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ORIGINAL SCIENTIFIC REPORT

Primary Tumor Versus Liver-First Approach for Synchronous Colorectal Liver Metastases: An Association Française de Chirurgie (AFC) Multicenter-Based Study with Propensity Score Analysis

Francesco Esposito[1] · Chetana Lim[1] · Antonio Sa Cunha[2] · Patrick Pessaux[3,4] · Francis Navarro[5] · Daniel Azoulay[1,6] · On behalf of the French Colorectal Liver Metastases Working Group, Association Française de Chirurgie (AFC)

Abstract

Objectives Multicenter studies comparing the reverse strategy (RS) with the classical strategy (CS) for the management of stage IVA liver-only colorectal cancer (CCR) are scarce. The aim of this study was to compare long-term survival and recurrence patterns following use of the CS and RS.

Method This retrospective multicenter review collected data from all consecutive patients with stage IVA liver-only CCR who underwent staged resection of CCR and liver metastases (LM) at 24 French hospitals between 2006 and 2013 and were retrospectively analyzed. Patients who underwent simultaneous liver and CCR resection, those with synchronous extra-hepatic metastasis, and those who underwent emergent CCR resection were excluded. Overall survival (OS) and recurrence-free survival (RFS) rates and recurrence patterns were investigated before and after propensity score matching (PSM).

Results A total of 653 patients were included: 587 (89.9%) in the CS group and 66 (10.1%) in the RS group. Compared with the CS patients, RS patients were more likely to have rectal cancer (43.9 vs. 24.9%; $p = 0.006$), larger liver tumor size (52.5 ± 38.6 vs. 39.6 ± 30 mm; $p = 0.01$), and more positive lymph nodes (62.1 vs. 44.8%; $p = 0.009$). OS was not different between the two groups (75 vs. 72% at 5 years; $p = 0.77$), while RFS was worse in the RS group (24 vs. 33% at 5 years; $p = 0.01$). Time to recurrence at any site (1.8 vs. 2.4 years, $p = 0.024$) and intrahepatic recurrence (1.7 vs. 2.2 years, $p = 0.014$) were significantly shorter in the RS group than in the CS group. After PSM (63 patients in each group), no significant difference was found between the two groups in OS ($p = 0.35$), RFS ($p = 0.62$), time to recurrence at any site ($p = 0.19$), or intrahepatic recurrence ($p = 0.13$).

Conclusions In this study, approximately 10% of patients with CCR and synchronous LM were offered surgery with the RS. Both strategies ensured similar oncological outcomes.

Introduction

Surgical resection of primary colorectal cancer (CCR) and liver metastases (LM) is the only curative treatment for patients with synchronous CCR. Two strategies are proposed: (1) a one-stage surgical procedure (i.e., simultaneous resection of the primary tumor (PT) and LM) [1] and a

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✉ Daniel Azoulay
daniel.azoulay@hmn.aphp.fr

1 Department of Hepatobiliary and Pancreatic Surgery and Liver Transplantation, Henri Mondor Hospital, Université Paris-Est (UPEC), 51 Avenue de Lattre de Tassigny, 94010 Créteil, France

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two-stage surgical procedure [the classical strategy (CS) vs. the reverse strategy (RS)]. The one-stage procedure is associated with good outcomes when applied to young patients with colon cancer who require colectomy combined with minor liver resection [2–4]. The latter two strategies ensure similar long-term outcomes (Supplementary Table 1). However, most studies have been limited to monocentric studies or did not specifically focus on recurrence patterns. Recently, two studies have shown that the RS may be associated with worse RFS [5, 6], and our group has suggested that extrahepatic recurrence occurs earlier after the RS.

Using the French National Surgical Association multicenter registry, the goal of this study was to compare long-term outcomes and recurrence patterns between the CS and RS.

Method

All data were collected from a multicenter French registry of patients who underwent hepatectomy for colorectal LM at 24 hospitals from 2006 to 2013 as previously described [7–11].

Patients and outcomes

The study inclusion criteria were as follows: (1) synchronous LM (LM discovered at or before diagnosis of CCR) and (2) delay between CCR resection and liver resection of at least 7 days. The surgical strategy (i.e., CS or RS) was identified by comparing the dates of hepatic and colorectal surgeries. In this database, determining whether patients underwent resection of the PT and LM at the same center was not possible.

Patients in the following categories were excluded: (1) patients who underwent the one-stage surgical procedure, (2) patients with metachronous LM, (3) patients with synchronous extrahepatic metastases, and (4) patients who required emergent CCR resection.

[2] Department of Hepatobiliary and Pancreatic Surgery and Liver Transplantation, Paul Brousse Hospital, Villejuif, France

[3] Institut Hospitalo-Universitaire, Institute for Minimally Hybrid Invasive Image-Guided Surgery, Université de Strasbourg, Strasbourg, France

[4] Institut de Recherche sur les Cancers de l'Appareil Digestif (IRCAD), Strasbourg, France

[5] Department of Surgery, Saint-Eloi Hospital, Université de Montpellier, Montpellier, France

[6] INSERM, U955, Créteil, France

As the number of patients who did not complete the surgical strategy (i.e., CS or RS) was not available from the database, an intention-to-treat analysis could not be performed.

The primary outcomes were OS and RFS. The secondary outcomes included the recurrence pattern and time to recurrence. Major hepatectomy was defined as resection $\geq$3 segments. Short-term outcomes were evaluated at 90 days following surgery.

Resectability was defined as the predicted possibility to remove both PT and LM with clear margins (at least 1 mm) [12].

Statistical analysis

Continuous variables are presented as the mean $\pm$ standard deviations. These variables were compared using Student's *t* test or the nonparametric Mann–Whitney test as appropriate. Categorical variables are presented as numbers (percentages). These variables were compared using the Chi-square test or Fisher exact test as appropriate.

OS was calculated from the date of CCR diagnosis to the date of death; and RFS was calculated from the date of the second surgery (i.e., CCR resection for the RS strategy and liver resection for the CS strategy) to the date of the first recurrence at any site. Survival rates were calculated using the Kaplan–Meier method and compared using log-rank tests.

PSM was then performed to account for differences in the clinicopathologic variables that may influence survival. The propensity scores were estimated using a logistic regression model that included the following eight covariates: age, body mass index (BMI), sex, PT location, neoadjuvant chemotherapy, lymph node status, tumor size, and tumor number. A 1:1 "nearest neighbor" match was used.

All statistical analyses were performed with SPSS (IBM SPSS Statistics, version 23 for Macintosh; IBM, Armonk, NY). This study complies with the RECORD guidelines [13].

Results

The entire population included 653 patients. Overall, 1967 patients were excluded: 1076 for metachronous metastases, 361 for urgent PT resection, 124 for synchronous extrahepatic metastases, 161 for simultaneous resection of the PT and LMs, and 245 due to a lack of sufficient data. The RS and CS were used in 66 (10.1%; Supplementary Table 2) and 587 (89.9%) patients, respectively.

When the period of analysis was divided into two periods (2003–2008 vs. 2009–2013), the number of RS patients during the second period was significantly higher than that in the first period (13 vs. 6.7%; $p = 0.009$, Fig. 1).

Patients

RS patients were more likely to have rectal tumors (43.9 vs. 24.9%; $p = 0.006$), larger liver tumor size (52.5 ± 38.6 vs. 39.6 ± 30 mm; $p = 0.01$), more positive lymph nodes

Fig. 1 Classical (CS) and reverse (RS) strategies in this study

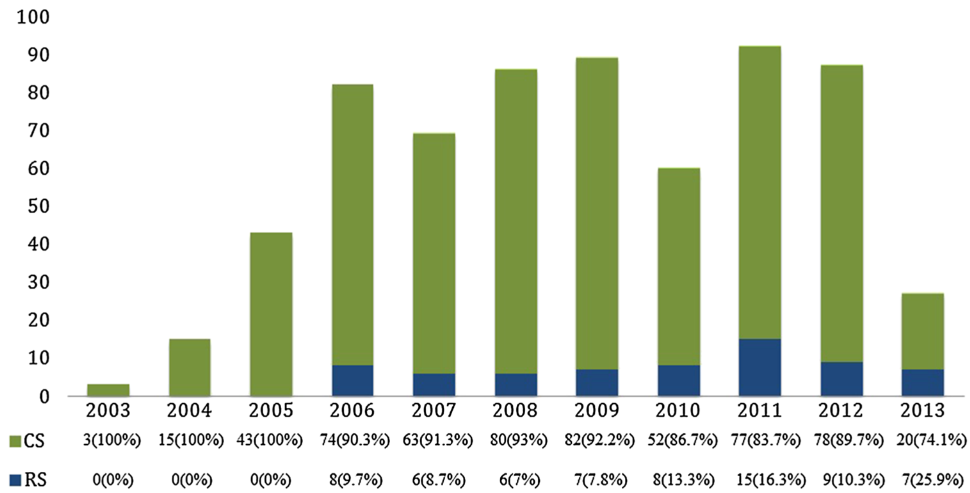

Table 1 Preoperative characteristics

	All patients $N = 653$	Reverse strategy $N = 66$ (10.1%)	Classical strategy $N = 587$ (89.9%)	p
Age (years)	60.5 ± 10.6	60.3 ± 11.1	60.6 ± 10.5	0.85
Age >70 years, *n* (%)	139 (21.3%)	15 (22.7%)	124 (21.1%)	0.76
BMI (kg/m^2)	25.4 ± 4.4	25 ± 3.7	25.5 ± 4.5	0.30
Male sex, *n* (%)	378 (57.9%)	39 (59.1%)	339 (57.8%)	0.83
ASA score, *n* (%)				
I	75 (11.5%)	3 (4.5%)	72 (12.3%)	0.24
II	465 (71.2%)	49 (74.3%)	416 (70.9%)	
III	111 (17%)	14 (21.2%)	97 (16.5%)	
IV	2 (0.3%)	0 (0%)	2 (0.3%)	
Preoperative CEA levels (ng/mL)	230.7 ± 1517.1	812.36 ± 3913.2	152.6 ± 734.4	0.23
Primary disease, *n* (%)				
Right colon	199 (30.4%)	15 (22.7%)	184 (31.3%)	0.006
Transverse colon	19 (2.9%)	0 (0%)	19 (3.2%)	
Left colon	260 (39.9%)	22 (33.4%)	238 (40.6%)	
Rectal location	175 (26.8%)	29 (43.9%)	146 (24.9%)	
T 4	113 (17.3%)	11 (16.7%)	102 (17.4%)	0.88
Lymph node positive	304 (46.6%)	41 (62.1%)	263 (44.8%)	0.009
Liver metastases				
Portal vein embolization, *n* (%)	145 (22.3%)	18 (27.3%)	127 (21.7%)	0.30
Mean maximum tumor size (mm)[a]	41 ± 31.2	52.5 ± 38.6	39.6 ± 30	0.01
Tumor size >50 mm[a], *n* (%)	141 (21.6%)	23 (34.8%)	118 (20.1%)	0.01
Tumor number[a]	3.5 ± 3.4	4.3 ± 3.9	3.4 ± 3.3	0.08
Tumor number >3[a], *n* (%)	220 (33.7%)	30 (45.5%)	190 (32.4%)	0.03

BMI body mass index, *ASA* American Society of Anesthesiologists, *CEA* carcinoembryonic antigen
[a]Pathology

Table 2 Postoperative data

	All patients $N = 653$	Reverse strategy $N = 66$ (10.1%)	Classical strategy $N = 587$ (89.9%)	p
Posthepatectomy course, n (%)				
90-Day mortality	4 (0.6%)	0 (0%)	4 (0.7%)	0.49
Overall morbidity	212 (32.4%)	30 (45.5%)	182 (31%)	0.02
Infectious complications	83 (12.2%)	8 (12.2%)	75 (12.7%)	0.32
Biliary leakage	19 (2.9%)	4 (6.1%)	15 (2.6%)	0.11
Hemorrhage	12 (1.8%)	2 (3%)	10 (1.7%)	0.34
Hepatic insufficiency	26 (3.9%)	4 (6.1%)	22 (3.7%)	0.32
Recurrence, n (%)				
Overall	342 (52.3%)	36 (54.5%)	306 (52.1%)	0.62
Intrahepatic	166 (25.4%)	15 (25.7%)	151 (25.7%)	0.59
Extrahepatic	72 (11%)	9 (13.6%)	63 (10.7%)	0.47
Loco-regional	39 (6%)	5 (7.6%)	34 (5.8%)	0.58
Pulmonary recurrence	110 (16.9%)	11 (16.7%)	99 (16.9%)	0.95
Peritoneal carcinomatosis	34 (5.2%)	3 (4.5%)	31 (5.3%)	0.79
Time to recurrence (years), n (%)				
Overall	2.3 ± 1.4	1.8 ± 1.2	2.4 ± 1.5	0.02
Intrahepatic	2.2 ± 1.2	1.7 ± 0.7	2.2 ± 1.2	0.01
Extrahepatic	2.2 ± 1.2	2.4 ± 1.9	2.2 ± 1.1	0.68

(62.1 vs. 44.8%; $p = 0.009$), and a higher number of metastases, though this last factor was not statistically significant (4.3 ± 3.9 vs. 3.4 ± 3.3; $p = 0.08$).

There were no significant differences regarding the age ($p = 0.85$), BMI ($p = 0.30$), sex ($p = 0.83$), American Society of Anesthesiologists score ($p = 0.24$), or carcinoembryonic antigen ($p = 0.23$) (Table 1) between the two groups. No significant difference was found in terms of major liver resection ($p = 0.14$), two-stage hepatectomy ($p = 0.70$), laparoscopic surgical approach ($p = 0.56$), and surgical margin ($p = 0.82$) between the two groups (Supplementary Table 3).

Preoperative chemotherapy was used in 509 patients (77.9%) (Supplementary Table 4), and targeted therapies (bevacizumab and cetuximab) were used in 261 (56.7%) patients in the CS group and 28 (57.2%) patients in the RS group ($p = 0.95$). In addition, 465 (71.2%) patients received adjuvant chemotherapy after hepatectomy, and no difference was observed between the two groups in terms of chemotherapy protocols ($p = 0.50$).

Postoperative mortality and morbidity

Although it was not the main goal of this study, no significant difference was found in 90-day mortality following either liver resection or colorectal resection between the two groups (0 vs. 0.7%). A significant difference was observed in overall postoperative morbidity following liver resection (30/66 in the RS group and 193/587 in the CS group, $p = 0.04$) (Table 2), but no difference was found in postoperative infections ($p = 0.32$), hemorrhage ($p = 0.34$), biliary leakage ($p = 0.11$), or hepatic insufficiency ($p = 0.32$).

Long-term survival

OS at 1, 3, and 5 years was 100, 88, and 72%, respectively, in the RS group versus 99, 89, and 75%, respectively, in the CS group ($p = 0.77$, Fig. 2a). RFS at 1, 3, and 5 years was 89, 38, and 24% in the RS group, respectively, versus 94, 54, and 33% in the CS group, respectively ($p = 0.01$, Fig. 2b).

Timing and pattern of recurrence

Recurrence was observed in 36 (54.5%) patients following RS and 306 (52.1%) patients following CS ($p = 0.62$). The liver was the first site of recurrence (48.5%), followed by the lung (32.1%) and loco-regional recurrence (11.4%). No significant difference was found in intrahepatic and extrahepatic recurrence between the two groups (Table 2).

In the RS group, the mean time to overall recurrence was shorter (1.8 years) than that in the CS group (2.4 years) ($p = 0.02$). Furthermore, the RS was associated with a shorter time to intrahepatic recurrence (1.7 ± 0.7 vs. 2.2 ± 1.2 years; $p = 0.01$), but no difference was found in time to extrahepatic recurrence (2.4 ± 1.9 vs. 2.2 ± 1.1 years; $p = 0.68$).

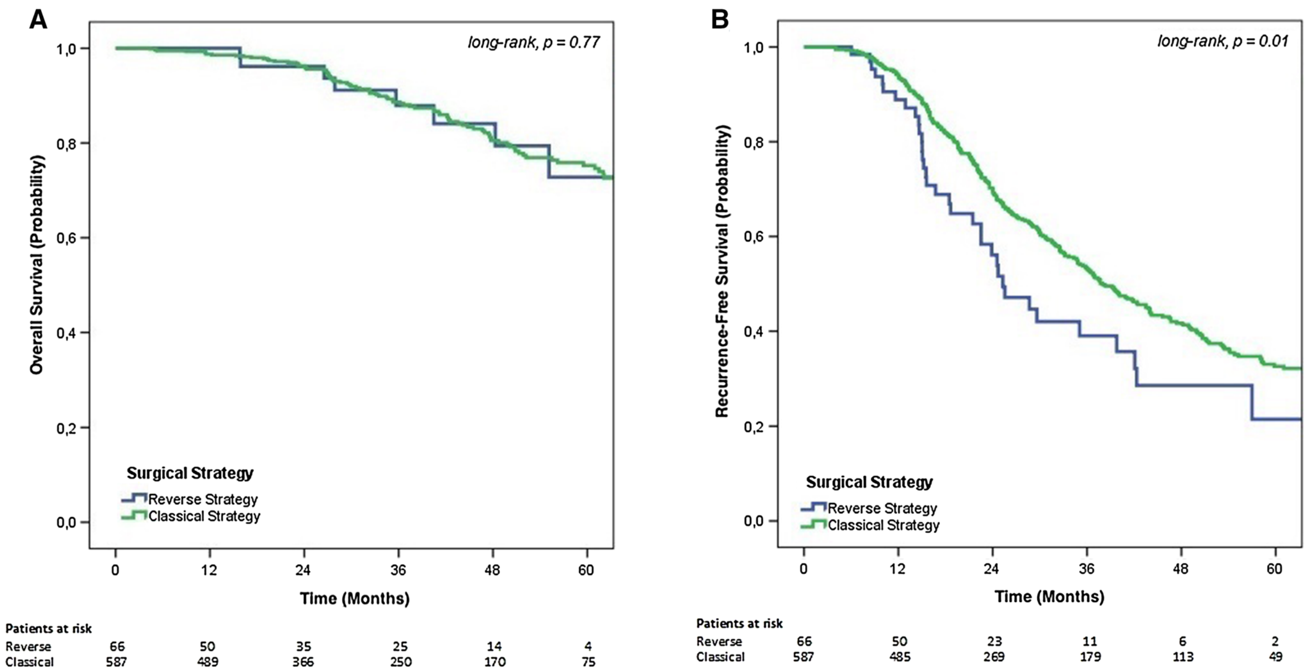

Fig. 2 Before propensity score matching. **a** Overall survival stratified according to the surgical strategy. **b** Recurrence-free survival stratified according to the surgical strategy

After propensity score matching

In total, 63 of 66 RS patients were matched with 63 of 587 CS patients (Table 3). No covariates had a standardized mean difference >0.2 [14]. There were no significant differences in the baseline or intraoperative data between the two groups.

The RS group had similar 1-, 3-, and 5-year OS (96, 90, and 69%) as the CS group (96, 82, and 59%; $p = 0.35$) (Fig. 3a). No significant difference was found in 1-, 3-, and 5-year RFS between the two groups (88, 37, and 24% in the RS group vs. 97, 35, and 17% in the CS group; $p = 0.62$) (Fig. 3b). The median time to recurrence at any site was comparable between the two groups ($p = 0.19$). There were no significant differences in intrahepatic ($p = 0.24$) or extrahepatic recurrences ($p = 1.00$), as well as in time to intrahepatic recurrence ($p = 0.13$) or extrahepatic recurrence ($p = 0.46$).

Discussion

To our knowledge, this is the second national multicenter study comparing the RS with the CS [15]. The present report, including patients treated during a contemporary period with recent chemotherapy, confirmed that these two approaches yield similar long-term survival and recurrence outcomes.

In France, approximately 10% of patients with stage IVA disease underwent surgery with the RS, which was three times less than the rate found in Sweden [15]. One explanation may be that the Swedish registries were prospective and included more than 90% of all colorectal cancers; this was not the case in this retrospective study including 24 French centers.

We confirmed, like others, that patients who underwent the RS more often had primary rectal cancer and more advanced liver disease compared with those who underwent the CS. The rationale behind these findings is intuitively logical: resection of the LM before the PT should (1) remove the more advanced tumors that may immediately jeopardize patient survival and (2) limit the risk of LM progression during the delay between radiochemotherapy and removal of the rectal cancer. However, we do not have information about the initial number of patients for whom the RS was planned but who did not have resection of the rectal cancer. This precluded an intention-to-treat analysis. Previous studies [16, 17], including ours [5], suggest that the dropout rate may vary from 16 to 35% [18]. This should be interpreted with caution, as these three studies [5, 16, 17] were performed before the use of advanced targeted therapies.

The present study showed that the 5-year survival rates in both groups were particularly high (around 70%) compared to those in other multicentric series (approximately 50%) [2, 3, 9]. The reasons for this difference may be

Table 3 Clinicopathologic characteristics and outcomes after matching

	Reverse strategy (n = 63)	Classical strategy (n = 63)	p
Variables used for propensity score matching			
Age (years)	60.8 ± 10.9	60.6 ± 10.7	0.91
Age >70 years, n (%)	15 (23.8%)	8 (12.7%)	0.16
Male sex, n (%)	38 (60.3%)	39 (61.9%)	1.00
BMI (kg/m^2)	25.1 ± 3.8	24.5 ± 3.9	0.42
Colon/rectum, n (%)	36 (57.1%)/27 (42.9%)	35 (55.6%)/28(44.4%)	1.00
Neoadjuvant chemotherapy, n (%)	48 (76.2%)	48 (76.2%)	1.00
Mean maximum tumor size[a], mm	48.7 ± 32.9	45.4 ± 35.6	0.58
Tumor number[a]	4.2 ± 3.7	4.3 ± 3.7	0.91
Lymph node positive, n (%)	39 (61.9%)	32 (50.8%)	0.28
Other variables			
Tumor size >50 mm[a], n (%)	21 (33.3%)	16 (25.4%)	0.43
Tumor number >3[a], n (%)	29 (46%)	25 (39.7%)	0.59
Positive resection margin[a], n (%)	7 (11.1%)	6 (9.5%)	1.00
90-Day mortality, n (%)	0 (0%)	0 (0%)	–
Overall mortality at the last follow-up	10 (15.9%)	18 (28.6%)	0.13
Overall morbidity, n (%)	30 (47.6%)	20 (31.7%)	0.11
Recurrence, n (%)			
Overall	34 (54%)	39 (61.9%)	0.47
Intrahepatic	15 (23.8%)	22 (34.9%)	0.24
Extrahepatic	8 (12.7%)	8 (12.7%)	1.00
Time to recurrence (years)			
Overall	1.8 ± 1.2	2.1 ± 0.8	0.19
Intrahepatic	1.7 ± 0.7	2.1 ± 0.7	0.13
Extrahepatic	2.5 ± 2.1	1.9 ± 0.9	0.46

BMI body mass index

[a]At specimen analysis

multifactorial. First, this may partially reflect the selection of patients who underwent liver resection [>75% of patients had <70 years, mean tumor size: 41 mm, >75% of patients had tumor size <50 mm, mean tumor number: 3.5, >65% of patients had less than 3 tumors (Table 1), and >50% of patients received more efficient chemotherapy protocols, including targeted therapies (Supplementary Table 4)]. Second, considering the definition of survival after the date of diagnosis of the disease rather than the date of surgery, the survival rate in our study was more likely to be higher than that in other studies [3]. Third, the study period and heterogeneity in targeted therapy-based chemotherapy protocols may also explain the difference in survival rates [2, 3]. Fourth, this may be explained by the surgical management of hepatic and extrahepatic recurrences after initial hepatectomy [19]. Fifth, repeat hepatectomy yielded a survival rate similar to that of initial hepatectomy in this study cohort, leading to cumulative long-term survival from initial hepatectomy [20].

The two strategies ensured similar survival, which was in line with most published studies (Supplementary Table 1) and discordant with one [16]. This was confirmed after PSM for the variables related to liver disease (which was more advanced in the RS group). In our previous single-center study with 16 patients in the RS group and 141 in the CS group, we found no difference in RFS or recurrence pattern between the two groups [16]. The only difference we found was that the time to recurrence was significantly shorter in the RS group than in the CS group. However, after adjusting for variables related to liver disease (as RS patients had more advanced liver disease), no difference was found in terms of time to recurrence between the two groups. In the present report, no difference in the pattern of recurrence was found between the two groups before and after PSM.

There are several limitations in this study, including the retrospective study design and a mixture of high and low volume centers. Despite the use of the PSM methodology, we cannot exclude bias in the selection of patients who underwent surgery with the RS. In addition, despite the presence of a multidisciplinary oncology meeting at each center relying on consensus recommendations, we cannot

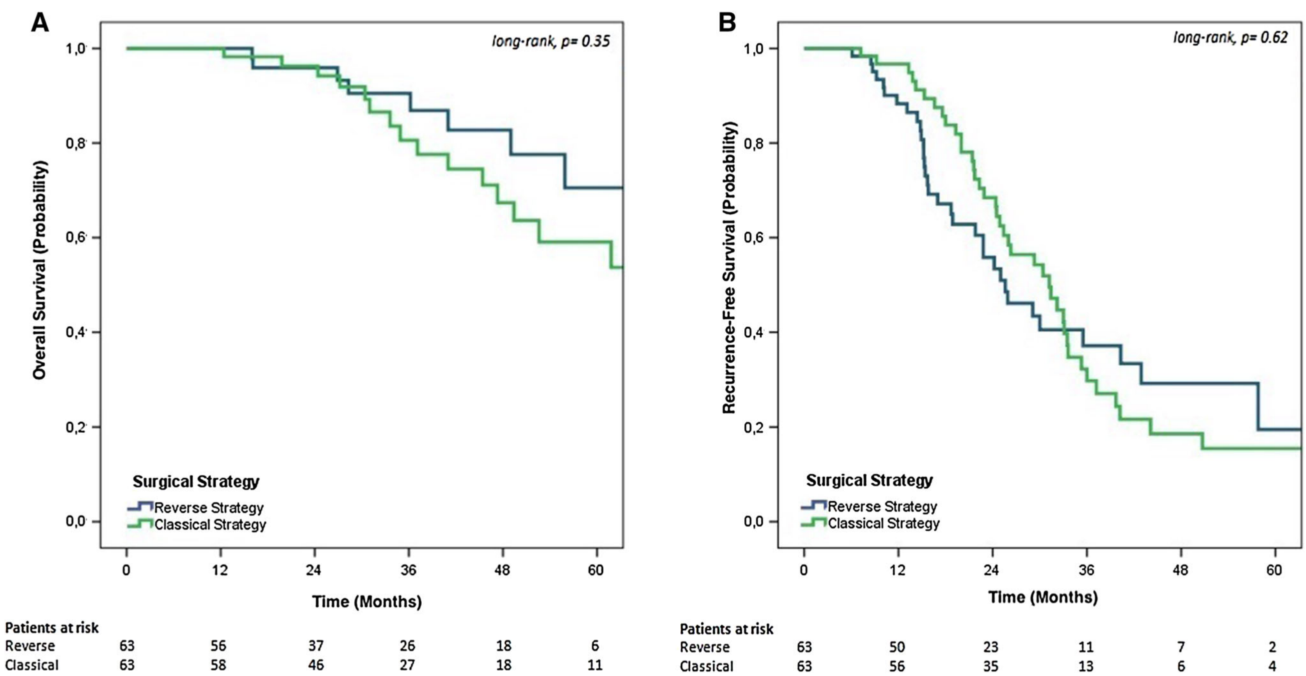

Fig. 3 After propensity score matching. **a** Overall survival stratified according to the surgical strategy. **b** Recurrence-free survival stratified according to the surgical strategy

exclude local bias of selection for one strategy over another. A randomized comparison will probably never be performed for several reasons, including the heterogeneity of patients and the subjective definition of resectability. Furthermore, we missed possible differences regarding the delay after surgery to restart chemotherapy that may have influenced outcomes.

As for the variables used for PSM, we did not use the Basingstoke Predictive Index as Welsh et al. [16] did. More importantly, we think that the more severe liver disease and the presence of primary rectal cancer represent the main inherent differences between the two groups.

Another important shortcoming is the impossibility of analyzing the strategies on an intent-to-treat basis, i.e., including patients who were intended to undergo the CS or RS and who did not have the second surgery, due to data file limits. Our previous study showed that the dropout rate due to tumor progression was higher in the RS group (20%) than in the CS group (2%), while this variable was comparable in another recent study (35% for the RS vs. 29% for the CS) [5]. Further larger studies are required to clarify this point. The strength of this study is that it is a national multicenter-based study using the PSM methodology to overcome the inherent selection bias of the two groups and the largest study to focus on recurrence patterns and timing to recurrence.

Finally, the 63 patients in each group might have been adequately underpowered to show any differences. The present study is one of the largest studies (Supplementary Table 1), and even the recent study including 246 patients who underwent the RS did not show any difference in terms of OS or RFS [9].

Conclusions

In this national multicenter study, patients who underwent surgery with the RS more often had rectal tumors and had more advanced liver disease. After the PSM methodology, survival, recurrence pattern, and timing to recurrence were comparable to those observed in patients who underwent the classical approach. The reversed and classical strategies should not be mutually exclusive but rather proposed to different types of patients.

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Contributors: Amiens, CHU Amiens Picardie: Cyril Cosse, Delphine Lignier, Jean Marc Regimbeau; Angers, CHU Angers: Julien Barbieux, Emilie Lermite, Antoine Hamy; Beauvais, CH Beauvais: François Mauvais; Bordeaux, Groupe Hospitalier Saint André: Christophe Laurent; Chambery, CH Chambery: Irchid Al Naasan; Créteil, CHU Henri Mondor: Daniel Azoulay, Chady Salloum, Philippe Compagnon, Chetana Lim; Eaubonne, Hôpital Simone Veil: Mohammed Sbai Idrissi; Epinal, Polyclinique de la Ligne Bleue: Fréderic Martin; Gap, CH des Alpes du Sud: Jerôme Atger; Lyon, Hôpital de la Croix Rousse: Jacques Baulieux, Benjamin Darnis, Jean Yves; Mabrut; Lyon, Hôpital Edouart-Herriot: Vahan Kepenekian, Julie Perinel, Mustapha Adham; Lyon, CH Lyon Sud: Olivier Glehen;

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Author contributions Esposito, Lim, and Azoulay contributed to the study concept and design and statistical analysis. All authors involved in acquisition, analysis, and interpretation of data. Esposito, Lim, and Azoulay drafted the manuscript. Lim, Azoulay, Sa Cunha, Navarro, and Pessaux critically revised the manuscript for important intellectual content. Navarro, Sa Cunha, and Pessaux provided administrative, technical, and material support. Lim and Azoulay supervised the study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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