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ORIGINAL ARTICLE

Impact of the strategy for curative treatment of synchronous colorectal cancer liver metastases

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HIGHLIGHTS

- At the time of diagnosis, 14% to 17% of colorectal cancer patients have synchronous liver metastases.
- Surgical resection is the only curative treatment for colorectal liver metastases.
- Three curative treatment strategies (''combined'', ''classic'' and ''liver-first'') are possible for synchronous colorectal cancer liver metastases.
- All three strategies were feasible and there were no differences regarding overall and recurrence-free survivals between the three approaches.
- The ''combined'' strategy group had significantly more severe complications despite less aggressive liver disease and more limited liver resections.

KEYWORDS
Colorectal liver metastasis;
Neoadjuvant chemotherapy;
Hepatectomy;
Synchronous metastasis;
Liver resection

Summary
Aim of the study: Fourteen to seventeen percent of patients suffering from colorectal cancer have synchronous liver metastases (sCRLM) at the time of diagnosis. There are currently three possible strategies for curative management of sCRLM: ''classic'', ''combined'', and ''liver-first''. The aim of our research was to analyze the effects of the three surgical management strategies for sCRLM on postoperative morbidity and mortality and overall and recurrence-free survival.
Patients and Methods: Patients treated for sCRLM between October 2000 and May 2015 were included. We defined three groups: (1) ''classic'': surgery of primary tumor and then surgery of sCRLM; (2) ''combined'': combined surgery of primary tumor and sCRLM: and (3) ''liver-first'': surgery of sCRLM and then surgery of primary tumor.

Abbreviations: ALPPS, Associated Liver Partition with Portal Vein Ligation for Staged Hepatectomy; SD, Standard Deviation; MDTM, Multidisciplinary Team Meeting; CRC, Colorectal Cancer; CRLM, Colorectal Liver Metastasis; sCRLM, Synchronous Colorectal Liver Metastasis; OS, Overall Survival; RFS, Recurrence-free Survival; NAC, Neoadjuvant Chemotherapy; IA, Intra-arterial.

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Results: During this period, 170 patients who underwent 209 hepatectomies were included (''classic'': 149, ''combined'': 34, ''liver-first'': 26). The rate of severe complications was higher in the ''combined'' group compared to the ''classic'' group (35% vs. 12%, $P = 0.03$), and the ''liver-first'' group (35% vs. 19%, $P = 0.25$), while there were significantly fewer liver resections. Overall survival at 5 years in our cohort was 46%, without significant differences between the groups, and a median survival of 54 months. Recurrence-free survival of the patients in our cohort was 24% at 5 years, with a median survival time without recurrence of 14 months, without significant differences between the groups.

Conclusion: All three strategies were feasible and there were no differences regarding overall and recurrence-free survivals between the three approaches. The ''combined'' strategy group had significantly more severe complications and did not provide better oncological results, despite less aggressive liver disease and more limited liver resections.

Introduction

Half of all patients with colorectal cancer present with liver metastases [1,2], but only 20% of these patients are eligible for surgical resection [3]. However, surgical resection is the only curative option and results in 60% 5-year survival rate according to the most recent series [4].

At the time of diagnosis, 14% to 17% of colorectal cancer patients present with synchronous liver metastases (sCRLM) [5]. This is considered to be a poor prognostic factor [6] with less than 5% of 5-year survival rate in the 1990s [7], overall survival rate now exceeds 40% [8] as a result of recently implemented multidisciplinary approaches and chemotherapy regimens that have led to an increase in the number of patients amenable to surgery with curative intent. Resection can be carried out either immediately or after the chemotherapy.

Several strategies are currently used for curative surgical management of patients with synchronous liver metastases. The final objective of these strategies is R0 resection of the primary tumor and hepatic metastases. A specific feature of this type of management of synchronous liver metastases is the difficulty with defining the right chronology for the surgical procedures that enable treatment of the primary tumor and the secondary liver lesions without progression of the disease. Three types of management of sCRLM have been described: (1) The ''classic'' strategy [9], which consists of an initial surgery of the primary tumor, followed by surgery of the liver metastases with chemotherapy in the intervening period. The advantage of this option is that it precludes exposing the patient to the risk of complications related to progression of the primary tumor, including bowel obstruction. The main disadvantage is the risk of postoperative complications of colorectal surgery, which can delay management of the liver metastases and thereby result in their progression to the point that they become non-resectable; (2) The ''combined'' strategy [10], which consists of simultaneous surgery of the primary tumor and of the liver metastases. This strategy has the advantage of avoiding multiple surgeries and has been mostly used to treat right-sided colon cancers associated with minor hepatectomies [11]. The main disadvantage lies with the increase in postoperative morbidity and mortality and the delay in administration of adjuvant chemotherapy; (3) The ''liver-first'' strategy [12], which consists of an initial surgery of the liver metastases, followed by management of the primary tumor after chemotherapy in the intervening period. This strategy is particularly used for patients with significant metastatic liver disease and an asymptomatic primary tumor. Indeed, for patients with numerous sCRLM, the prognosis of the disease is in the liver. Moreover, for rectal cancer, the primary tumor resection can lead to life discomfort especially in the case of low resection, which is a risk that should not be taken if the liver cannot be controlled.

To date, five studies have compared the outcomes for these different types of management, including one meta-analysis and one review [8,13—16]. However, the series on the subject [13—16] suffered from biases and they mainly comprised small numbers of patients, with inclusion periods that extended over tens of years, thereby resulting in a high level of heterogeneity in the medical and surgical management.

The aim of our research was to analyze the effects of the three surgical management strategies for synchronous colorectal cancer liver metastases on postoperative morbidity and mortality and overall and recurrence-free survival.

Methods

Patients

All of the patients who consecutively underwent surgery at the Toulouse Rangueil University Hospital for synchronous liver metastases (metastases discovered at diagnosis or within three months after diagnosis) between October 2000 and May 2015 were included.

Inclusion criteria

A diagnosis of synchronous liver metastases was defined by the presence of liver lesions at the time of diagnosis of the primary tumor, or the presence of liver lesions that led to the discovery of the primary tumor.

Patients for whom the primary tumor was resected at another center were also included. A diagnosis of synchronous liver metastases had always been made at the time of the surgery.

Patient groups

Each patient was included to one of three groups: the ''classic'' strategy, the ''combined'' strategy, or the ''liver-first'' strategy.

Data collected

For each patient, the preoperative parameters included: age, height, weight, BMI, diabetes, history of liver surgery or liver procedures, neoadjuvant chemotherapy, radiological evaluation, two-stage hepatectomy, the surgical strategy proposed at the MDTM (Multidisciplinary Team Meeting), the location of the primary, the treatment date, and the preoperative test results.

The perioperative parameters included: the duration of the surgery, the type of procedure, the number of segments resected, the estimated blood loss, perioperative transfusion, laparoscopy, drainage, whether or not there was clamping of the liver pedicle, and the duration of the clamping.

The postoperative parameters included: the occurrence of a severe or mild complication (according to the Clavien-Dindo classification [17]), postoperative hepatic insufficiency was defined according to the 50-50 criteria on D5 [18], mortality after 30 days, repeat procedures, biliary complication and percutaneous drainage, the length of the hospitalization, the initiation of postoperative chemotherapy, and the type of chemotherapy.

The histological data comprised: the number of lesions on the resected specimens, the resection margins (a resection was considered to be R0 if the minimum microscopic margin was more than or equal to 1 mm), the weight of the resected specimen, the presence of emboli, and the tumor differentiation grade.

The follow-up data included: the most recent update, the date of death (if applicable), and the date of recurrence (if any).

Outcome measures

The outcome measures were: overall survival at 3 years and at 5 years after the surgery; recurrence-free survival; and the occurrence of postoperative complications at 90 days. Postoperative complications were classified into two groups and according to the Clavien-Dindo classification [19]: non-severe complications (Dindo I and II) and severe complications (Dindo $\geq$ III).

Multidisciplinary team meeting

All of the patients' records were reviewed in a digestive oncology multidisciplinary team meeting that included at least one interventional radiologist, one hepatic surgeon, one digestive oncologist, and one anatomical pathologist.

Curative treatment was administered either anatomically according to Couinaud, by non-anatomical atypical resection, or by intraoperative radiofrequency ablation. Non-atypical resections and the use of radiofrequency ablations were generally preferred by our team when possible, for parenchymal preservation. Surgical management of patient by one of the three procedures (''classic'', ''liver-first'' or ''combined'') was decided in a digestive oncology multidisciplinary team meeting according to the French recommendations for clinical practice [20] and the literature on ''liver-first'' approach [12].

Surgical technique

Surgical resections were performed in either one or two stages, irrespective of the strategy, preceded by preoperative percutaneous portal vein embolization, if necessary, when the volume of the future remaining liver was insufficient.

Surgical resections were systematically performed with perioperative ultrasound. An Erbejet (Erbejet, RBE Elektromedizin GmbH, Waldhornlestrasse, Tübingen, Germany) or an ultrasonic dissector (Dissectron, Satelec Medical, Mérignac, France) was used for the liver transection, with total intermittent or selective pedicle clamping according to the surgeon's assessment. Perioperative radiofrequency ablation was performed by a radiologist trained in this technique. A 15 Gauge electrode connected to a generator (RITA® Medical Systems, Inc., California, USA) was directly introduced into the liver under ultrasound guidance, and the needles were then deployed progressively in the tumor. Thermoablation was then performed over a variable period according to the tumor volume. A control CT scan was performed at 8 weeks to ensure sterilization of the lesion.

Statistical analysis

The data were acquired from a secure, monocentric internet database that had been prospectively compiled since October 2000, and that comprised all of the patients managed for hepatectomy (all causes included) in the Toulouse Rangueil Hospital digestive surgery department. Approval was obtained from the local ethics committee.

The quantitative variables were reported as the mean, standard deviation, median, and maximal values. The qualitative variables were reported as frequencies and percentages. According to the type of variable and their distribution, an inter-group comparison was performed using the Student's *t*-test or the Wilcoxon signed-rank test for quantitative variables and the Chi^2 test or the Fisher's exact test for qualitative variables. Overall survival and recurrence-free survival were determined by the Kaplan-Meier method. The log-rank test was used to compare the groups. A Cox model was used to determine the significant factors associated with overall and recurrence-free survival of patients who underwent surgery for sCRLM. Univariate and multivariate analyses of survival were carried out. In the univariate analysis, the significant variables at a threshold of 10% ($P \leq 0.1$) were introduced in a multivariate model. The variables were selected for inclusion in the model to avoid the retention of co-linear factors. A ''backward'' selection was used in order to only retain the significant factors associated with overall and recurrence-free survival, at a threshold of 5% ($P \leq 0.05$). The statistical analyses were performed with R software (version 3.1.2). The ''survival'' software package (version 2.37-7) was used for the analyses of survival.

Results

Between October 2000 and May 2015, 756 hepatectomies were performed in the Toulouse Rangueil Hospital Digestive Surgery Department. During this period, 170 patients underwent 209 hepatectomies for synchronous colon or rectal cancer liver metastases.

The hepatectomies were assigned to three groups according to the surgical strategy proposed at the MDTM: 149

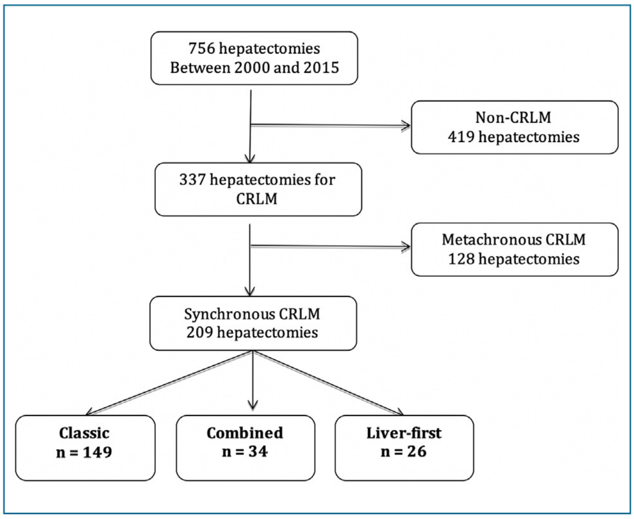

Figure 1. Flowchart. CRLM, Colorectal Liver Metastasis.

hepatectomies (71%) in the ''classic'' treatment group, 34 hepatectomies (16%) in the ''combined'' treatment group, and 26 hepatectomies (13%) in the ''liver-first'' treatment group (Fig. 1).

Preoperative characteristics

There was no significant difference in the number of liver lesions and whether or not they were bilobar (Table 1).

The patients in the ''classic'' and the ''liver-first'' groups had significantly more courses of neoadjuvant chemotherapy (NAC) than those in the ''combined'' group, twice as many NAC treatments, and more combined dual cytotoxic therapy and targeted therapy.

There were significantly fewer radiological responses to chemotherapy, fewer portal vein embolizations, and fewer repeat hepatectomies in the ''combined'' treatment group.

Perioperative characteristics

Fewer liver ablations were performed in the ''combined'' group because there were significantly fewer major hepatectomies (Table 2). There was also a lower number of resected segments and less clamping for this group. The clamping was for a significantly shorter duration in the ''combined'' group.

Postoperative outcomes

Mortality at one month was 0.4%: a 73 years old patient in the ''liver-first'' group operated by left trisegmentectomy extended to segments 5, 8 and 1 after portal embolization developed hepatocellular insufficiency (Table 3). The anatomopathological analysis of the specimen did not show chemotherapy lesions in the non-tumoral liver. The rate of postoperative complications was 35% (n=74). The complications were severe in 49% of the cases.

There were no statistically significant differences between the three groups in terms of the non-severe complications. The non-severe complications comprised: five cases of intra-abdominal collection treated medically, four wall abscesses, six prolonged drainages, six postoperative cases of ileus, six cardiovascular complications (paroxysmal atrial fibrillation, thrombophlebitis, and left ventricular overload), and twelve infectious complications (urinary, central or peripheral venous infections, and pneumopathies).

The rate of severe complications was significantly higher in the ''combined'' group compared to the ''classic'' group (35% vs. 12%, $P = 0.03$), and the ''liver-first'' group (35% vs. 19%, $P = 0.25$), although the latter difference was not significant. These complications comprised of two drainages for pleural effusion and eight repeat procedures: six in the ''combined'' group: two cases of biliary peritonitis, three colorectal complications (one anastomotic fistula, one intra-abdominal sepsis, open wall abscess drained in the operating room); and two in the ''classic'' group: one postoperative hemorrhage and one peritonitis from an anastomotic fistula of a restoration of gastrointestinal continuity after a Hartmann procedure that was performed at the same time. Two patients (one in the ''classic'' group and one in the ''combined'' group) had both a repeat surgery and a percutaneous drainage (for bilioma). There were no significant differences between the three groups in terms of liver morbidity.

Seventeen patients (26%) for whom a two-stage procedure had been scheduled did not undergo the second stage of the procedure due to progression of the disease: 11 in the ''classic'' group and 6 in the ''combined'' group. There was no failure in the two-stage strategy in the ''liver-first'' group.

Histological characteristics

The patients in the ''combined'' group had significantly fewer liver lesions and the weight of the resected specimens was less (Table 4). On the other hand, the resection margins and the rates of R0 were similar for the three groups.

Disease recurrence

The mean duration of follow-up was 44 ± 30 months, with a median of 38 months (0—173). There were no significant differences in the follow-up between the three groups: 40 months (2—173) for the ''classic'' group, 33 months (2—95) for the ''combined'' group, and 32 months (0—101) for the ''liver-first'' group.

Recurrence occurred in 74% of the patients. There were no significant differences ($P = 0.38$) between the three groups: 78% in the ''classic'' group; 64% in the ''combined'' group; and 65% in the ''liver-first'' group. The liver was the only site of recurrence in 47 patients (22%). The median time until recurrence was 14 months (0—173), with a significant difference according to the strategy: 13 months (0—173) for the ''classic'' group; 17 months (1—94) for the ''combined'' group and 17 months (3—95) for the ''liver-first'' group.

Overall survival

Overall survival of the patients in our cohort was 68% at 3 years and 46% at 5 years, with a median survival time of 54 months (0—173).

There were no statistically significant differences in the overall survival rates between the three groups (Fig. 2) at 3 years and at 5 years: 66% and 44%, respectively, with a median of 50 months (3—173) for the ''classic'' group; 73% and 48%, respectively, with a median of 59 months (4—95) for the ''combined'' group; and 74% and 50%, respectively, with a median of 64 months (0—101) for the ''liver-first'' group.

Table 1 Preoperative criteria.

	Total $n = 209$ (%)	Classic $n = 149$ (%)	Combined $n = 34$ (%)	Liver-first $n = 26$ (%)	*P*-value*	*P*-value**	*P*-value***
Male gender (%)	102 (49)	70 (47)	16 (47)	16 (62)	1	0.25	0.39
Age	62 ± 9	62 ± 10	62 ± 6	59 ± 10	0.56	0.11	0.20
Body Mass Index	25 ± 4	25 ± 4	24 ± 4	24 ± 4	0.50	0.52	0.96
Diabetes (%)	12 (6)	6 (4)	5 (15)	1 (4)	0.03	1	0.21
Number of lesions	4 ± 3	4 ± 3	4 ± 3	4 ± 3	0.90	0.90	0.67
Bilobar lesions	138 (66)	96 (64)	23 (68)	19 (73)	0.88	0.53	0.86
NAC	180 (86)	138 (93)	17 (50)	25 (96)	< 0.001	1	< 0.001
Number of treatments	8 ± 5	8 ± 5	4 ± 4	8 ± 5	< 0.001	0.96	0.001
Dual cytotoxic therapy	60 (29)	53 (36)	4 (12)	3 (12)	0.01	0.02	1
Dual therapy + targeted therapy	83 (40)	61 (41)	7 (21)	15 (58)	0.04	0.17	0.01
Triple cytotoxic ± targeted therapy	24 (11)	12 (8)	5 (15)	7 (27)	0.32	0.01	0.33
Intra-arterial	5 (2)	5 (3)	0	0	—	—	—
Other chemotherapy	8 (4)	7 (5)	1 (3)	0	—	—	—
Response to NAC							
Yes	136 (66)	99 (67)	15 (44)	22 (84)	< 0.001	0.52	0.001
No	16 (8)	14 (9)	1 (3)	1 (4)	—	—	—
Stable	26 (13)	23 (16)	1 (3)	2 (8)	—	—	—
Portal vein embolization	50 (24)	41 (28)	1 (3)	8 (31)	0.001	0.92	0.01
Two-stage procedure	64 (34)	42 (32)	16 (48)	6 (24)	0.12	0.57	0.10
Repeat hepatectomy	32 (17)	27 (21)	2 (6)	3 (12)	0.07	0.41	0.64
Primary rectal tumor	41 (20)	32 (22)	4 (12)	5 (23)	0.24	1	0.29

NAC: neoadjuvant chemotherapy.
* Comparison: classic vs. combined.
** Classic vs. liver-first.
*** Combined vs. liver-first.

Table 2 Perioperative criteria.

	Total $n = 209$	Classic $n = 149$	Combined $n = 34$	Liver-first $n = 26$	*P*-value*	*P*-value**	*P*-value***
Duration of the surgery	210 (60—540)	210 (60—540)	240 (150—400)	210 (120—400)	0.01	0.60	0.08
Major hepatectomy	99 (47)	76 (51)	5 (15)	18 (69)	< 0.001	0.13	< 0.001
Number of resected segments	3 (0.5—6)	3 (0.5—6)	1 (1—5)	4 (0.5—6)	< 0.001	0.09	< 0.001
Combined radiofrequency	55 (26)	38 (25)	8 (24)	9 (35)	0.98	0.47	0.51
Blood loss (ml)	600 (50—3,500)	600 (50—3,000)	500 (150—1,500)	625 (100—3,500)	0.43	0.24	0.12
Perioperative transfusion (%)	60 (31)	40 (29)	8 (25)	12 (48)	0.78	0.11	0.13
Laparoscopy	17 (8)	7 (5)	8 (24)	2 (8)	0.001	0.62	0.16
Drainage (%)	136 (66)	98 (66)	19 (58)	19 (73)	0.46	0.64	0.34
No clamping (%)	58 (29)	31 (21)	21 (68)	6 (23)	< 0.001	1	0.005
Clamping (min)	23 ± 18	25 ± 17	9 ± 14	28 ± 20	< 0.001	0.33	< 0.001

* Comparison: classic vs. combined.
** Classic vs. liver-first.
*** Combined vs. liver-first.

The factors identified by univariate analysis as having an unfavorable influence on OS were: the absence of NAC, more than five metastases, the absence of a radiological response with NAC, a two-stage hepatectomy, the presence of vascular emboli, an R1 status of the resection, and the occurrence of a postoperative biliary complication.

In the multivariate analyses, the factors for a poor prognosis for overall survival (Table 5) were: the absence of NAC,

Table 3 Postoperative outcomes.

	Total $n = 209$	Classic $n = 149$	Combined $n = 34$	Liver-first $n = 26$	*P*-value*	*P*-value**	*P*-value***
Non-severe complication	38 (18)	24 (16)	6 (18)	8 (31)	1	0.13	0.38
Severe complication	36 (17)	19 (12)	12 (35)	5 (19)	0.03	0.36	0.25
Invasive treatment	31 (15)	15 (10)	12 (35)	4 (15)	0.001	0.49	0.14
Repeat procedure	8 (4)	2 (1)	6 (18)	0 (0)	0.001	1	0.03
Radiological drainage	25 (12)	14 (9)	7 (21)	4 (15)	0.12	0.31	0.74
Resuscitation	5 (2)	3 (2)	2 (6)	0	0.23	1	0.5
Deaths < D30	1	0	0	1	—	—	—
Biliary complication	24 (12)	15 (10)	5 (15)	4 (15)	0.54	0.49	1
Duration of stay (days)	11 (4—61)	11 (4—50)	13 (7—61)	12 (5—50)	0.005	0.37	0.24
Postoperative chemotherapy	140(67)	94 (63)	29 (88)	17 (65)	0.01	0.99	0.12
Dual cytotoxic therapy	64 (31)	41 (28)	17 (50)	6 (23)	0.02	0.82	0.06
Dual + targeted therapy	52 (25)	37 (25)	8 (24)	7 (27)	1	1	1
Triple cytotoxic ± targeted therapy	7 (3)	1 (1)	3 (9)	3 (12)	0.02	0.01	1
Intra-arterial	6 (3)	6(4)	0	0	—	—	—
Other chemotherapy	12 (6)	10 (7)	1 (3)	1 (4)	0.69	1	1

* Comparison: classic vs. combined.
** Classic vs. liver-first.
*** Combined vs. liver-first.

Table 4 Histological criteria.

	Total $n = 209$	Classic $n = 49$	Combined $n = 34$	Liver-first $n = 26$	*P*-value*	*P*-value**	*P*-value***
Number of lesions	3 ± 3	3 ± 3	2 ± 2	4 ± 3	0.04	0.50	0.06
Resection margins (mm)	6 ± 8	6 ± 8	6 ± 5	5 ± 9	0.31	0.43	0.16
Quality of the resection							
R0 (%)	159 (76)	112 (75)	28 (82)	19 (73)	0.46	0.71	0.75
R1 (%)	45 (22)	34 (23)	5 (15)	6 (23)	0.46	0.71	0.75
Specimen weight (g)	508	568	186	600	0.01	0.82	0.03
Vascular emboli (%)	27 (14)	22 (16)	4 (13)	1 (4)	1	0.21	0.36
Differentiation grade							
Good (%)	73 (42)	40 (34)	18 (56)	15 (65)	0.08	0.08	0.86
Average (%)	73 (42)	58 (49)	10 (31)	5 (22)	0.08	0.08	0.86
Low (%)	6 (3)	3 (3)	2 (6)	1 (4)	0.08	0.08	0.86

* Comparison: classic vs. combined.
** Classic vs. liver-first.
*** Combined vs. liver-first.

the absence of a radiological response with NAC, a two-stage hepatectomy, and the presence of a postoperative biliary complication.

Recurrence-free survival

Recurrence-free survival of the patients in our cohort was 28% at 3 years and 24% at 5 years, with a median survival time without recurrence of 14 months (1—173 months).

There were no statistically significant differences in the recurrence-free survival rates between the three groups (Fig. 3) at 3 years and at 5 years: 27% and 24%, respectively, with a median of 13 months (1—173 months) for the ''classic'' group; 31% and 31%, respectively, with a median of 17 months (1—94 months) for the ''combined'' group; and 22% and 15%, respectively, with a median of 17 months (3—95) for the ''liver-first'' group.

The factors identified by the univariate analysis as having an unfavorable influence on the RFS were: > 5 NAC treatments, perioperative blood loss of > 1000 ml, clamping that lasted more than 30 min, the presence of vascular emboli, and postoperative radiological drainage.

In the multivariate analysis, the three factors for a poor prognosis for recurrence-free survival (Table 5) were: > 5 NAC treatments, perioperative blood loss of > 1000 ml, and the occurrence of vascular emboli. The administration of adjuvant chemotherapy was a factor that correlated with a good prognosis for RFS.

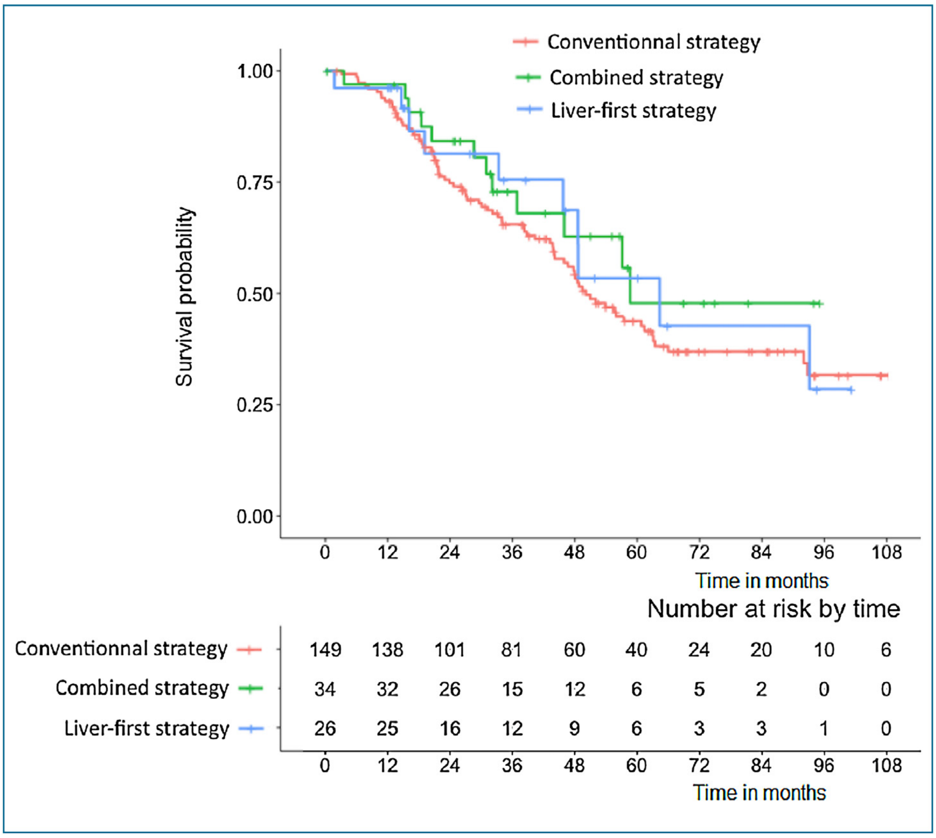

Figure 2. Overall Survival.

Table 5 Prognostic factors for overall survival and recurrence-free survival (multivariate analysis).

	OR	95% CI	*P*-value
Prognostic Factors for Overall Survival			
Number of NAC	3.53	[1.21—10.28]	0.02
Number of lesions > 5	—	—	—
Radiological stability after NAC	4	[2.06—7.78]	< 0.001
Two-stage procedure	2.61	[1.49—4.57]	0.001
No clamping	—	—	—
Vascular emboli	3.10	[1.65—5.83]	0.001
R1 resection	—	—	—
Biliary complication	2.67	[1.32—5.38]	0.01
Disease recurrence	3.95	[1.66—9.44]	0.002
Prognostic factors for recurrence-free survival			
Number of NAC treatments > 5	1.85	[1.18—2.91]	0.01
Blood loss > 1000 ml	1.86	[1.28—2.71]	0.01
Vascular emboli	2.08	[1.26—3.45]	0.004
Radiological drainage	—	—	—
Adjuvant chemotherapy (dual cytotoxic therapy)	0.65	[0.42—0.99]	0.04

NAC: neoadjuvant chemotherapy.

Literature review

The Table 6 summarizes the main results of studies, which compared the three strategies of management of sCRLM (Table 6).

Discussion

This research indicates that the type of curative strategy (i.e., ''classic'', ''combined'', or ''liver-first'') did not result in a significant difference in the OS or the RFS. This is consistent with the findings of previously published studies [13—15] and a recent meta-analysis [8]. However, our series shows that the three strategies were used to different extents with different types of patients. Thus, the ''combined'' strategy was preferentially used with patients who had less advanced disease and less extensive liver surgery. The following preoperative features were noted for this group: less NAC, fewer treatments in case of NAC, fewer preoperative portal vein embolizations; and perioperatively: fewer major hepatectomies, fewer resected

Table 6 Main recent comparative studies comparing the 3 strategies to manage simultaneous colorectal liver metastases.

					Severe complications (Clavien >III)					90-days mortality					Recurrence of CRLM at last follow-up				
Reference	Total	Classic group	Combined group	Liver-first group	Total (%)	Classic group (%)	Combined group (%)	Liver-first group (%)	*P*-value	Total (%)	Classic group (%)	Combined group (%)	Liver-first group (%)	*P*-value	Total (%)	Classic group (%)	Combined group (%)	Liver-first group (%)	*P*-value
Mayo et al., 2012 [13]	1004	647	329	28	113 (11)	74 (11)	39 (12)	0 (0)	> 0.05	30 (30)	21 (3)	9 (3)	0 (0)	> 0.05	556 (55)	373 (60)	171 (53)	12 (43)	> 0.05
Brouquet et al, 2010 [14]	142	72	43	27	22 (15)	12 (17)	8 (19)	2 (7)	> 0.05	5 (4)	2 (3)	2 (5)	1 (4)	> 0.05	93 (65)	51 (71)	23 (53)	19 (70)	> 0.05
Van der Pool et al., 2010 [15]	57	29	8	20	5 (9)	4 (14)	0 (0)	1 (5)	> 0.05	NS	NS	NS	NS	NS	42 (74)	NS	NS	NS	NS

NS: not assessed.

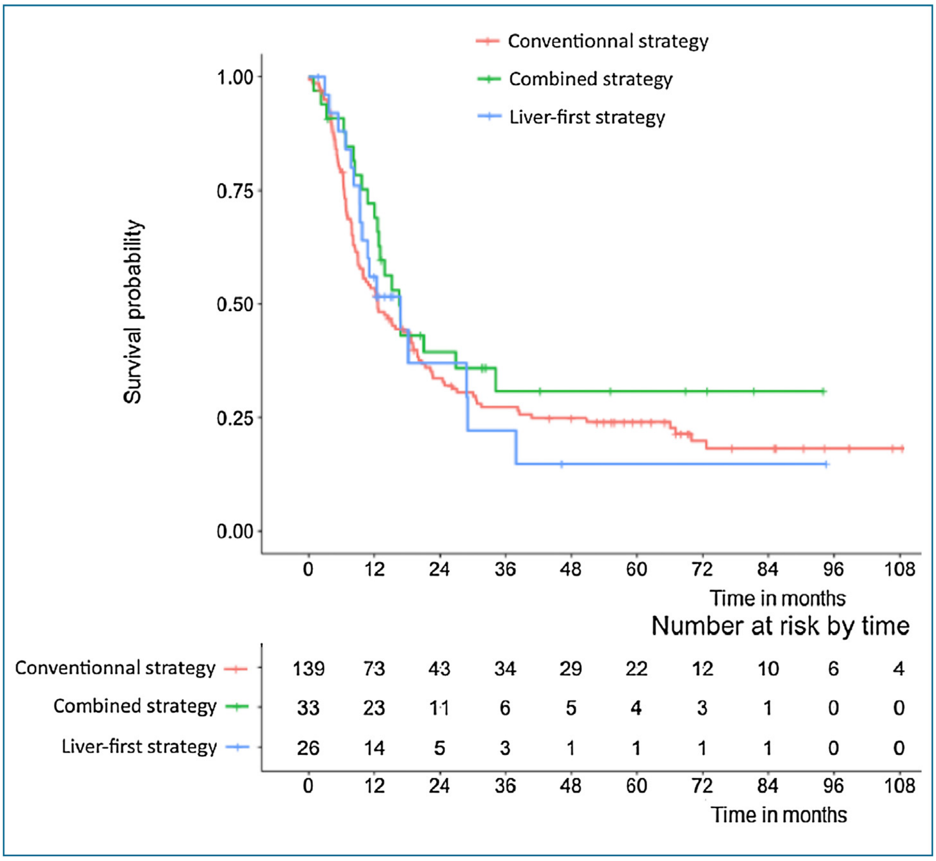

Figure 3. Recurrence-free survival.

segments, less clamping, smaller resected specimens and fewer metastases. Despite this, the ''combined'' group had a significantly higher rate of severe complications and the survival rate was not higher than for the two other groups. Therefore, it would appear that the ''combined'' strategy had an adverse impact, with a higher rate of severe immediate sequelae that may have decreased the rate of survival. Moreover, these complications lead to a delay in the completion of adjuvant chemotherapy, negatively impacting the prognosis of these patients [21]. Controversially, these complications cannot be explained by the increase of anastomotic leakage and intestinal mucosal edema caused by Pringle maneuver. Indeed, several authors have shown that Pringle maneuver did not correlate with occurrence of complication or anastomotic leakage in patients treated by ''combined'' strategy [11,22].

There is currently no consensus regarding the curative surgical strategy to adopt for sCRLM. Our series is one of the largest to date, and second only to the one by Mayo et al. [13] (which involved 1004 patients). The largest series [13—15] included patients between 1982 and 2011, which resulted in major biases due to advances in chemotherapy and liver surgery over this very long period of time.

The overall survival rates at 3 years and at 5 years in our population were 68% and 45%, respectively. These figures are in keeping with those obtained in a meta-analysis of the topic [8]. The independent prognostic factors for overall survival in this series were the absence of NAC and radiological stability after NAC, a two-stage hepatic procedure, the occurrence of neoplastic vascular emboli, and the occurrence of a postoperative biliary complication. The effect of NAC had been demonstrated previously by the EORTC study [23] and has subsequently been confirmed, as has the absence of a radiological response with NAC [23,24]. The effect of a two-stage hepatectomy procedure can be explained by the fact that 26% of the patients did not undergo the 2nd stage of the procedure due to progression of the disease, which is comparable to the figures found in the literature, which vary from 15 to 31% [25—29]. The occurrence of microscopic neoplastic vascular emboli is a classical prognostic factor of OS after surgery for CRLM [30]. The occurrence of postoperative complications has been reported to be an unfavorable oncological prognosis [21], although no description of the types of complications was provided. Our series is the first to find that biliary complications are a distinct prognostic factor in OS, which can be explained by the immunosuppressed status that follows surgery, particularly when it is complicated [31], and by the fact that the administration of adjuvant chemotherapy for these patients was either late or cancelled.

The recurrence-free survival rates at 3 years and at 5 years in our population were 28% and 24%, respectively. These figures are consistent with those obtained in a meta-analysis of the topic [8]. The independent prognostic factors of recurrence-free survival that were identified in this series were more than 5 NAC treatments, a blood loss of more than 1 l, the presence of neoplastic vascular emboli, and the absence of adjuvant chemotherapy. A high number of chemotherapy treatments are undoubtedly an indication of chemoresistance of the disease, more advanced liver disease, and probably a poorer histological response [30]. The role of adjuvant chemotherapy is now well established for recurrence-free survival, with a statistically significant beneficial role of dual cytotoxic therapies alone [32]. Blood transfusions and the quantities are classical prognostic factors for RFS, mainly due to their immunosuppressant effect [33].

Our research is a retrospective analysis of prospectively collected data, with the consequent biases that this involves. The pre- and post-operative chemotherapy treatments were heterogeneous, whether in terms of the drugs used or the number of treatments. This can be explained by the fact that a significant number of patients were sent to us in 2nd or 3rd line with medical management that had already been initiated or completed, as is the case in all tertiary reference centers. Thus, the colonic resection was performed prior liver resection without the primary opinion of hepatobiliary surgeons. Consequently, we couldn't know the initial resectability of the patients in the ''classic'' group. Consequently, neither could we know the initial resectability of the patients in the ''classic'' group. Moreover, another bias is the length of the study, which does not allow to obtain comparable groups. This study depends on the evolution of the sCRLM management over time. Initially, minor liver resections were managed by ''combined'' strategy and major hepatectomy by ''classic strategy''. After the publication of Mentha et al. [12], sCRLM management has evolved with the introduction of ''liver-first'' strategy. Consequently, this work could not be a comparative study but a clinical practice analysis of synchronous colorectal liver metastases in a hepato-biliary center over time.

Conclusions

All three strategies were feasible and there were no differences regarding overall and recurrence-free survivals between the three approaches. The ''combined'' strategy group had significantly more severe complications and did not provide better oncological results, despite less aggressive liver disease and more limited liver resections.

Ethics Statement

The analysis used anonymous clinical data. Each patient agreed to treatment by written consent.

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Author contributions

Loïc Raoux, Charlotte Maulat, Bertrand Suc and Fabrice Muscari performed research and wrote the paper. Fatima-Zohra Mokrane and Nadim Fares provided critical revision of the manuscript for important intellectual content.

Authorship

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Disclosure of interest

The authors declare that they have no competing interest.

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