Ann Surg Oncol (2023) 30:5390–5400
https://doi.org/10.1245/s10434-023-13656-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Hepatectomy Before Primary Tumor Resection as Preferred Approach for Synchronous Liver Metastases from Rectal Cancer

Harufumi Maki, MD, PhD, Reed I. Ayabe, MD, Yujiro Nishioka, MD, PhD, Tsuyoshi Konishi, MD, PhD, Timothy E. Newhook, MD, Hop S. Tran Cao, MD, Yun Shin Chun, MD, Ching-Wei D. Tzeng, MD, Y. Nancy You, MD, MHSc, and Jean-Nicolas Vauthey, MD

Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas

ABSTRACT

Background. For patients with synchronous liver metastases (LM) from rectal cancer, a consensus on surgical sequencing is lacking. We compared outcomes between the reverse (hepatectomy first), classic (primary tumor resection first), and combined (simultaneous hepatectomy and primary tumor resection) approaches.

Methods. A prospectively maintained database was queried for patients with rectal cancer LM diagnosed before primary tumor resection who underwent hepatectomy for LM from January 2004 to April 2021. Clinicopathological factors and survival were compared between the three approaches.

Results. Among 274 patients, 141 (51%) underwent the reverse approach; 73 (27%), the classic approach; and 60 (22%), the combined approach. Higher carcinoembryonic antigen level at LM diagnosis and higher number of LM were associated with the reverse approach. Combined approach patients had smaller tumors and underwent less complex hepatectomies. More than eight cycles of pre-hepatectomy chemotherapy and maximum diameter of LM > 5 cm were independently associated with worse overall survival (OS) ($p = 0.002$ and 0.027, respectively). Although 35% of reverse-approach patients did not undergo primary tumor resection, OS did not differ between groups. Additionally, 82% of incomplete reverse-approach patients ultimately did not require diversion during follow-up. *RAS/TP53* co-mutation was independently associated with lack of primary resection with the reverse approach (odds ratio: 0.16, 95% CI 0.038–0.64, $p = 0.010$).

Conclusions. The reverse approach results in survival similar to that of combined and classic approaches and may obviate primary rectal tumor resections and diversions. *RAS/TP53* co-mutation is associated with a lower rate of completion of the reverse approach.

Keywords Rectal cancer · Synchronous liver metastasis · Liver resection · Somatic gene alteration

In patients with synchronous liver metastases (LM) from colorectal cancer, curative-intent local treatment is associated with improved survival.[1,2] The so-called combined approach of simultaneous resection of the primary tumor and LM appears to be oncologically ideal and can be safely performed with careful considerations of the associated surgical risks.[3,4] However, other studies report higher complication rates with the combined approach than with sequential resection.[5,6] A recent analysis of the American College of Surgeons National Surgical Quality Improvement Program database revealed that only 7.4% of total liver resections for colorectal LM were performed with the combined approach.[5] In addition, three-quarters of patients undergoing combined resection had only non-anatomic partial hepatectomies, suggesting that major hepatectomy may not be feasible in the combined approach.[1]

In rectal cancer, the surgical risk is even higher than in colon cancer because of the anatomical complexity of rectal surgery as well as the frequent need for preoperative chemoradiation and diversion. Low anterior resection with diversion and abdominoperineal resection are classified as high-risk colorectal resections, with major complications occurring in approximately 20% of patients.[7] The frequency

First Received: 10 February 2023
Accepted: 2 May 2023
Published online: 7 June 2023

J.-N. Vauthey, MD
e-mail: jvauthey@mdanderson.org

of complications, including anastomotic leakage, has not changed in the era of laparoscopic and robotic-assisted surgery.[8,9] Resection of the primary rectal tumor also carries a risk of low anterior resection syndrome, a combination of incontinence, fecal urgency, stool clustering, and fragmentation, with major symptoms occurring in over 60% of patients undergoing proctectomy with primary anastomosis.[10] Complications after rectal resection also lead to the discontinuation or postponement of effective multidrug chemotherapy. This may result in disease progression off chemotherapy and even death. These concerns led to increased advocacy for the reverse approach,[11–13] in which systemic chemotherapy is followed by hepatic resection and then primary tumor resection. Reported rates of completion of the reverse approach (i.e., primary tumor resection in patients treated with the reverse approach) range from 70 to 97%.[2,14–20]

Meanwhile, it has been reported that 10–20% of patients with rectal cancer who receive preoperative chemotherapy, radiation, or chemoradiation could achieve pathologic complete response.[21] Said patients can be offered the "watch and wait" strategy for organ preservation.[22] However, it has been rarely applied to patients with synchronous LM.[23]

A consensus has not been reached regarding the optimal timing of resection of the primary tumor and LM in rectal cancer patients with synchronous LM. The purpose of this study was to compare the results of different surgical approaches to synchronous LM from rectal cancer at our institution and to analyze both clinicopathological and biological tumor factors associated with completion of the reverse approach.

METHODS

Patient Selection

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study protocol (PA#17-0841_MOD002) and waived the requirement for informed consent. From a prospectively maintained database, we identified patients who underwent R0 or R1 hepatic resection for LM from colorectal cancer between January 2004 and April 2021. Patients with two or more hepatectomies and patients with the first hepatectomy of two-stage hepatectomy were excluded. Patients with primary tumors at sites other than the rectum were excluded. Patients with metachronous LM diagnosed more than 365 days after the diagnosis of the primary tumor were excluded. In addition, patients with LM diagnosed on the same day as or after the primary tumor resection were excluded from the study. This was because these patients and their surgeons did not have time to consider the treatment approach. In other words, only patients who were potential candidates for the reverse approach were selected. The years of diagnosis were divided into two time periods of equal length: 2004–2012 and 2013–2021.

Definitions

Rectal cancer was defined as a tumor whose distal end was within 20 cm of the anal verge.[24] T staging was classified according to the *AJCC Cancer Staging Manual*, eighth edition. Diversion was defined as temporary or permanent diversion because of progression of the primary tumor or rectal resection. Positive hilar or para-aortic lymph nodes were included in the extrahepatic metastasis category. The surgical complexity of liver resection was classified using a previously validated three-level complexity classification system: grade I, wedge resection of anterolateral or posterosuperior segment and left lateral sectionectomy; grade II, segmentectomy of anterolateral segment and left hepatectomy; and grade III, posterosuperior segmentectomy, right posterior sectionectomy, right hepatectomy, central hepatectomy, and extended left/right hepatectomy.[25] In the case of multiple excisions, the highest grade was adopted. Liver resection with concomitant bile duct resection and reconstruction was classified as grade III. Postoperative complications were graded according to the Clavien-Dindo classification.[26] Post-hepatectomy liver failure was defined as clinically relevant liver failure according to the definition of the International Study Group of Liver Surgery.[27] A pathological major response was defined as less than 50% of tumor cells viable.[28] As previously reported, our institution uses a panel of next-generation sequencers to test for somatic gene mutations.[29] Survival time was calculated from the date of the last resection of the primary tumor or LM to the date of death or the last follow-up.[30]

Institutional Approach for Management of LM

As previously reported, our institution usually offered preoperative multidrug chemotherapy including oxaliplatin in combination with anti-vascular endothelial growth factor therapy for LM from colorectal cancer.[28] A short course of radiation was administered prior to resection of the primary tumor. Among patients treated with the reverse approach, the primary tumor was not resected in: (1) patients who developed a recurrence after the initial hepatectomy and were not candidates for radical hepatectomy before primary tumor resection, or (2) patients who had both endoscopic and pathologic complete primary tumor response.

Statistical Analyses

Continuous variables were compared using the Mann-Whitney *U* test or the Kruskal-Wallis test, while categorical variables were compared using the chi-squared test. Survival

curves were generated using the Kaplan-Meier method and compared using the log-rank test. Differences in survival between groups were evaluated using Cox proportional hazards model analyses. In the reverse approach group, factors related to completion of the approach (i.e., primary tumor resection) were analyzed using a binary logistic regression model analysis. Factors to be included in the multivariate analysis were selected based on a p value less than 0.10 in the univariate analysis or clinical relevancy.[31,32] Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for each factor. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant. Statistical analysis was conducted with SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

In total, 274 patients met the inclusion criteria. Patient selection is summarized in Fig. 1. The classic, combined, and reverse approaches were used in 73 (27%), 60 (22%), and 141 (51%) patients, respectively. Figure 2 shows the annual trends in use of the three approaches over the observation period. In patients with synchronous LM from colon cancer treated at our institution during the same period of time, with the same definition of synchronous LM, the reverse approach was used in 95 of 455 patients (21%).

The clinicopathological characteristics of the patients in the three groups in our study are summarized in Table 1. The percentage of patients in the classic-approach group decreased from 37% in the 2004–2012 period to 17% in 2013–2021. There was no significant difference among the three groups in distance of the primary tumor from the anal verge, but diversion was less frequent in the reverse-approach group ($p < 0.001$). The reverse-approach group had a higher rate of serum carcinoembryonic antigen (CEA) level at diagnosis of LM > 5 ng/ml ($p = 0.001$) and a larger median number of LM ($p < 0.001$). The combined-approach group had a smaller maximum LM tumor diameter ($p < 0.001$) and lower rates of more than eight cycles of pre-hepatectomy chemotherapy ($p = 0.003$), grade III hepatectomy ($p < 0.001$), and portal vein embolization ($p = 0.019$).

Bleeding was the most common symptom caused by the primary tumor ($n = 154$, 56%), followed by change of bowel habits ($n = 39$, 14%), obstruction ($n = 26$, 9.5%) and perforation ($n = 6$, 2.2%). Pre-hepatectomy chemotherapy was administered to 217 of the 225 (96%) symptomatic patients, including 148 of the 154 patients with bleeding, all 39 patients with change of bowel habits, 25 of the 26 patients with obstruction, and 5 of the 6 patients with perforation.

Oncologic Outcome

The median survival for all 274 patients was 4.9 years (interquartile range [IQR]: 2.2–14.0), and there were 119 deaths during the observation period. The median survival times of the classic-, combined-, and reverse-approach groups were 4.7 years (IQR: 2.5–not reached), 5.6 years (IQR: 2.2–13.8), and 4.9 years (IQR: 1.9–14.0), respectively. There was no significant difference between the groups ($p = 0.899$) (Fig. 3A). In the reverse-approach group, the median survival was 14.4 years (IQR: 3.9–not reached) in the 91 patients (65%) who underwent primary tumor resection and 2.2 years (IQR: 0.88–3.5) in the 50 patients (35%) who did not undergo primary tumor resection ($p < 0.001$) (Fig. 3B).

Table 2 shows the results of univariate and multivariate analyses of factors related to survival. The following factors were significantly associated with poor prognosis on multivariate as well as univariate analysis: more than eight

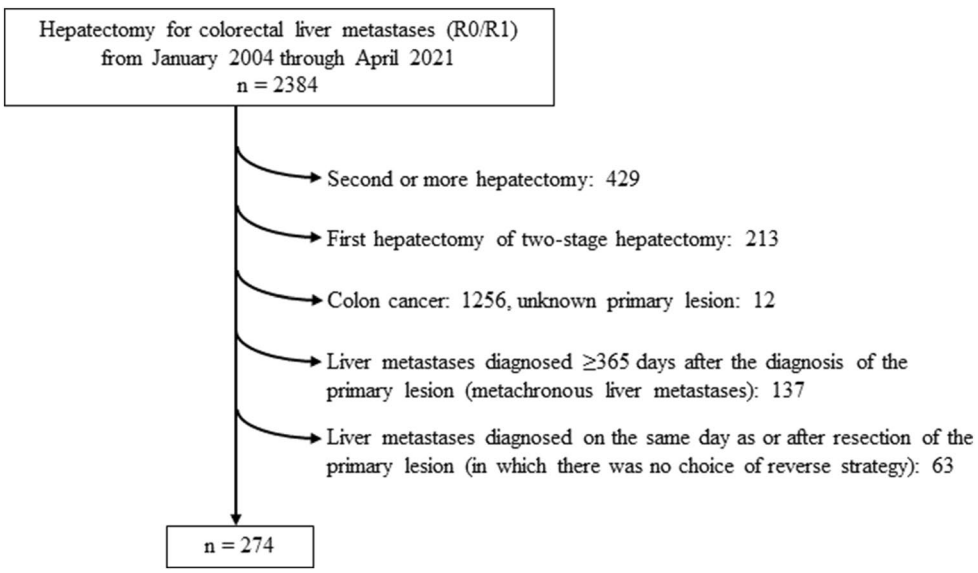

FIG. 1 Patient selection

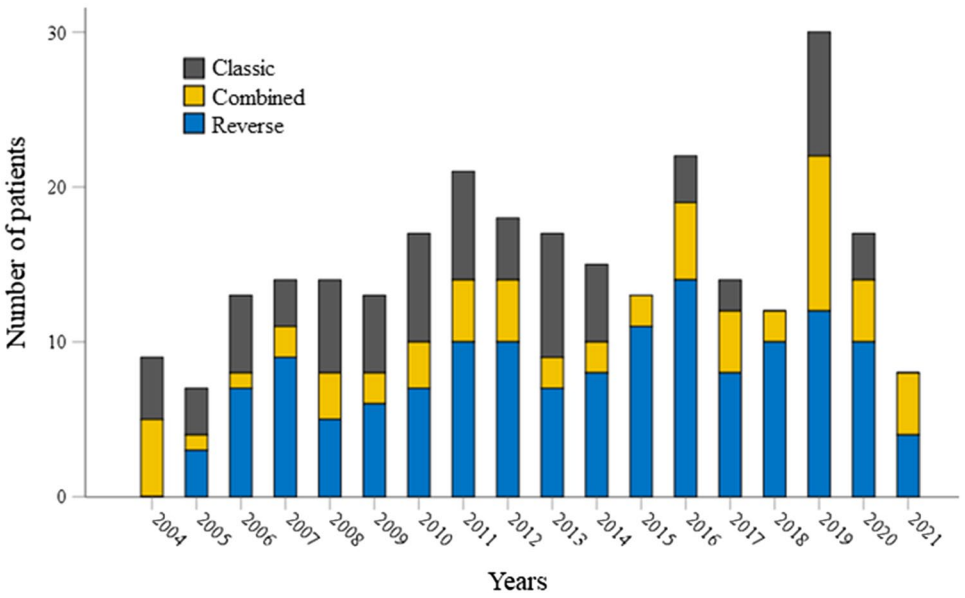

FIG. 2 Annual trends in use of the classic, combined, and reverse treatment approaches during the study period

cycles of pre-hepatectomy chemotherapy (HR: 1.94, 95% CI 1.29–2.94, $p = 0.002$) and maximum diameter of LM > 5 cm (HR: 1.83, 95% CI 1.07–3.13, $p = 0.027$). The difference in the treatment approach was not significantly associated with overall survival.

Completion of the Reverse Approach

In the reverse-approach group, among the 50 patients who did not undergo primary tumor resection, reasons for incompletion included disease progression in 38 patients (76%), death from post-hepatectomy liver failure in 5 patients (10%), complete response of the primary tumor in 3 patients (6%), patient preference in 2 patients (4%), and loss to follow-up in 2 patients (4%). Characteristics of the patients in the reverse-approach group with and without completion of the approach (i.e., resection of the primary tumor) are summarized in Table 3. Of the 50 patients, 41 (82%) did not undergo any diversion. The number of positive lymph nodes in the primary tumor was unknown in the group without completion. On univariate analysis, the group without completion had significantly higher rates of extrahepatic metastases ($p = 0.005$), receipt of more than eight cycles of pre-hepatectomy chemotherapy ($p = 0.019$), and post-hepatectomy liver failure ($p = 0.008$). Patients without completion also tended to be older ($p = 0.098$), had a higher frequency of primary tumor ≤ 10 cm from the anal verge ($p = 0.077$), had larger LM ($p = 0.096$), and had a higher rate of *RAS/TP53* co-mutation ($p = 0.077$). On multivariate analysis, *RAS/TP53* co-mutation was the only factor associated with a lower completion rate (odds ratio: 0.16, 95% CI 0.038–0.64, $p = 0.010$).

DISCUSSION

The optimal sequencing of primary tumor and liver resection for patients with synchronous LM from rectal cancer is a matter of debate. In this series, we found that patients treated with the reverse approach had higher preoperative CEA levels, more LM, larger LM, and more extensive liver resections. Despite this, the reverse approach was associated with long-term survival similar to that of the classic and combined approaches, corroborating the results of previous reports.[2,12,13] Interestingly, these similar outcomes occurred even though 35% of patients treated with the reverse approach did not undergo primary tumor resection.

On multivariate analysis, we found that *RAS/TP53* co-mutation was independently associated with lack of completion of the reverse approach. Nierop et al. reported a high CEA value as an independent risk factor for lack of completion of the reverse approach.[20] We previously reported that *RAS/TP53* co-mutation was associated with worse prognosis after resection of LM as well as extrahepatic metastases, higher rates of micrometastases, higher rates of intrahepatic recurrence, and early detection of circulating tumor DNA after liver resection in patients with colorectal LM.[33–36] The findings reported in this study further demonstrate the aggressive biology associated with *RAS/TP53* co-mutant tumors.

The completion rate for the reverse approach in this study was 65%, which is lower than previously reported.[2,14–20] Of 50 patients who did not complete the reverse approach, 38 (76%) did not undergo primary resections due to disease progression. This may be explained by our patient population, as many patients with complex and often advanced diseases are referred to our center. However, the resection rate is not

TABLE 1 Characteristics of patients by treatment approach ($n = 274$)

Factor	Classic ($n = 73$)	Combined ($n = 60$)	Reverse ($n = 141$)	p value*
Patient factors				
Years of diagnosis, 2004–2012/2013–2021	51/22	26/34	62/70	0.001
Age, median (IQR), years†	55 (47–62)	57 (47–63)	54 (43–63)	0.701
Sex, male	55 (75.3)	39 (65.0)	80 (56.7)	0.027
Primary tumor factors				
Distance from anal verge ≤ 10 cm‡	40 (74.1)	41 (71.9)	113 (82.5)	0.189
T category ≥ 3‡	67 (93.1)	53 (89.8)	119 (91.5)	0.804
Pathologically positive lymph nodes, median (IQR)†,‡	2 (0–2)	1 (0–3)	1 (0–3)	0.839
Any diversion‡	55 (77.5)	55 (93.2)	89 (64.0)	< .001
Extrahepatic metastasis	12 (16.4)	11 (18.3)	29 (20.6)	0.758
LM factors				
CEA level at diagnosis of LM > 5 ng/ml‡	27 (37.0)	22 (36.7)	83 (59.3)	0.001
Pre-hepatectomy chemotherapy	67 (91.8)	56 (93.3)	140 (99.3)	0.015
Cycles of pre-hepatectomy chemotherapy > 8	22 (31.0)	4 (7.3)	41 (29.1)	0.003
Hepatectomy grade, I/II/III, n	25/4/44	53/3/4	52/14/75	< .001
Portal vein embolization	10 (13.7)	1 (1.7)	22 (15.6)	0.019
Tumor number, median (IQR)†,‡	2 (1–4)	1 (1–2)	3 (2–6)	<.001
Maximum diameter, median (IQR), cm†,‡	2.5 (1.7–4.2)	1.2 (0.8–1.9)	2.3 (1.5–4.1)	<.001
Major pathologic response‡	28 (51.9)	28 (60.9)	79 (65.8)	0.215
Clavien-Dindo complication grade ≥ 3	14 (19.2)	5 (8.3)	19 (13.5)	0.194
Post-hepatectomy liver failure (ISGLS)‡	13 (18.8)	3 (5.8)	19 (14.8)	0.115
Post-hepatectomy chemotherapy‡	49 (70.0)	42 (71.2)	111 (78.7)	0.299
Somatic gene alteration‡				
RAS	22 (56.4)	26 (63.4)	54 (56.8)	0.748
BRAF	0 (0.0)	2 (3.3)	2 (1.9)	0.313
TP53	23 (76.7)	26 (70.3)	64 (75.3)	0.800
RAS/TP53 co-mutation	9 (30.0)	15 (40.5)	35 (41.2)	0.541

IQR, interquartile range; *LM*, liver metastases; *CEA*, carcinoembryonic antigen; *ISGLS*, International Study Group of Liver Surgery.

Data are n (%) unless indicated otherwise.

*Chi-squared test unless indicated otherwise.

†Kruskal-Wallis test.

‡Data not available for distance from anal verge in 26 patients, T category in 13 patients, number of pathologically positive lymph nodes in 59 patients, any diversion in 5 patients, CEA level at diagnosis of LM in 1 patient, cycles of pre-hepatectomy in 7 patients, tumor number in 1 patient, maximum diameter in 1 patient, major pathologic response in 54 patients, post-hepatectomy liver failure in 25 patients, post-hepatectomy chemotherapy in 4 patients, *RAS* status in 100 patients, *BRAF* status in 91 patients, *TP53* status in 123 patients, and *RAS/TP53* co-mutation status in 123 patients.

an endpoint in treating such patients. The main advantage of the reverse approach is the ability to select patients who may not ultimately benefit from resection of the primary tumor. From an oncologic point of view, a recent multicenter randomized controlled trial showed that resection of the primary tumor has no prognostic impact in patients with LM from colorectal cancer.[37,38] Some surgeons are concerned about the risk of colorectal obstruction or perforation due to progression of the primary tumor. However, in the study reported here, only 18% of patients without completion of the reverse approach required diversion.

Another advantage of the reverse approach is to potentially afford patients with rectal lesions eligibility for a "watch-and-wait strategy." In our study, complete clinical response of the primary tumor was achieved in 6% of patients in the reverse-approach group without completion. The rate of complete response was lower than previously reported in typical locally advanced rectal cancer.[21,22] This might be because the patients who had more advanced diseases and aggressive biology among stage IV rectal cancers were included in the reverse approach. In fact, 4.9% of patients were diagnosed with synchronous stage IV rectal cancer in the Dutch watch-and-wait registry.[23] Further studies are needed to evaluate the watch-and-wait strategy in the synchronous stage IV rectal cancer population.

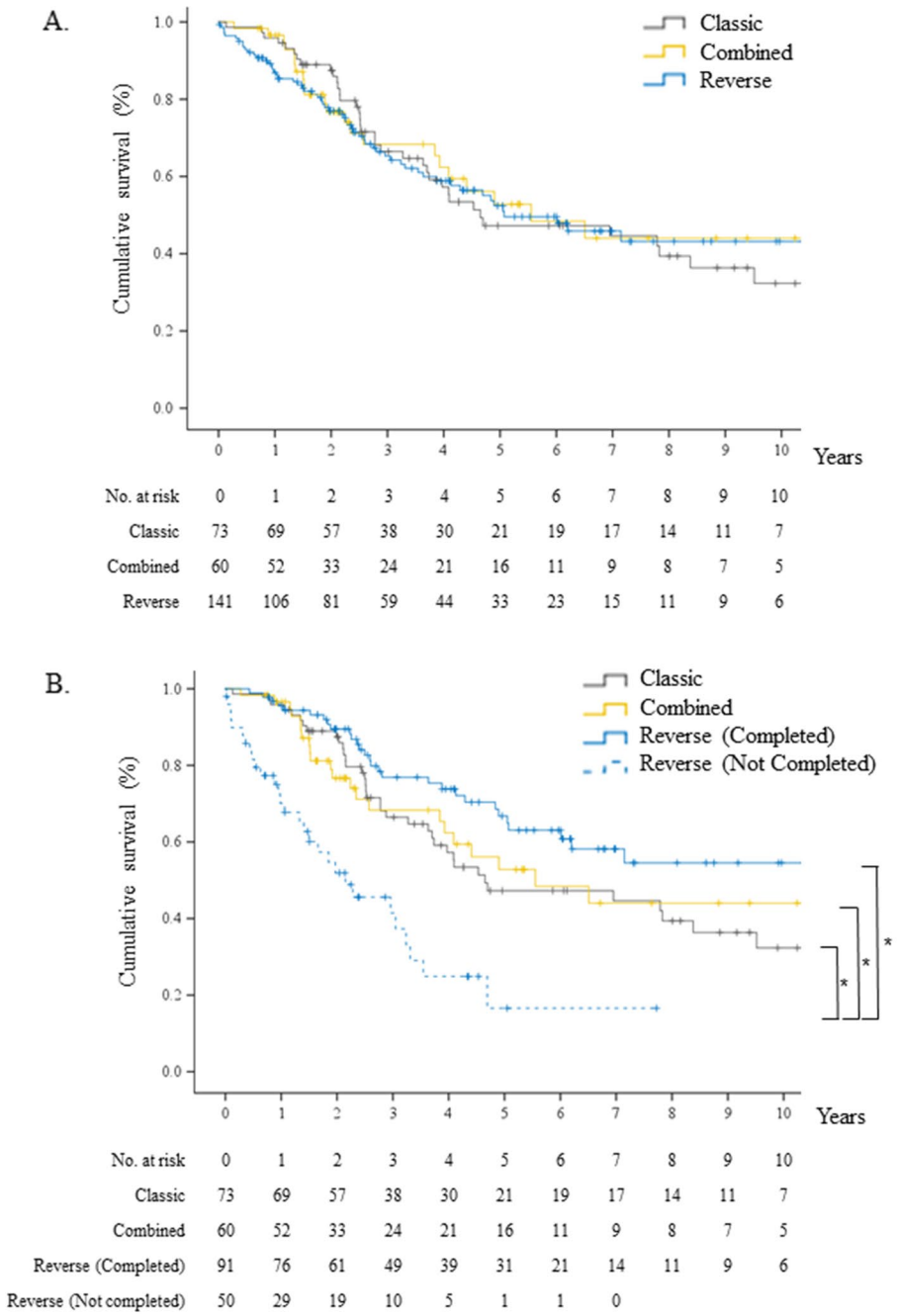

FIG. 3 Overall survival of patients with synchronous liver metastases from rectal cancer by treatment approach (**a**) and by treatment approach with the reverse approach subdivided according to whether or not it was completed (**b**). *$p < 0.001$

On the basis of the results of this study, we are currently making decisions according to a practical treatment algorithm tailored to individual patient subsets (Fig. 4). Specialized, multidisciplinary evaluation by colorectal surgeons, liver surgeons, medical oncologists, and radiation oncologists is required for all primary tumors and LM.[39] Conventional recommendations state that the treatment plan in patients with LM from colorectal cancer should be modified depending on the presence or absence of symptoms.[1] However, in our cohort, which was limited to patients with LM from rectal cancer, symptoms were present in 225 of the 258 patients (87%) for whom information about symptoms was available, and preoperative chemotherapy was safely administered to almost all these patients, even those with obstruction or perforation. Thus, our algorithm does not consider symptoms. This algorithm includes the option of diversion at the primary institution and referral to a higher-level institution where multidisciplinary treatment is available if the primary tumor is accompanied by obstruction or perforation. In the algorithm, the combined approach should be used when the complication rate is expected to be equivalent to the sequential approach in both primary tumor resection

TABLE 2 Cox proportional hazard model analysis for OS in patients with LM from rectal cancer ($n = 274$)

Factor		Univariate			Multivariate		
		HR	95% CI	*p* value	HR	95% CI	*p* value
Patient factors							
Years of diagnosis	2004–2012	Reference		Reference			
	2013–2021	0.72	0.48–1.07	0.099	0.75	0.49–1.16	0.199
Age, decade		1.16	0.99–1.35	0.071	1.12	0.95–1.31	0.172
Sex, male		0.95	0.65–1.38	0.790			
Treatment approach	Combined	Reference					
	Reverse	1.14	0.71–1.85	0.591	0.84	0.47–1.50	0.565
	Classic	1.06	0.63–1.78	0.834	0.75	0.41–1.35	0.333
Primary lesion factors							
Distance from anal verge ≤ 10 cm, yes*		0.79	0.46–1.35	0.389			
T category ≥ 3, yes*		2.01	0.82–4.93	0.127			
Extrahepatic metastasis, yes		1.49	0.95–2.33	0.087	1.44	0.91–2.28	0.121
Liver metastases factors							
CEA level at diagnosis of LM > 5 ng/ml, yes*		1.29	0.90–1.86	0.168	1.11	0.71–1.74	0.641
Cycles of pre-hepatectomy chemotherapy > 8, yes		2.25	1.53–3.31	< .001	1.94	1.29–2.94	0.002
Multiple, yes		1.37	0.91–2.06	0.130	1.23	0.77–1.97	0.380
Maximum diameter > 5 cm, yes		2.12	1.34–3.35	0.001	1.83	1.07–3.13	0.027
Major pathologic response, yes*		0.92	0.58–1.43	0.699			
Clavien-Dindo classification 3 or more, yes		1.53	0.95–2.49	0.083	1.48	0.89–2.44	0.129
Post-hepatectomy chemotherapy, yes*		0.89	0.57–1.39	0.602			
Somatic gene alteration§							
RAS or *BRAF**		0.79	0.46–1.34	0.375			
*TP53**		2.02	0.99–4.15	0.054			
RAS/TP53 co-mutation*		1.39	0.76–2.54	0.280			

LM, liver metastasis: *HR*, hazard ratio: *CI*, confidence interval: *CEA*, carcinoembryonic antigen.

*Data not available for distance from anal verge ≤ 10 cm in 26 patients, T category ≥ 3 in 13 patients, CEA level at diagnosis of LM > 5 ng/ml in 1 patient, major pathologic response in 54 patients, post-hepatectomy chemotherapy in 4 patients, *RAS* or *BRAF* in 106 patients, *TP53* in 123 patients, *RAS/TP53* co-mutation in 123 patients.

§Factors of somatic gene alteration were not included in the multivariate analysis due to large missing data.

and LM resection. In patients with rectal cancer with synchronous LM, the primary rectal tumor is often advanced, which limits applicability of the combined approach, which was used in 22% of the patients in our study. In this study, 53 of 60 patients (88%) in the combined-approach group underwent minor liver resections. Our data suggest that grade III hepatectomy is inappropriate for combined resection. The algorithm indicates that the role of the classic approach has been shrinking. Of the 73 patients in our study treated with the classic approach, 35 (48%) underwent primary tumor resection before referral to our institution. In our opinion, the classic approach should be performed selectively for easily resectable upper rectal tumors with obstruction, perforation, or when patients cannot accept chemotherapy without rectal resections.

There are limitations to this study. The first is that it was a single-center retrospective study, so the number of cases was limited. The results of our study also contain selection bias. However, patients with synchronous LM from rectal cancer are a heterogeneous and diverse population, making it difficult to conduct a randomized controlled trial.[4] Second, it was impossible to evaluate lymph node metastasis of the primary tumor, a well-known predictor of worse prognosis.[40] In the present study, lymph node metastasis was not included in the multivariate analysis because it would have excluded the group of patients in the reverse-approach group who did not undergo primary tumor resection, i.e., the group with worse prognosis. Third, data on somatic gene mutations were missing for many patients. However, we did not intentionally select for genetic testing depending on the approach, so we determined that it was acceptable to include somatic gene mutations in our analyses (Table 3).[41] Fourth, this study did not include patients who developed unresectable LM during treatment with the classic approach. Since these patients are considered to have a worse prognosis, the prognosis for the classic-approach group may be overestimated. Fifth,

TABLE 3 Characteristics of patients with and without completion of the reverse approach ($n = 141$)

Factor	Univariate			Multivariate		
	Completed	Not completed	*p* value*	OR	95% CI	*p* value*
Patient factors						
Age, median (IQR), years†	54 (43–63)	55 (50–66)	0.098	0.99	0.94–1.04	0.661
Sex, male	50 (54.9)	30 (60.0)	0.598			
Primary tumor factors						
Distance from anal verge ≤ 10 cm‡	71 (78.0)	42 (84.0)	0.077	0.28	0.040–1.90	0.191
T category ≥ 3‡	83 (91.2)	36 (92.3)	1.000			
Any diversion‡	80 (88.9)	9 (18.4)				
Extrahepatic metastasis	12 (13.2)	17 (34.0)	0.005	0.34	0.082–1.44	0.143
LM factors						
CEA level at diagnosis of LM > 5 ng/ml‡	49 (53.8)	34 (69.4)	0.104			
Cycles of pre-hepatectomy chemotherapy > 8	20 (22.0)	21 (42.0)	0.019	0.27	0.055–1.36	0.113
Hepatectomy grade I/II/III, n	33/7/51	19/7/24	0.425			
Portal vein embolization	17 (18.7)	5 (10.0)	0.228			
Tumor number, median (IQR)†	3 (2–6)	4 (2–6)	0.970			
Maximum diameter, median (IQR), cm†	2.3 (1.5–4.1)	2.8 (1.9–4.2)	0.096	0.85	0.65–1.12	0.247
Major pathologic response‡	51 (56.0)	28 (56.0)	0.829			
Clavien-Dindo complication grade ≥ 3	10 (11.0)	9 (18.0)	0.304			
Post-hepatectomy liver failure(ISGLS)‡	7 (8.3)	12 (27.3)	0.008	0.45	0.027–7.68	0.583
Post-hepatectomy chemotherapy	73 (80.2)	38 (76.0)	0.668			
Somatic gene alteration‡						
RAS	36 (53.7)	18 (64.3)	0.373			
BRAF	1 (1.4)	1 (3.4)	0.486			
TP53	45 (71.4)	19 (86.4)	0.251			
RAS/TP53 co-mutation	22 (34.9)	13 (59.1)	0.077	0.16	0.038–0.64	0.010

OR, odds ratio; *CI*, confidence interval; *IQR*, interquartile range; *LM*, liver metastases; *CEA*, carcinoembryonic antigen; *ISGLS*, International Study Group of Liver Surgery.

Data are n (%) unless indicated otherwise.

*Chi-squared test unless indicated otherwise.

†Kruskal-Wallis test.

‡Data not available for distance from anal verge in 4 patients, T category in 11 patients, any diversion in 2 patients, CEA level at diagnosis of LM in 1 patient, major pathologic response in 21 patients, post-hepatectomy liver failure in 13 patients, *RAS* in 46 patients, *BRAF* in 38 patients, *TP53* in 56 patients, *RAS/TP53* co-mutation in 56 patients.

this study excluded patients with incidental LM found at the time of rectal resection because treatment of such LM may require only a minor surgical procedure. For example, if a tumor smaller than 1 cm is incidentally found in the anterolateral segment of the liver during rectal resection, it is reasonable to perform wedge resection for diagnostic and therapeutic purposes. In this case, the postoperative complication rate may not be increased, and the hospital stay may not be prolonged because of the low risk of hepatic resection. The combined approach is considered cost-effective in such cases because it reduces the number of hospitalizations for surgical operations if no postoperative complications arise. Finally, the algorithm presented in this paper is the latest policy of our institution and needs to be validated by prospective studies.

CONCLUSIONS

In patients with synchronous LM from rectal cancer, we found that the reverse approach resulted in survival similar to that in the combined and classic approaches, despite patients in the reverse-approach group having more advanced LM. The reverse approach may obviate primary rectal tumor resections and diversions. Among patients treated with the reverse approach, *RAS/TP53* co-mutation is associated with lower rates of primary tumor resection.

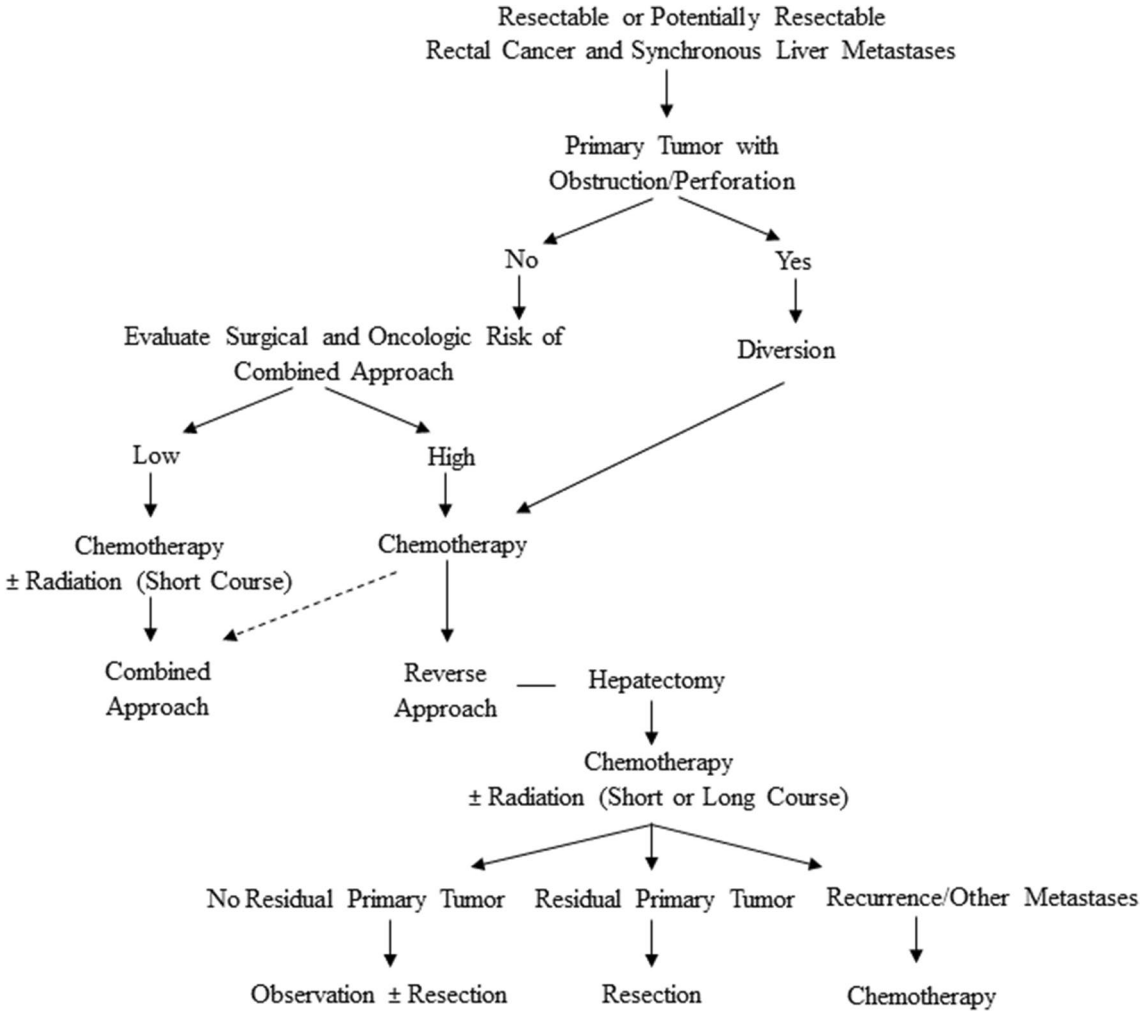

FIG. 4 Individualized treatment algorithm for synchronous rectal cancer with liver metastases

ACKNOWLEDGMENT This research was not pre-registered in an independent, institutional registry. The authors thank Ms. Ruth Haynes for administrative support in the preparation of this manuscript and Ms. Stephanie Deming, Senior Scientific Editor at MD Anderson Cancer Center, for copyediting the manuscript.

AUTHOR CONTRIBUTIONS Study concept and design: HM and JNV. Data acquisition: HM, YN, TEN, HSTC, YSC, CWDT. Quality control of data and algorithms: HM, TK, YNY, and JNV. Data analysis and interpretation: HM. Article preparation: HM and RIA. Article editing: all authors. Final approval: all authors.

FUNDING Supported by the National Cancer Institute under award number P30CA016672, which supports the MD Anderson Cancer Center Clinical Trials Support Resource.

DATA AVAILABILITY The authors are willing to make their data, analytical methods, and study materials available to other researchers upon reasonable request, including relevant ethical and legal permissions to the corresponding author.

DISCLOSURE Nothing to disclose.

REFERENCES

1. Adam R, de Gramont A, Figueras J, et al. Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus. *Cancer Treat Rev*. 2015;41(9):729–41. https://doi.org/10.1016/j.ctrv.2015.06.006.
2. Ghiasloo M, Kahya H, Van Langenhove S, et al. Effect of treatment sequence on survival in stage IV rectal cancer with synchronous and potentially resectable liver metastases. *J Surg Oncol*. 2019;120(3):415–22. https://doi.org/10.1002/jso.25516.
3. Boudjema K, Locher C, Sabbagh C, et al. Simultaneous versus delayed resection for initially resectable synchronous colorectal cancer liver metastases: A prospective, open-label, randomized Controlled Trial. *Ann Surg*. 2021;273(1):49–56. https://doi.org/10.1097/SLA.0000000000003848.
4. Chan AKC, Mason JM, Baltatzis M, Siriwardena AK, Co SC. Management of colorectal cancer with synchronous liver metastases: An inception cohort study (CoSMIC). *Ann Surg Oncol*. 2022;29(3):1939–51. https://doi.org/10.1245/s10434-021-11017-7.
5. Snyder RA, Hao S, Irish W, Zervos EE, Tuttle-Newhall JE, Parikh AA. Thirty-day morbidity after simultaneous resection of colorectal cancer and colorectal liver metastasis:

American college of surgeons NSQIP analysis. *J Am Coll Surg*. 2020;230(4):617–27. https://doi.org/10.1016/j.jamcollsurg.2019.12.018.
6. Yoshioka R, Hasegawa K, Mise Y, et al. Evaluation of the safety and efficacy of simultaneous resection of primary colorectal cancer and synchronous colorectal liver metastases. *Surgery*. 2014;155(3):478–85. https://doi.org/10.1016/j.surg.2013.10.015.
7. Shubert CR, Habermann EB, Bergquist JR, et al. A NSQIP review of major morbidity and mortality of synchronous liver resection for colorectal metastasis stratified by extent of liver resection and type of colorectal resection. *J Gastrointest Surg*. 2015;19(11):1982–94. https://doi.org/10.1007/s11605-015-2895-z.
8. Jayne D, Pigazzi A, Marshall H, et al. Effect of robotic-assisted vs conventional laparoscopic surgery on risk of conversion to open laparotomy among patients undergoing resection for rectal cancer: the ROLARR randomized clinical trial. *JAMA*. 2017;318(16):1569–80. https://doi.org/10.1001/jama.2017.7219.
9. Fleshman J, Branda M, Sargent DJ, et al. Effect of laparoscopic-assisted resection vs open resection of Stage II or III rectal cancer on pathologic outcomes: The ACOSOG Z6051 randomized clinical trial. *JAMA*. 2015;314(13):1346–55. https://doi.org/10.1001/jama.2015.10529.
10. Bolton WS, Chapman SJ, Corrigan N, et al. The incidence of low anterior resection syndrome as assessed in an international randomized controlled trial (MRC/NIHR ROLARR). *Ann Surg*. 2021;274(6):e1223–9. https://doi.org/10.1097/SLA.0000000000003806.
11. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg*. 2006;93(7):872–8. https://doi.org/10.1002/bjs.5346.
12. Welsh FK, Chandrakumaran K, John TG, Cresswell AB, Rees M. Propensity score-matched outcomes analysis of the liver-first approach for synchronous colorectal liver metastases. *Br J Surg*. 2016;103(5):600–6. https://doi.org/10.1002/bjs.10099.
13. Giuliante F, Vigano L, De Rose AM, et al. Liver-first approach for synchronous colorectal metastases: Analysis of 7360 patients from the livermetsurvey registry. *Ann Surg Oncol*. 2021;28(13):8198–208. https://doi.org/10.1245/s10434-021-10220-w.
14. Salvador-Roses H, Lopez-Ben S, Casellas-Robert M, et al. Oncological strategies for locally advanced rectal cancer with synchronous liver metastases, interval strategy versus rectum first strategy: a comparison of short-term outcomes. *Clin Transl Oncol*. 2018;20(8):1018–25. https://doi.org/10.1007/s12094-017-1818-8.
15. Labori KJ, Guren MG, Brudvik KW, et al. Resection of synchronous liver metastases between radiotherapy and definitive surgery for locally advanced rectal cancer: Short-term surgical outcomes, overall survival and recurrence-free survival. *Colorectal Dis*. 2017;19(8):731–8. https://doi.org/10.1111/codi.13622.
16. D'Hondt M, Lucidi V, Vermeiren K, Van Den Bossche B, Donckier V, Sergeant G. The interval approach: An adaptation of the liver-first approach to treat synchronous liver metastases from rectal cancer. *World J Surg Oncol*. 2017;15(1):54. https://doi.org/10.1186/s12957-017-1123-6.
17. Buchs NC, Ris F, Majno PE, et al. Rectal outcomes after a liver-first treatment of patients with stage IV rectal cancer. *Ann Surg Oncol*. 2015;22(3):931–7. https://doi.org/10.1245/s10434-014-4069-8.
18. van der Pool AE, de Wilt JH, Lalmahomed ZS, Eggermont AM, Ijzermans JN, Verhoef C. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases. *Br J Surg*. 2010;97(3):383–90. https://doi.org/10.1002/bjs.6947.
19. Verhoef C, van der Pool AE, Nuyttens JJ, Planting AS, Eggermont AM, de Wilt JH. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2009;52(1):23–30. https://doi.org/10.1007/DCR.0b013e318197939a.
20. Nierop PMH, Verseveld M, Galjart B, et al. The liver-first approach for locally advanced rectal cancer and synchronous liver metastases. *Eur J Surg Oncol*. 2019;45(4):591–6. https://doi.org/10.1016/j.ejso.2018.12.007.
21. Sammour T, Price BA, Krause KJ, Chang GJ. Nonoperative management or "watch and wait" for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy: A critical appraisal. *Ann Surg Oncol*. 2017;24(7):1904–15. https://doi.org/10.1245/s10434-017-5841-3.
22. Fleming C, Vendrely V, Rullier E, Denost Q. Organ preservation in rectal cancer: Review of contemporary management. *Br J Surg*. 2022;109(8):695–703. https://doi.org/10.1093/bjs/znac140.
23. Custers PA, Hupkens BJP, Grotenhuis BA, et al. Selected stage IV rectal cancer patients managed by the watch-and-wait approach after pelvic radiotherapy: A good alternative to total mesorectal excision surgery? *Colorectal Dis*. 2022;24(4):401–10. https://doi.org/10.1111/codi.16034.
24. Conrad C, Vauthey JN, Masayuki O, et al. Individualized treatment sequencing selection contributes to optimized survival in patients with rectal cancer and synchronous liver metastases. *Ann Surg Oncol*. 2017;24(13):3857–64. https://doi.org/10.1245/s10434-017-6089-7.
25. Kawaguchi Y, Hasegawa K, Tzeng CD, et al. Performance of a modified three-level classification in stratifying open liver resection procedures in terms of complexity and postoperative morbidity. *Br J Surg*. 2020;107(3):258–67. https://doi.org/10.1002/bjs.11351.
26. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
27. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery*. 2011;149(5):713–24. https://doi.org/10.1016/j.surg.2010.10.001.
28. Chun YS, Vauthey JN, Boonsirikamchai P, et al. Association of computed tomography morphologic criteria with pathologic response and survival in patients treated with bevacizumab for colorectal liver metastases. *JAMA*. 2009;302(21):2338–44. https://doi.org/10.1001/jama.2009.1755.
29. Kawaguchi Y, Kopetz S, Kwong L, et al. Genomic sequencing and insight into clinical heterogeneity and prognostic pathway genes in patients with metastatic colorectal cancer. *J Am Coll Surg*. 2021;233(2):272–84. https://doi.org/10.1016/j.jamcollsurg.2021.05.027.
30. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: Classic, combined or reverse strategy? *J Am Coll Surg*. 2010;210(6):934–41. https://doi.org/10.1016/j.jamcollsurg.2010.02.039.
31. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. *Fam Med Commun Health*. 2020;8(1):e000262. https://doi.org/10.1136/fmch-2019-000262.
32. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007;165(6):710–8. https://doi.org/10.1093/aje/kwk052.
33. Chun YS, Passot G, Yamashita S, et al. Deleterious effect of RAS and evolutionary high-risk TP53 double mutation in colorectal

liver metastases. *Ann Surg*. 2019;269(5):917–23. https://doi.org/10.1097/SLA.0000000000002450.
34. Lillemoe HA, Passot G, Kawaguchi Y, et al. RAS/TP53 co-mutation is associated with worse survival after concurrent resection of colorectal liver metastases and extrahepatic disease. *Ann Surg*. 2020. https://doi.org/10.1097/SLA.0000000000004672.
35. Nishioka Y, Paez-Arango N, Boettcher FO, et al. Neither surgical margin status nor somatic mutation predicts local recurrence after R0-intent resection for colorectal liver metastases. *J Gastrointest Surg*. 2022;26(4):791–801. https://doi.org/10.1007/s11605-021-05173-0.
36. Nishioka Y, Chun YS, Overman MJ, et al. Effect of co-mutation of RAS and TP53 on postoperative ctDNA detection and early recurrence after hepatectomy for colorectal liver metastases. *J Am Coll Surg*. 2022;234(4):474–83. https://doi.org/10.1097/XCS.0000000000000093.
37. Kanemitsu Y, Shitara K, Mizusawa J, et al. Primary tumor resection plus chemotherapy versus chemotherapy alone for colorectal cancer patients with asymptomatic, synchronous unresectable metastases (JCOG1007; iPACS): A randomized clinical trial. *J Clin Oncol*. 2021;39(10):1098–107. https://doi.org/10.1200/JCO.20.02447.
38. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol*. 2009;27(20):3379–84. https://doi.org/10.1200/JCO.2008.20.9817.
39. You YN, Eng C, Aloia T. Multidisciplinary management of stage IV colon cancer. *Semin Colon Rectal Surg*. 2016;27(4):213–8. https://doi.org/10.1053/j.scrs.2016.04.020.
40. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230(3):309–18. https://doi.org/10.1097/00000658-199909000-00004.
41. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. *J Clin Epidemiol*. 2019;110:63–73. https://doi.org/10.1016/j.jclinepi.2019.02.016.