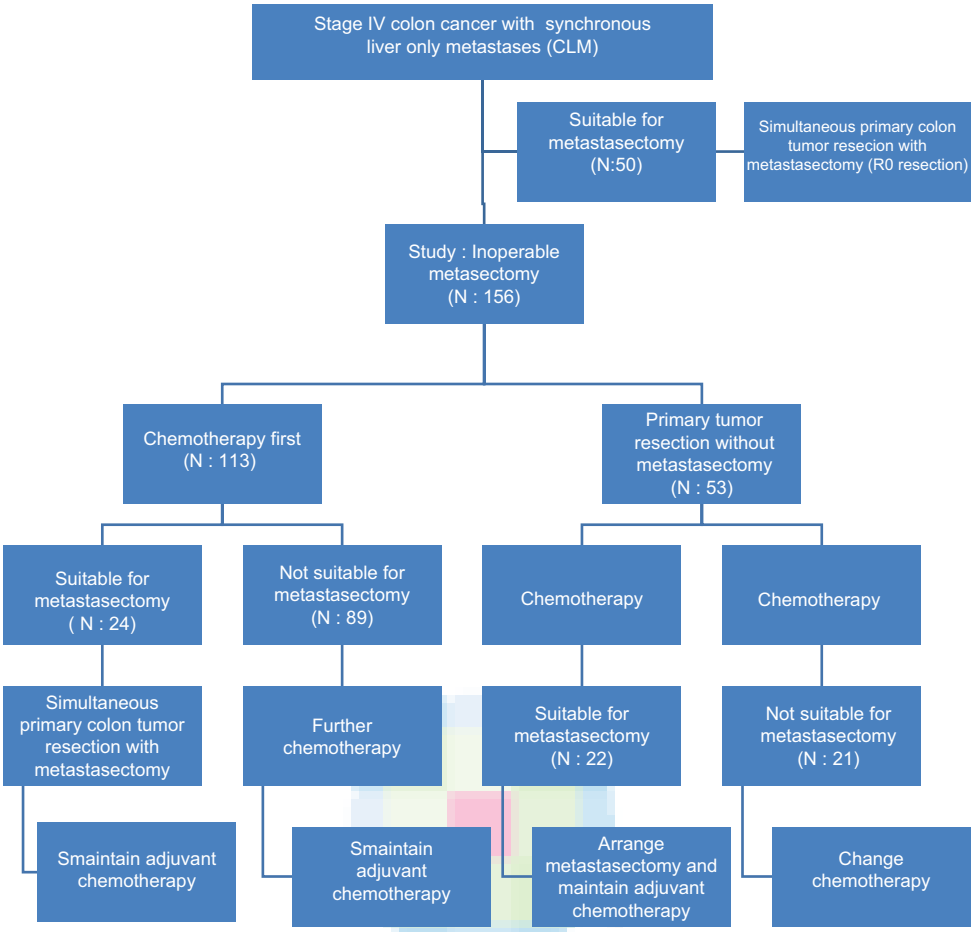

Figure 1: Flowchart of the study design of the stage IV colon cancer with unresectable synchronous liver-only-metastases patients

aged 51–60 years (30.7%). The patient population was predominantly 96 male individuals (61.54%). Regarding tumor location, 112 (71.79%) and 44 (28.21%) were left and right colon carcinomas, respectively. The average number of the lymph nodes examined in each specimen was 16.24 ± 4.80 (3–43). Most primary tumors were located at the sigmoid colon (35%). The patients had a mean of 5.18 liver metastatic lesions, and most metastatic liver tumors were located at segments 6 (18%) and 7 (18%). The distribution of the clinicopathological features of the 156 study patients is stratified by their demographic characteristics in Tables 1 and 2. Major segmentectomy and lobectomy were often considered for resectable liver tumor patients.

A univariate analysis and multivariate analysis revealed that R0 resection ($P < 0.001$) was the only independent factor that effectively predicted the 5-year OS rate [Figures 2, 3 and Tables 3, 4]. The other risk factors, such as age (≦70 or >70), sex (male or female), primary tumor size (≤49 mm, or >49 mm), preoperative CEA and CA 19-9 levels, and metastatic liver tumor size did not significantly affect the DFS or 5-year OS rates. The 5-year OS rates of the simultaneous surgical resection of primary colon and liver metastectomy (R0 resection) and primary colon tumor colectomy first followed by two-stage metastasectomy were 51% and 37.5% ($P = 0.034$), respectively. A metastatic liver resection was considered with surgical resection and RFA for increasing the number of patients suitable for two-stage metastasectomy. The 5-year OS rate was 37.5% for these patients after completing both treatments required for two-stage metastasectomy. Other patients were considered for palliative chemotherapy alone and surgery alone was considered for patients with a <20% 5-year OS rate.

The conversion resection rate for two-stage metastasectomy in primarily colon tumor resection without metastasectomy first was 51.2% (22/43) and that for chemotherapy first in the initially unresectable liver metastasis group was 21.2% (24/113). Chemotherapy resulted enhanced the resection rate to approximately 32.3% and 25.4% in the FOLFOX and FOLFIRI treatment groups, respectively. FOLFIRI regimen with a target therapy yielded the highest conversion rate of

Table 1: Distribution of clinicopathological features of the study patients stratified by demographic characteristics and treatment groups

Characteristic	Number of patients (%)
Age (years), mean (SD)	61.28±12.58
≦70	124 (79.49)
>70	32 (20.51)
Sex	
Male	96 (61.54)
Female	60 (38.46)
CEA (ng/mL), mean (SD)	
≦5	38 (24.36)
>5	118 (75.64)
CA-199 (U/mL), mean (SD)	
≦25	53 (33.98)
>25	103 (66.02)
Primary tumor location	
Right colon	44 (28.21)
Left colon	112 (71.79)
Metastatic liver tumor location	
Right liver	54 (34.61)
Left liver	27 (17.31)
Bilateral liver	75 (48.08)
Number of liver metastatic lesion	
1	25 (16.02)
2-6	54 (34.63)
Multiple	77 (49.35)

SD = Standard deviation; CEA = Carcinoembryonic antigen; CA = Cancer antigen

Table 2: Clinicopathological distribution of total Stage IV colon cancer with unresectable liver-only metastasis patients included in the analyses stratified by their characteristics and treatment group

	Surgery first (*n*=43) *n* (%)	Chemotherapy first (*n*=113) *n* (%)	*P*
Age (years), mean (SD)	60.10±1.75	56.90±1.73	0.197
≦70	32 (74.42)	98 (86.72)	0.178
>70	11 (25.58)	15 (13.28)	
Sex			
Male	25 (58.14)	76 (67.26)	0.453
Female	18 (41.86)	37 (32.74)	
Primary tumor location			
Right colon	12 (27.91)	34 (30.08)	0.899
Left colon	31 (72.09)	79 (69.92)	
Metastatic liver tumor location			
Right liver	14 (32.56)	41 (36.28)	0.294
Left liver	6 (13.96)	27 (23.89)	
Bilateral liver	23 (53.48)	45 (39.83)	
Number of liver metastatic lesion			
1	6 (13.95)	20 (17.69)	0.619
2-6	13 (30.23)	43 (38.06)	
Multiple	24 (55.82)	50 (44.25)	
CEA (ng/mL), mean (SD)			
≦5	8 (18.60)	35 (30.98)	0.373
>5	35 (81.40)	78 (69.02)	
CA-199 (U/mL), mean (SD)			
≦25	20 (46.50)	25 (22.13)	0.087
>25	23 (53.50)	88 (77.87)	
Tumor size (mm), mean (SD)	55.78±2.74	37.23±4.27	<0.001
≦49	18 (36.00)	84 (74.33)	0.002
>49	32 (64.00)	29 (25.67)	
Histopathological classification			
Not poorly differentiated	37 (86.05)	87 (77.00)	0.164
Poorly differentiated	6 (13.95)	26 (23.00)	

HR = Hazard ratio; CI = Confidence interval; CEA = Carcinoembryonic antigen; CA = Cancer antigen; SD = Standard deviation

approximately 67%. No significant difference was observed in the PFS and 5-year OS rates between the patients with stage IV CLM who received surgical resection of primary colon tumor resection without metastasectomy first or chemotherapy first followed by two-stage metastasectomy [Figures 3 and 4].

DISCUSSION

In Taiwan, CRC is the most common cancer and the third leading cause of cancer-related deaths.[1] CRC remains a major public health problem worldwide, with approximately 5698 deaths occurring in 2012 in Taiwan. In Taiwan, CLM is reported in younger patients. In Taiwan, approximately 80% of patients with CLM present with unresectable disease at diagnosis because the number of symptomatic cases is nearly three times higher than that of the screening cases.[12] For patients not undergoing therapy, 5-year OS rates do not exceed a 2%.[1,13] The introduction of novel chemotherapeutic regimens, such as oxaliplatin and irinotecan, has increased the median survival rate for these patients.[14,15] However, chemotherapy responses remain inferior to those of curative hepatic resection, which yields a 5-year OS rate of 40%.[15]

Considerable developments in chemotherapy and surgical procedures have improved the outcomes of patients with CLM.[16,17] In this study, we investigated the influence of

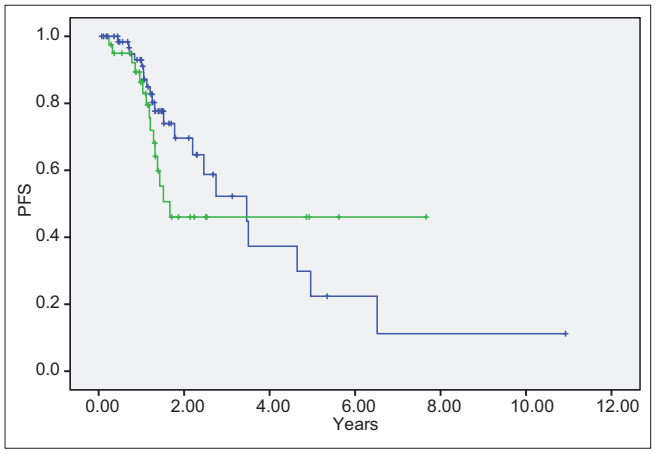

Figure 2: Progression-free survival rates of two groups with primarily unresectable metastatic liver tumor: Aggressive surgical resection of the primary tumor without metastasectomy first (blue) and neoadjuvant chemotherapy first (green) ($P = 0.515$)

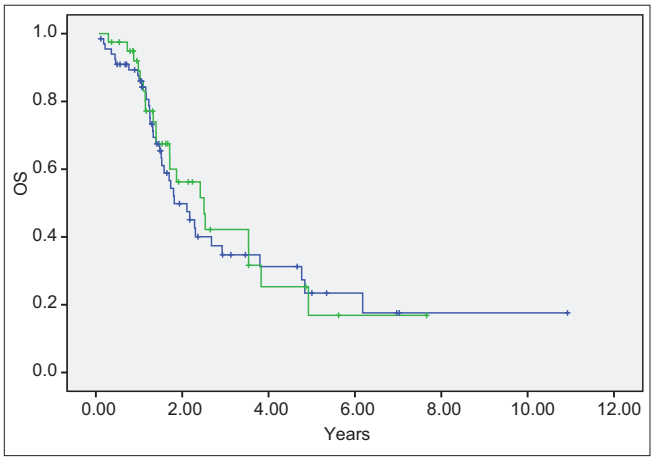

Figure 3: Five-year overall survival rates of two subgroups with primarily unresectable metastatic liver tumor: Aggressive surgical resection of the primary tumor without metastasectomy first (blue) and neoadjuvant chemotherapy first (green) ($P = 0.742$)

combining a surgery and chemotherapy (whether before or after the surgical resection of primary colon tumor) on the survival benefit of surgery only or chemotherapy only. In addition, we assessed the long-term 5-year OS rates for patients with initially unresectable CLM treated with a combination of chemotherapy and surgery. Chemotherapy followed by two-stage R0 resection yielded a 5-year OS rate of 37.5% in patients with primarily unresectable metastases. However, the 5-year OS rates for the groups of palliative chemotherapy only and surgery only did not exceed 10%. This observation is notable because these patients were considered for palliative chemotherapy only or surgery only without expectations of long-term survival.

Initial R0 resection yielded an excellent outcome in patients with advanced CLM because of both selections for combined modality therapy (CMT) and complete resection of metastatic disease. Jonas *et al*. stated that the outcome of liver metastasectomy for CLM has improved over the past 15 years.[18] A formally curative resection is the most relevant prognostic parameter and remains the therapeutic goal. When simultaneous primary tumor resection with metastasectomy is possible, curative surgery is the mainstay of the treatment and the most crucial predictor of the postoperative outcome, with most patients exhibiting relatively favorable outcomes (5-year OS rate, 50–90%). The administration of adjuvant chemotherapy followed by a simultaneous primary tumor resection with metastasectomy treatment for CLM exhibits nondamaged chemotoxicity to the liver parenchyma. A few surgeons suggest that simultaneous resections increase the risk of both anastomotic leak (splanchnic congestion after liver surgery) and liver failure (septic complications caused by the combination of clean and contaminated procedures).[19-21] In 2007, Capussotti *et al*.[22] compared 31 simultaneous major liver resections with 48 staged liver resection and reported that considering the two hospitalizations during delayed resections, morbidity and hospital stay were low in the simultaneous group. In our study, we compared the outcomes of the long-term survival rates between the two subgroups; the simultaneous resection subgroup had a higher 5-year OS rate (51% vs. 34%, $P = 0.034$). However, PFS benefits were indistinguishable.

For patients whose metastatic liver tumor was unresectable initially, the optimizing treatment of an aggressive surgical resection of the primary tumor without metastasectomy with adjuvant CMT or initial neoadjuvant chemotherapy remains controversial. To achieve the best possible two-stage liver metastasectomy rate in patients with CLM, optimizing the treatment guidelines is crucial. Although neoadjuvant chemotherapy is an effective treatment, few patients do not receive its survival benefits because of the risk of delaying surgical treatment in poor chemotherapy responders, which hinders the curative-intent treatment by local progression or distant metastases. Systemic and hepatic toxicity could increase the risk of intraoperative and postoperative complications. Neoadjuvant chemotherapy could be potentially used for examining the sensitivity and responsiveness of a tumor, thereby aiding the selection of the most favorable regimen for the postoperative treatment with the adjuvant intent.[23,24] If neoadjuvant chemotherapy is recommended, the number of courses should be minimized and surgical re-evaluation is advised for evaluating the chemotherapy response and avoiding unnecessary chemotoxicity.

Furthermore, we discussed the most common treatment options with particular emphasis on the role of systemic therapy. We set PFS and 5-year OS rates as the primary

Table 3: Prognostic factors for progression-free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)						
≦70	1.00	0.12-1.29	0.124	1.00	0.13-1.37	0.148
>70	0.39			0.41		
Sex						
Male	1.00	0.78-2.96	0.217	1.00	0.81-3.22	0.171
Female	1.52			1.62		
Chemotherapy						
With CMT	1.00	0.00-3.95	0.169			
Without CMT	0.04			-		
CMT regimen						
Oxaliplatin	1.00	0.52-2.12	0.900			
Irinotecan	1.05			-		
R0 resection						
With R0 resection	1.00	0.50-1.95	0.858			
Without R0 resection	0.94			-		
CEA (ng/mL), mean (SD)						
≦5	1.00	0.43-2.17	0.970			
>5	0.97			-		
CA-199 (U/mL), mean (SD)						
≦25	1.00	0.56-3.31	0.501			
>25	1.36			-		
Tumor size (mm), mean (SD)						
≦49	1.00	0.37-1.73	0.573			
>49	0.80			-		
Metastatic tumor size (cm), mean (SD)						
≦4.9	1.00	0.66-3.49	0.325			
>4.9	1.52			-		
Albumin						
≦3.8	1.00	0.27-1.48	0.295			
>3.8	0.64			-		
LNs						
≦12	1.00	0.29-1.35	0.229			
>12	0.62			-		
Grade						
Well + moderate	1.00	0.14-2.55	0.491			
Poor	0.60			-		
Treatment plan						
Surgery first	1.00	0.64-2.42	0.515	1.00	0.62-2.50	0.531
Chemotherapy first	1.25			1.25		

HR = Hazard ratio; CI = Confidence interval; CEA = Carcinoembryonic antigen; CA = Cancer antigen; LNs = Lymph nodes

Table 4: Prognostic factors for overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age (years)						
≦70	1.00	0.79-2.74	0.224	1.00	0.56-3.22	0.518
>70	1.47			1.34		
Sex						
Male	1.00	0.59-1.69	0.994	1.00	0.59-2.41	0.616
Female	1.00			1.20		
Chemotherapy						
With	1.00	2.22-7.74	<0.001	1.00	3.51-17.67	<0.001
Without	4.15			7.87		
Chemotherapy						
Oxaliplatin	1.00	0.50-1.89	0.940			
Irinotecan	0.98			-		
R0 resection						
With R0 resection	1.00	0.40-1.32	0.293			
Without R0 resection	0.72			-		
CEA (ng/mL), mean (SD)						
≦5	1.00	0.71-4.03	0.241			
>5	1.69			-		
CA-199 (U/mL), mean (SD)						
≦25	1.00	0.44-2.02	0.870			
>25	0.94			-		
Tumor size (mm), mean (SD)						
≦49	1.00	0.47-1.61	0.649			
>49	0.87			-		
Metastatic tumor size (cm), mean (SD)						
≦4.9	1.00	0.96-3.68	0.067	1.00	1.17-5.72	0.018
>4.9	1.89			2.59		
Albumin						
≦3.8	1.00	0.43-2.07	0.885			
>3.8	0.94			-		
LNs						
≦12	1.00	0.52-1.71	0.843			
>12	0.94			-		
Grade						
Well + moderate	1.00	0.85-4.40	0.114			
Poor	1.94			-		
Treatment plan						
Surgery first	1.00	0.53-1.56	0.742	1.00	0.39-1.76	0.626
Chemotherapy first	0.91			0.83		

HR = Hazard ratio; CI = Confidence interval; CEA = Carcinoembryonic antigen; CA = Cancer antigen; LNs = Lymph nodes

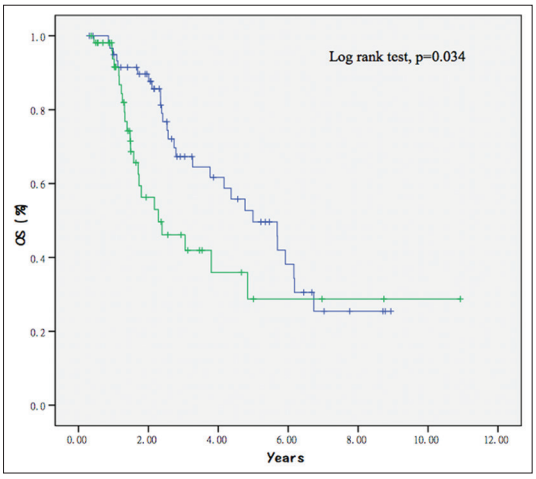

Figure 4: Five-year overall survival rates of two subgroups: R0 resection with initially resectable liver metastatic tumor (blue) and R0 resection followed two-stage resection with initially unresectable liver metastatic tumor (green) ($P = 0.034$)

evaluation endpoints for determining the effects conferred by surgical resection of the primary tumor with metastastectomy first group or chemotherapy first group of the patients with initially unresectable CLM. Patients receiving surgical resection of primary tumor without metastasectomy did not exhibit an improved PFS and 5-year OS rate compared with those receiving adjuvant chemotherapy first. Vauthey *et al*. revealed that chemotherapy should always be administered as an additional treatment for potential metastatic liver resection cases, which increases the PFS rate but does not affect the OS rate.[9] Our results are not consistent with previous studies and without significant differences between the groups, which is attributable to the small number of patients in the subgroups.

In terms of the chemotherapy, after the FOLFOX/FOLFIRI/FOLFOXIRI regiment era, no substantial improvement has been achieved for optimally transforming CLM to a resectable state.[25-28] Based on our experience with different chemotherapy regimens, the FOLFOX treatment was the most effective, with a survival rate of approximately 41%. Chemotherapy regimens, such as FOLFOX and FOLFIRI, are currently used along with monoclonal antibodies (bevacizumab or cetuximab) for increasing the chemotherapy response rates. Our data revealed that the FOLFIRI regimen with a targeted therapy yielded the highest survival rate of approximately 67%. However, no significant difference was observed, indicating that this finding could be attributed only to the small number of patients in this subgroup.

Jonas *et al*. demonstrated that liver resection could possibly yield a long-term survival rate for patients responding to chemotherapy and that the survival rate after liver resection for CLM constantly improved.[18] Therefore, our results support that a liver surgery should be aimed for all patients with unresectable metastases responding to chemotherapy. The potential benefit of resectability in long-term survival has facilitated the development of oncosurgical strategies for patients with primarily unresectable metastases. We previously reported a 20.1% conversion rate to resectability of patients with unresectable metastases after downsizing tumors through chemotherapy, with a 5-year OS of 37.5% after liver metastasectomy. Moreover, patients with unresectable CLM who were treated with palliative chemotherapy or surgery alone had a modest chance of long-term survival. Advances in chemotherapy combined with a target regimen could reduce unresectable CLM and in some cases, convert them to resectable cancers that qualify for surgery.

CONCLUSIONS

A simultaneous R0 surgical resection is the only possible cure for initially resectable CLM, which yields 5-year OS rates of up to 50%. However, the primary goal is to enhance the chemotherapy responsiveness for a potential resection surgery. Regarding staged liver metastasectomy, the differences in the survival rates were nonsignificant between the aggressive surgical resection of the primary tumor without metastasectomy first and primarily neoadjuvant chemotherapy first groups. However, staged R0 resection yielded a higher 5-year OS rate than did palliative chemotherapy or surgery alone. For patients with initially unresectable CLM, systemic chemotherapy with a targeted therapy offers the possibility of considerably reducing tumors and increasing the conversion rate for R0 resection, thus increasing the survival rate after liver resection in patients with CLM.

Limitation

The present study has some limitations. Our single-center retrospective study design lacked randomization. The decision to administer adjuvant chemotherapy after a potentially curative operation was dependent on the clinical judgment of the corresponding attending physicians. Trials to compare neoadjuvant and adjuvant chemotherapy followed by the primary tumor resection with sufficient potential are extremely difficult to organize. Additional randomized studies are required for clarifying the role of adjuvant therapy for patients with stage IV CLM.

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Conflicts of interest

There are no conflicts of interest.

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