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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Primary Tumor Versus Liver-First Strategy in Patients with Stage IVA Colorectal Cancer: A Propensity Score Analysis of Long-term Outcomes and Recurrence Pattern

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ABSTRACT

Background. The optimal strategy in patients with stage IVA colorectal cancer remains debated. This study was designed to compare the long-term outcomes and the pattern of recurrence following classical (CS) versus reverse (RS) strategy.

Methods. Data from all consecutive patients, who have completed the CS and RS, were retrospectively reviewed. A propensity score matching (PSM) was performed on 1:2 (RS:CS) ratio to obtain two groups matched for tumor characteristics. Survival and recurrence pattern were investigated before and after matching.

Results. The study population included 161 patients: 145 treated with CS versus 16 with RS. Five-year overall survival (OS, 51.5 vs. 42.7 %, $p = 0.91$) and recurrence-free survival (RFS, 20.5 vs. 20.6 %, $p = 0.15$) were not different between the two strategies. The median time to recurrence (TTR) whatever the site was significantly shorter in the RS group than in the CS group (3.5 vs. 13 months, $p = 0.02$). Extrahepatic recurrence was significantly more frequent (37.5 vs. 16.6 %; $p = 0.04$) and occurred earlier after treatment completion in the RS group than in the CS group (3.4 vs. 16.4 months, $p = 0.009$). Similar findings in terms of OS, RFS, median TTR whatever the site and proportion of extrahepatic recurrence were observed after PSM.

Conclusions. Stage IVA colorectal cancer patients who have completed the CS or RS had similar OS. Extrahepatic recurrence is more frequent and occurs earlier after RS. Postoperative locoregional therapy and active follow-up strategies should be considered in RS patients.

Multimodal management of stage IVA colorectal cancer may achieve long-term survival, and even cure, provided it includes complete resection of the primary tumor (PT) and the liver metastases (LM).[1] The optimal timing of resection of the PT and LM in this setting remains actively debated. Three strategies are available: 1) classic strategy (CS, so-called primary-first strategy), 2) reverse strategy (RS, so-called liver-first strategy), and 3) combined strategy.[2] The latter includes simultaneous PT and LM resection and avoids delaying surgical resection of both tumor sites. However, this approach often is associated with higher rates of morbidity and mortality and might even impair recurrence-free survival.[3–6] This strategy is proposed to a highly selected subset of stage IVA patients younger than age 70 years who had colectomy rather than rectal resection combined with minor rather than major hepatectomy.[7]

The dilemma between CS and RS questions when both PT and LM are considered resectable (either upfront or after some form of neoadjuvant treatment) but require more than one operation. The CS improves the selection of patients for liver surgery by the "double test of time and chemotherapy": patients with an appropriate response to chemotherapy following the PT resection are subsequently operated on for their LM. However, this strategy may abort "half way" because of liver disease progression beyond resectability or appearance of additional extrahepatic metastases. The

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advantage of the RS is to treat the liver first, particularly in patients with marginally resectable liver disease before becoming not resectable in case of progression.[8] However, in this setting, resection is generally major and associated with operative risk, whereas the PT might progress beyond resectability due to local complications or invasion into surrounding structures.[9,10]

CS and RS achieve similar overall (OS) and recurrence-free survival (RFS) according to several retrospective studies (Table 1).[10–15] However, these reports and the subsequent systematic reviews suffer from numerous bias, including the heterogeneity in terms of tumor characteristics, endpoints, and outcomes monitoring.[10–14,16–25] Furthermore, a better understanding of recurrence patterns and their timing could help not only to adapt postoperative screening for recurrence, but also to tailor adjuvant treatment strategies including locoregional therapies.[26]

This background motivated us to assess the long-term outcomes of patients who underwent surgical treatment for stage IVA colorectal cancer according to surgical strategy (i.e., CS or RS) and to assess differences, if any, in the timing and patterns of recurrence. This retrospective, single-center analysis of consecutive patients was performed before and after propensity-score matching (PSM) for comparing both strategies.

METHODS

Patients and Study Design

From 1989 to 2013, the charts of all consecutive patients who underwent surgical treatment for synchronous LM were retrieved from a prospectively maintained data file and retrospectively reviewed. The Institutional Review Board approved this study. These two questions were assessed: (1) From the time of the last surgical procedure (i.e., PT resection for RS or LM resection for CS), are the long-term outcomes similar following completed CS and RS? (2) Are the timing and patterns of recurrence similar following CS and RS?

To answer these questions, the study population included all consecutive patients having completed the CS or RS. Stage IVA patients entering into any of the following categories were excluded from the study: (1) simultaneous PT and LM resection; (2) any noncurative procedure; (3) presence of synchronous extrahepatic metastases; (4) patients who underwent urgent PT resection; and (5) death that occurred within 90 days after any surgery.

Oncological Strategy

The author's oncological strategy has been previously described.[27] For patients with PT in place and synchronous LM, our strategy has been tailored according to the

TABLE 1 Reported series of the literature comparing classical versus reverse strategy in patients with synchronous colorectal liver metastases

First author, study period (yr)	No. of patients who were planned/have completed the strategy		Extrahepatic disease	Rectal cancer, %		Main differences in patient and tumor characteristics	RFS following completed strategy 3/5-year, %			OS following completed strategy 3/5-year, %		
	CS	RS		CS	RS		CS	RS	*P* value	CS	RS	*P* value
Brouquet,[10] 1992–2009 (17)	72/72	41/27	–	48.6	70.4	Age, sex, primary tumor location, chemotherapy	–	–	–	58/79	48/39	0.389 ***
Andres,[11] 1974–2010 (36)	–/729	–/38	–	23.2	56.9	Propensity score but differences in terms of primary tumor location and lymph node metastases, radio- and chemotherapy	33/26	30/30	0.839	65/46	68/48	0.965
Mayo,[12] 1982–2011 (29)	–/647	–/28	Yes	26.4	53.6	Primary tumor location, extent of liver disease, chemotherapy	–	–		60/45	65/50	0.52 ***
Okuno,[14] 2006–2013 (7)	13/13	12/12	Yes	61.6	58.3	Age, number of hepatic metastases, CA 19-19	29.4/–	29.2/–	0.57	82.5/-	87.5/–	0.46
Tanaka,[13] 1992–2012 (20) ***	30/28	10/2	Yes	27	20	Propensity score	–/11.9 **	–/0 **	0.043	–	–	NS
Welsh,[15] 2004–2014 (10)	467/467	98/82	Yes	27.8	45	Propensity score	–/41.2 **	–/37 **	0.083	49.1 **	47 **	0.846
Present series, 1989–2013 (24)	148/145	20/16	No	20	50	Propensity score	28.3/10.6	20.5/20.5	0.21	67.6/47.6	80/64	0.88

CS classical; *RS* reverse strategy; *RFS* recurrence-free survival; *OS* overall survival; *NS* not significant

– Indicates not available

* Including "wait and see" policy in two patients

** Assessing in an intention-to-treat basis

*** Including patients who underwent simultaneous resection of colorectal and liver metastases

resectability of the metastatic disease and the location and the extent of the PT. Preoperative chemotherapy was considered before any surgery as described elsewhere.[10,11] In case of rectal cancer, chemoradiation was delivered before proctectomy. As in all other series, the program of RS was opened at our unit from the first report of liver-first strategy published by Mentha et al. in 2006.[8–13] For all patients, the surgical sequence to achieve complete PT and LM resection was decided on case-by-case basis at a multidisciplinary decision meeting.[9,12]

In brief, for patients who required a conventional hepatectomy of four segments or less (still maintaining more than 30 % of the parenchyma), surgery was performed before chemotherapy. For patients who required an extended hepatectomy, neoadjuvant chemotherapy was performed with the PT in place. Then, surgery was proposed when the metastatic disease was at least controlled by chemotherapy.

Combined PT and LM resection was attempted except for patients with complicated (bleeding, obstruction, perforation) or locally advanced (requiring preoperative radiotherapy and/or locoregional resection) PT. In these situations, delayed liver resection was performed and patients received interval chemotherapy (CS). Patients with initially unresectable LM were treated with chemotherapy. Patients who responded were offered a RS, as were patients with resectable but advanced LM, which might become unresectable if the PT was resected first (RS).

Postoperative Management

Tumor markers measurement and computed tomography (CT) scan for recurrence screening were performed the first month postoperatively and then every 3 months for the first 2 years and every 6 months for the following 3 years.[28] The diagnosis of recurrence was based on the above explorations completed by site-specific cross imaging in case of symptoms. Biopsy of suspicious lesions for liver and extrahepatic recurrence was performed, whenever needed.

Statistical Analysis

Continuous variables are presented as the means ± standard deviations and were compared using Student's *t* test or the nonparametric Mann–Whitney test, as appropriate. Categorical variables are presented as numbers (percentages) and were compared across groups using the χ^2 or Fischer's exact test, as appropriate.

Long-term outcomes were measured as follows: (1) OS from the last surgical procedure (PT resection for RS or resection of LM for CS) to the date of death; and (2) RFS from the date of the last surgical procedure to the date of the first recurrence at any site or death, respectively.[11] Survival rates were calculated using the Kaplan–Meier method and compared using log-rank tests.

In a second step, the PSM was performed to account for some differences in the patient and tumor characteristics in groups CS and RS that could have an impact on survival. The propensity scores were estimated using a logistic regression model that included the following six covariates primary tumor location, preoperative carcinoembryonic antigen (CEA) level, neoadjuvant chemotherapy, tumor size and number, and surgical resection margins. A 1:2 "nearest neighbor" match paradigm was used; each RS patient was matched with the two CS patients who had the closest estimated propensity score. After matching, the two groups were compared to control the covariate balance and the similarity in the baseline covariates between groups. Then, the two matched groups were compared with respect to the goals of the study. All statistical analyses and PSM were performed with SPSS software (Statistical Package for Social Science, IBM SPSS Statistics, version 23 for Macintosh; IBM, Armonk, NY). The present study complies with the RECORD guidelines.[29]

RESULTS

Study Population

As shown in Fig. 1, during the study period, a total of 244 patients with synchronous LM were evaluated at our liver unit working as a tertiary center. Overall, 83 patients were excluded from the study: 70 for simultaneous resection of PT and LM, 6 for synchronous lung metastases, 4 following death within the 90 days of surgery, and 3 for tumor progression following the first step of the planned strategy.

Among the 148 patients who were planned for CS, 2 patients died following surgery (of PT, $n = 0$; of LM, $n = 2$) and 1 patient did not undergo the second step of a two-stage procedure due to liver disease progression and lung metastatic appearance. Among the 20 patients who were planned for RS, 2 patients died following surgery (of PT, $n = 0$; of LM, $n = 2$) and two patients did not have PT resection due to tumor progression. Finally, CS and RS were considered as completed in 145 of 148 (98 %) and 16 of 20 (80 %) patients respectively ($p = 0.6$). The study population included these 161 patients.

Study Population Characteristics

Compared with CS patients, RS patients were more likely to have rectal cancer ($p = 0.007$), preoperative CEA >5 ng/mL ($p = 0.004$), and a larger liver tumor size ($p = 0.002$). The two groups were statistically similar

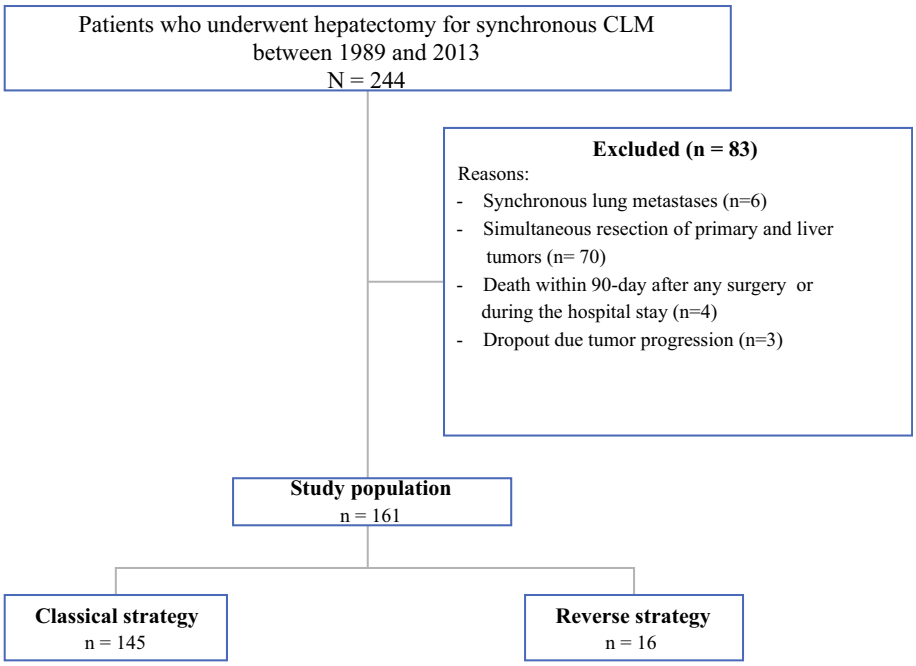

FIG. 1 Flow chart of the study

TABLE 2 Clinicopathologic characteristics of patients according to the type of strategy

	All patients $N = 161$	Classical strategy $n = 145$ (90 %)	Reverse strategy $n = 16$ (10 %)	P value
Age, year	61.4 ± 10.6	61.5 ± 10.8	60.3 ± 8.2	0.68
Age >70 year	34 (21.1)	32 (22)	2 (12.5)	0.37
Sex, male/female	91 (56.5)/70 (43.5)	83 (57.2)/62 (42.7)	8 (50)/8 (50)	0.58
Preoperative CEA levels, ng/mL	374 ± 1636	280 ± 1262	985 ± 3147	0.12
Preoperative CEA >5 ng/ml	76 (47.2)	63 (43.4)	13 (81.3)	0.004
Primary disease				
Colon/rectum	124 (77)/37 5(23)	116 (80)/29 (20)	8 (50)/8 (50)	0.007
Liver metastases				
Neoadjuvant chemotherapy	135 (83.9)	121(83.4)	14 (87.5)	0.68
Mean maximum tumor size, mm (pathology)	46 ± 33	43 ± 30	71 ± 47	0.002
Maximum tumor size >50 mm (pathology)	43 (26.7)	34 (23.4)	9 (56.3)	0.005
Tumor number (pathology)	3 ± 2	3 ± 2	3 ± 2	0.73
Tumor number >3 (pathology)	49 (30.4)	43 (29.7)	6 (67.2)	0.52
Positive resection margin (pathology)	29 (18.0)	24 (16.6)	5 (47.8)	0.15
Two-stage hepatectomy	15 (9.3)	12 (8.3)	3 (18.8)	0.17

CEA carcinoembryonic antigen

Continuous data are given as mean (standard deviation) and categorical variables are presented as numbers (percentages)

regarding age ($p = 0.68$), sex ($p = 0.58$), neoadjuvant chemotherapy ($p = 0.68$), number of liver metastases ($p = 0.73$), and surgical margins ($p = 0.15$; Table 2). Preoperative antiangiogenic regimens (including bevacizumab and cetuximab) were administered in 41 (28 %) patients in the CS group and 11 (69 %) patients in the RS group ($p = 0.001$; Table 3). Preoperative bevacizumab was administered in 30 (21 %) patients in the CS group and 7 (44 %) patients in the RS group ($p = 0.04$). Yet, 88 (55 %) patients received adjuvant chemotherapy after hepatectomy. No liver-directed therapy was used.

Postoperative Morbidity

There was no significant difference in terms of postoperative complications (48/145 in the CS group vs. 7/16 in

TABLE 3 Chemotherapy regimens administered before and after hepatectomy according to the type of strategy

	All patients $N = 161$	Classical strategy $n = 145$ (90 %)	Reverse strategy $n = 16$ (10 %)
Preoperative chemotherapy	135 (84)	121 (83)	14 (88)
Conventional protocols	81 (50)	79 (54)	2 (13)
LV5FU2	16 (10)	15 (10)	1 (6)
Folfox	47 (29)	46 (32)	1 (6)
Folfiri	13 (8)	13 (9)	0
Xelox/xeloda	5 (3)	5 (3)	0
Conventional protocols and anti-angiogenic therapies	52 (32)	41 (28)	11 (69)
Bevacizumab	37 (23)	30 (21)	7 (44)
Cetuximab	15 (9)	11 (8)	4 (25)
5FU alone	2 (1)	1 (69)	1 (6)
Postoperative chemotherapy	88 (55)	76 (52)	12 (75)
Conventional protocols	59 (37)	51 (35)	8 (50)
LV5FU2	13 (8)	11 (8)	2 (13)
Folfox	23 (14)	21 (14)	2 (13)
Folfiri	17 (11)	13 (9)	4 (25)
Xelox/xeloda	6 (4)	6 (4)	0
Conventional protocols and anti-angiogenic therapies	26 (16)	22 (15)	4 (25)
Bevacizumab	14 (9)	12 (8)	2 (13)
Cetuximab	12 (7)	10 (7)	2 (13)
5FU alone	3 (2)	3 (2)	0

5FU 5-fluorouracil; *LV5FU2* combination 5-fluorouracil and folinic acid

the RS group; $p = 0.39$) and rate of reoperation (3/48 in the CS group vs. 2/7 in the RS group; $p = 0.06$) between the two groups.

Long-Term Outcomes

No patient was lost for follow-up, and the mean follow-up was 35 ± 28 months and 31 ± 47 months for groups CS ($n = 145$) and RS ($n = 16$), respectively ($p = 0.61$). OS at 1, 3, and 5 years was 93.1, 66.5, and 51.5 % respectively in group CS versus 100, 64, and 42.7 % respectively in group RS ($p = 0.91$; Fig. 2a). RFS at 1, 3, and 5 years was 68.5, 42.1, and 20.6 % respectively in group CS and 38.5, 30.8, and 20.5 % respectively in group RS ($p = 0.15$; Fig. 2b).

Timing and Pattern of Recurrence

During the follow-up period, recurrence was observed in 93 (64.1 %) patients in the CS group and 11 (68.8 %) patients in the RS group ($p = 0.80$). The median time to recurrence whatever the site was significantly shorter in the RS group than in the CS group (3.5 vs. 13 months, $p = 0.02$). The site of the first recurrence was as follows: intrahepatic ($n = 37$, 35.6 %), extrahepatic ($n = 30$; 28.8 %), and extra- and intrahepatic ($n = 37$; 35.6 %).

First recurrence site was extrahepatic in a significantly higher proportion following RS 6 of 16 (37.5 %) compared with CS (24/145; 16.6 %; $p = 0.04$). The median time to this pattern of recurrence was shorter in the RS group than in the CS group (3.4 vs. 16.4 months, $p = 0.009$). First recurrence site was intrahepatic in 32 of 145 (22.1 %) CS patients versus 5 of 16 (31.3 %) RS patients ($p = 0.41$). The median time to this pattern of recurrence was similar in both groups: 4 versus 14 months for RS versus CS patients respectively ($p = 0.36$).

First recurrence site was both extrahepatic and intrahepatic in a significantly higher proportion following CS (37/145; 25.5 %) compared with RS (0/16; 0 %; $p = 0.02$). The median time to this pattern of recurrence was 9 months in the CS group.

Survival and Recurrence Pattern Analysis using Propensity Score Matching

After PSM, 14 of 16 RS patients could be matched with 28 of 145 CS patients with a 1:2 ratio. No covariates had a standardized mean difference >0.2.[30] The baseline characteristics of the matched study population (42 patients) are summarized in Table 4. There were no significant differences in the demographic or operative characteristics between groups. Preoperative antiangiogenic regimens

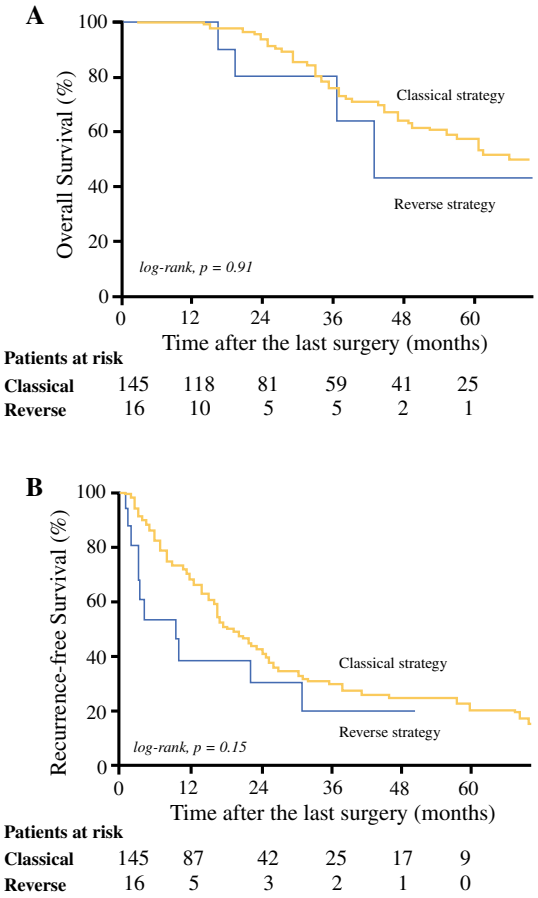

FIG. 2 Overall (**a**) and recurrence-free (**b**) survival curves stratified according to the strategy ($n = 161$)

(including bevacizumab or cetuximab) were administered in ten (36 %) patients in the CS group and ten (71 %) patients in the RS group ($p = 0.03$). Preoperative bevacizumab was administered in nine patients in the CS group and six patients in the RS group ($p = 0.5$).

CS and RS groups had similar 5-year OS (47.7 % vs. 46.7 %, respectively, $p = 0.94$). Although not statistically significant, a trend towards longer 3-year RFS was found following CS compared with RS (33.6 % vs. 24.2 %, respectively, $p = 0.08$; Fig. 3). The median time to recurrence at any site was significantly shorter in the RS group than in the CS group (3 vs. 13 months; $p = 0.04$; Fig. 3).

Recurrence patterns were significantly different between the two therapeutic strategies. First recurrence site was thus extrahepatic in a significantly higher proportion following RS group (6/14; 42.9 %) compared with CS group (3/28; 10.7 %; $p = 0.02$). First recurrence site was both extra- and intrahepatic in a significantly higher proportion following CS (7/28; 25 %) compared with RS (0 %; $p = 0.04$). There was no significant difference in the proportion of initial intrahepatic recurrence between the CS and RS groups (5/28; 17.9 % vs. 3/11; 24.4 %; $p = 0.78$).

DISCUSSION

The present study confirms that CS and RS achieve similar OS and RFS upon analysis of the whole population and after PSM. In addition time to recurrence was significantly shorter following RS. First recurrence site was

TABLE 4 Clinicopathologic characteristics of patients according to the type of strategy after matching

	Case liver-first approach $n = 14$	Matched primary-first approach $n = 28$	*P* value
Variables used for propensity score matching			
Colon/rectum	7 (50)/7 (50)	15 (54)/13 (46)	0.83
Preoperative CEA levels, ng/mL	197 ± 196	747 ± 2236	0.77
Preoperative CEA >5 ng/ml	12 (86)	23 (82)	0.77
Neoadjuvant chemotherapy	12 (86)	24 (85.7)	>0.99
Mean maximum liver tumor size, mm (pathology)	58.8 ± 38.1	58.0 ± 37.7	0.95
Maximum liver tumor size >50 mm (pathology)	7 (50)	13 (46)	0.83
Liver tumor number (pathology)	3.4 ± 2.6	2.6 ± 1.6	0.21
Liver tumor number >3 (pathology)	6 (43)	8 (29)	0.35
Positive resection margin after hepatectomy (pathology)	3 (21)	7 (25)	0.80
Other variables			
Age, year	59 ± 7	57 ± 12	0.60
Age >70 year	1 (7)	5 (18)	0.35
Sex, male/female	6 (43)/8 (57)	17 (61)/11(39)	0.27
2-stage hepatectomy	3 (21)	4 (14)	0.56

CEA carcinoembryonic antigen

Continuous data are given as mean (standard deviation) and categorical variables are presented as numbers (percentages)

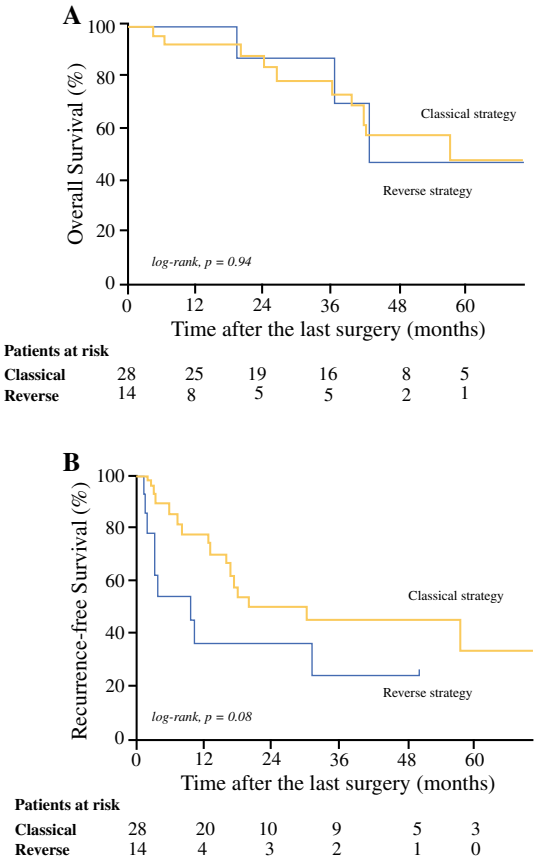

FIG. 3 Overall (**a**) and recurrence-free (**b**) survival curves stratified according to the strategy after propensity score matching

extrahepatic in a significantly higher proportion following RS compared with CS. First recurrence site was intrahepatic in similar proportions following RS or CS and within similar delay. First recurrence site was both extrahepatic and intrahepatic in a significantly higher proportion following CS.

However, our comparison from the whole study population suffers from the following main caveat: the intrinsic noncomparability of the two compared populations (Table 1): a significantly higher proportion of rectum cancer and as well a significantly higher proportion of patients with more advanced liver disease were found in the RS group. These limitations are common to most studies.[10–12,14] This heterogeneity weakens the value of recent systematic reviews, showing no difference in OS and RFS following CS compared with RS.[13–19]

We used propensity-score matching to overcome the problem of confounding from the prognostic variables–outcome association and to emulate a randomized comparison that will probably never be performed. Using this methodology, OS appeared to be similar between the two groups, as found by others.[11] We confirm with this methodology similar OS and RFS as recently reported by Welsh et al.[15] Although the latter included the largest single-centre population LM resection first reported ($n = 98$) and provided a sufficient follow-up to capture almost all recurrences, this recent study had the following limitations: (1) while they reported an intent to treat survival rate of 44 % at 5 years, the survival rate of 82 patients following completed liver-first approach is missing; (2) mortality was measured at 30 days and has not been excluded upon long-term outcome assessment, and (3) timing and pattern of recurrence were not reported.

To the best of our knowledge, this is the first study to evaluate the recurrence pattern of these two approaches in a homogeneous cohort of patients. An interesting finding in this study, although not significant, was a trend towards shorter RFS was found for patients who underwent a RS (24.2 %) compared with those who underwent a CS (33.6 %, $p = 0.08$) and RS was associated with high rate of extrahepatic recurrence. These results suggest that a high incidence of extrahepatic metastases may be the cause of the poor RFS observed after RS. This discrepancy might be explained by several reasons: 1) the liver first group was small, and 2) this study included patients treated (before 2000) with less efficient chemotherapy regimens (5-fluorouracil and combination 5-fluorouracil and folinic acid) and those treated with new standard chemotherapy regimens (Folfox regimens or Folfiri regimens). In addition, bevacizumab and cetuximab association with these new standard chemotherapy protocols can further improve survivals. These improvements in the effectiveness of chemotherapy represent a bias that may explain why there was no difference in OS following CS compared with RS.

Our results corroborate those of one recent study, which reported that the RS is significantly associated with poor RFS ($p = 0.043$) because of a relatively high incidence of number and site of recurrence.[13] However, this study includes several relevant limitations: extrahepatic disease was present in 10 % of patients and the rate of completion of the RS was only 20 %. These findings imply that postoperative locoregional therapy should be considered after resection of the PT in RS patients and these patients should undergo close follow-up with combined interval CT scan of the chest and fluorodeoxyglucose positron emission tomography.[31,32] Although the reasons for these findings are obviously multifactorial and controversial, these clinical results may be explained by a biological rationale suggesting that the behavior of metastatic disease could be dependent on whether the primary tumor stays or not in place.[33]

There are several shortcomings in this study. As with other retrospective studies, there is a patient selection bias inherent to a tertiary liver center. Although the limited sample size of patients included in the group RS may represent other limitation, one recent multicenter study included only 58 patients from 250 centers, which makes

our single-center study is an honorable series.[11] Yet, all patients included in the present study did not receive equally modern chemotherapy protocols, and some patients received targeted therapies when they became available. Finally, we could not investigate the differences in the survival outcomes and recurrence pattern between patients with wild-type KRAS and those with a KRAS gene mutation because of missing data.[34–36]

In conclusion, patients with synchronous CLM and intact PT managed with either CS or RS have similar OS and RFS. However, RS is associated with a relatively high incidence of and early time to extrahepatic recurrence. These data may be useful to tailor patients at high risk of recurrence for adjuvant locoregional therapy and for active follow-up strategies.

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