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ORIGINAL ARTICLE

Which surgical strategy for colorectal cancer with synchronous hepatic metastases provides the best outcome? A comparison between primary first, liver first and simultaneous approach

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Abstract

Background There is no clear consensus about the best surgical strategy for patients with colorectal cancer (CRC) and synchronous liver metastases (SCRLM).

Methods Between 2009 and 2019, patients with CRC and SCRLM considered for curative treatment were included. Perioperative and follow-up data were analysed to examine the safety and survival outcomes of primary first (PF), liver first (LF) and simultaneous resection (SR) strategies.

Results 204 patients were identified, consisting of PF ($n=129$), LF ($n=26$) and SR ($n=49$). Forty-five patients (22.1%) failed to have either the primary or the liver metastases resected following initial LF ($n=11$, 42.3%) or PF ($n=34$, 26.4%), respectively ($p<0.001$). The postoperative morbidity rates were 31.0%, 38.4% and 40.8% in PF, LF and SR group, respectively ($p=0.409$); the mortality rates were 2.3%, 0% and 4.1%, respectively ($p=0.547$). The 1-, 3- and 5-year overall survival (OS) were 94%, 72%, 53% in the PF group, 74%, 54%, 36% in the LF group, and 91%, 74%, 63% in the SR group. LF group had the worst OS compared to PF and SR ($p=0.040$, $p=0.052$). The 1-, 3- and 5-year disease-free survival (DFS) were 31%, 15%, 10% in PF, 21%, 9% and 9% in LF and 45%, 28% and 28% in SR group, respectively. SR group had a better DFS compared to PF and LF ($p=0.005$, $p=0.008$). At the multivariate analysis, there was no difference between the three strategies in terms of OS (PF vs SR OS-HR 1.090, $p=0.808$; LF vs SR OS-HR 1.582, $p=0.365$) and the PF had a worse DFS compared to the SR approach (PF vs SR DFS-HR 1.803, $p=0.007$; LF vs SR DFS-HR 1.252, $p=0.492$).

Conclusions PF, LF and SR had comparable postoperative morbidity and mortality. The three surgical strategies had similar OS outcomes. The PF strategy was associated with a worse DFS than SR, while the LF approach was associated with a high failure rate to progress to the second stage (primary tumour resection).

Keywords Colorectal cancer · Liver metastases · Primary first · Liver first · Simultaneous resection · Multidisciplinary team (MDT)

Introduction

Synchronous colorectal liver metastases (SCRLM), defined as liver metastases (CRLM) detected at or before the diagnosis of the primary tumour [1], are found in 16–21% of patients with colorectal cancer (CRC), with a growing trend over the years [2]. Synchronous metastatic disease is associated with a worse prognosis compared to metachronous disease, with a 5-year post-resection survival rate of 39% versus 48%, respectively [1, 3]. Surgical resection of both the primary tumour and liver metastases offers the only chance for cure and radicalisation of the disease. The timing of surgery often depends on the patient's symptoms from the primary tumour or resectability of the liver metastases. Therefore, a personalised strategy is often required [4, 5]. To date, it remains unclear as to the best surgical strategy for managing patients with CRC and SCRLM even in the presence of a dedicated multidisciplinary team (MDT) involving oncologists, colorectal and hepatic surgeons [5]. As such, a bespoke approach to planning the timing of surgery following systemic

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chemotherapy is the key to improve long-term outcomes [3, 6]. This study aims to assess the outcomes of patients with CRC and SCRLM following resection with either primary first (PF), liver first (LF) or simultaneous resection (SR) approach.

Methods

Between 2009 and 2019, consecutive patients diagnosed with synchronous colorectal adenocarcinoma and liver metastases were identified at our institute (Royal Marsden Hospital, London, UK). Those considered for a curative intent were included. The therapeutic strategy for each patient was decided at our MDT meetings, consisting of oncologists, colorectal and hepatic surgeons. Data were collected in a prospective database and retrospectively reviewed. The data collected consisted of the baseline characteristics, primary tumour and metastatic disease characteristics, neoadjuvant therapy, patient fitness status before the surgery, surgical strategies (PF, LF or SR), type of surgical resection, intraoperative data, postoperative outcomes, adjuvant therapy characteristics, further surgeries and percutaneous ablations, and long-term follow-up details (date of remission and progression of the disease, last follow-up date, date of death).

This study was reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [7]. Definitions and methods are detailed in the Supplementary material 1.

Aims

The main aim of this study is to provide the short- and long-term outcomes of different surgical strategies for the management of CRC with SCRLM: PF, LF and SR approaches. The primary endpoint is the safety of each approach, assessed by the perioperative morbidity and mortality data. The secondary endpoint is the long-term survival outcome assessed by the 1-, 3- and 5-year overall survival (OS) and the 1-, 3- and 5-year disease-free survival (DFS) rates.

Inclusion and exclusion criteria

Only patients with a confirmed colorectal adenocarcinoma diagnosis and SCRLM who were considered at the MDT for at least one surgical resection, either for the primary or the liver, with curative intent, were included. According to the aims of this study, patients who underwent only one surgery were included and classified as per the type of strategy chosen at the MDT meeting. Reasons for failure to progress to the second surgery were: (1) remission of the disease with medical therapy or percutaneous ablation, (2) disease progression with the patient becoming unfit to undergo the second surgery, and (3) death. Patients with different primary histopathology, metachronous liver metastases and recurrence of the disease at the diagnosis were excluded.

The decision-making algorithm of patients who underwent a bespoke approach to their disease is specified in Fig. 1. The MDT selected the treatment of the patients based on a case-by-case assessment. The PF approach was particularly preferred for tumours with a high risk of complications such as obstruction, bleeding or perforation. The LF approach was preferred for cases where the liver metastases could be resected at the time of the evaluation, associated with a primary tumour with low risk of complication or progression, or in case the primary could benefit from neoadjuvant therapy, such as rectal cancer.

Statistics

All the statistical analyses were performed using SPSS 26 (IBM®). Categorical variables were presented as frequency and ratio and compared between groups with the Pearson Chi-square test. Continuous variables were presented as a median with a 95% confidence interval (95% CI) and compared between groups using the Kruskal–Wallis test (one-way ANOVA). All calculations were made on the total available data, removing missing data or data from patients that did not receive one of the two surgeries in our institution, when appropriate.

All the intraoperative and postoperative outcomes were cumulatively considered. Only data from the first primary and the first liver surgery were taken into consideration for the comparison of the approaches. Data from further surgeries were recorded but not included in the analysis.

For the cumulative calculation of the length of hospital stay (LOS), length of intensive care unit (ICU) stay and operative time (OT), patients treated with a staged approach who received one of the two surgeries in another hospital were removed due to missing data; patients who received only one surgery overall or the two surgical stages at our institution were included in the calculation.

Postoperative morbidity and mortality were defined as the occurring of a complication or death, respectively, during the in-hospital stay or within 30 days from the surgeries. Postoperative complications were assessed according to the Clavien-Dindo classification in minor (1–2) and major (3–4) [8]. Whenever more complications occurred in the same patient, the major one was considered.

Survival estimates were performed with the life tables and the Kaplan–Meier analysis. The Mantel-Cox log-rank and Tarone-Ware tests were used to pairwise compare the groups. All the survival analyses were censored for loss to follow-up, determined by the last follow-up date available.

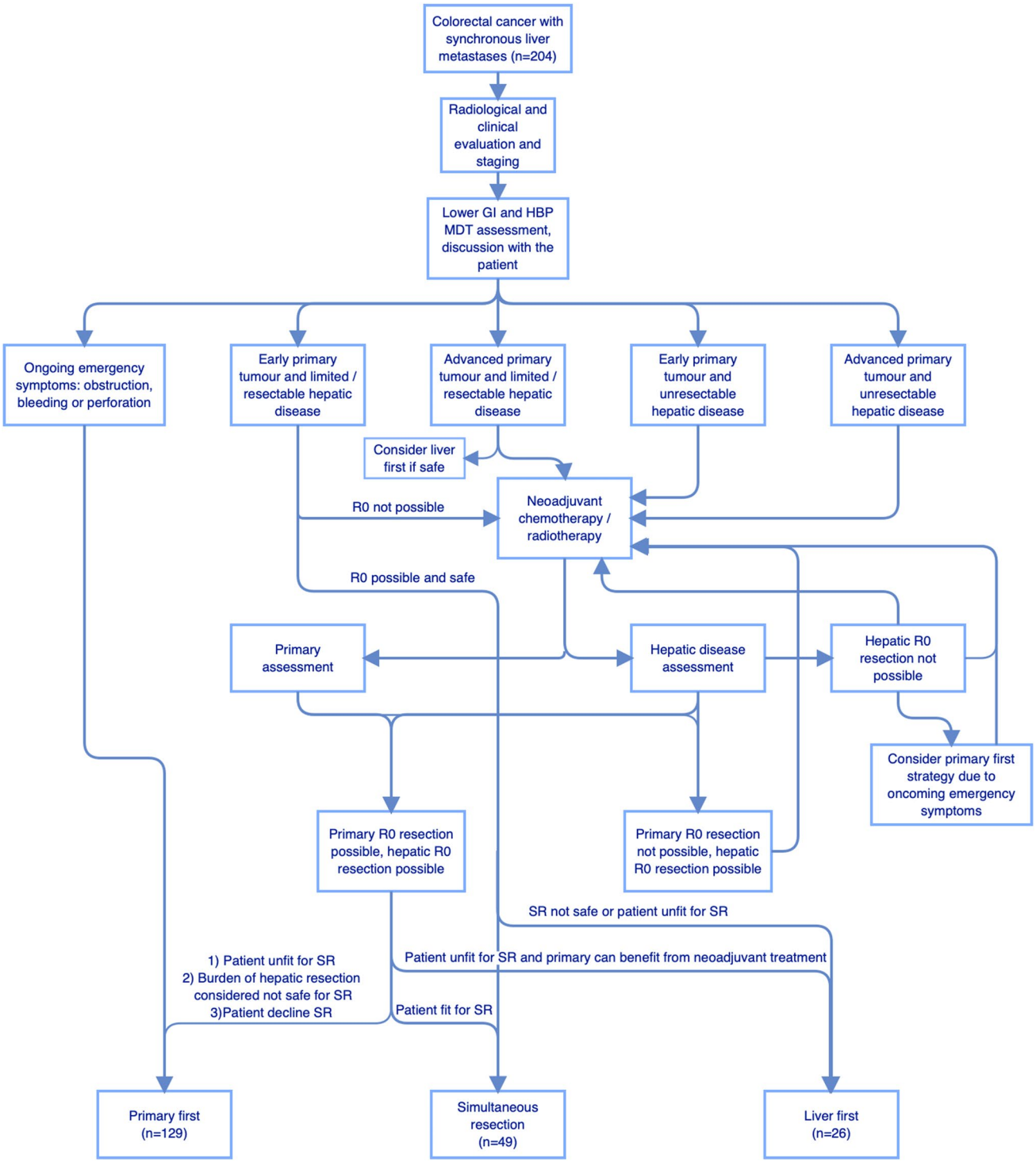

Fig. 1 Decision-making algorithm used by the MDT to select surgical treatment strategies for patients with colorectal cancer and synchronous liver metastases

Patients without a precise follow-up date were removed from the survival calculation. The Cox proportional hazard regression model was performed to pairwise quantify differences in the survival between the different approaches. A univariate analysis of preoperative factors possibly impacting survival was conducted to overcome the selection bias, followed

by a multivariate analysis of factors that resulted significant in the univariate analysis.

The OS was considered the time between the first surgery with curative intent and death. The DFS was considered the time from the date of the disease remission to the date of recurrence in any part of the body or death. The remission was achieved if the disease was radicalised from all the organs at any time of the treatment. OS and DFS were herein expressed as survival rate and standard error at the indicated time. A p-value ≤ 0.05 was considered significant.

Definitions and methods were further detailed in the supplementary material (*Supplementary material 1*).

Results

A total of 229 consecutive patients were identified, with 25 patients excluded according to the exclusion criteria and 204 included in the study, consisting of 129 patients who underwent PF (63.2%), 26 LF (12.8%) and 49 SR (24.0%).

Preoperative characteristics

In 45 patients (22.1%) the primary tumour was located in the rectum, which made up 50.0% of cases who underwent LF ($p < 0.001$). There was no difference between the groups in hepatic disease load in terms of the number of liver metastases ($p = 0.254$), the size of the biggest liver metastasis ($p = 0.411$), the number of segments involved by metastases ($p = 0.080$) and the liver metastases lobar distribution ($p = 0.430$) at the diagnosis. Difference was noticed in the CEA level, higher in the LF group (≥ 200 ng/ml in 38.1% of LF, $p = 0.009$). There were similar preoperative BMI ($p = 0.592$), performance status ($p = 0.488$) and blood test results ($p = 0.184$–0.478) in each group. However, 57.7% of LF patients had a higher ASA score of 3 compared with the other groups ($p = 0.015$).

A total of 34 patients (16.7%) had an extra-hepatic disease (EHD) at the time of the diagnosis, but it did not influence the choice of one strategy over the others ($p = 0.075$).

Preoperative neoadjuvant chemotherapy was given to 190 patients (93.6%, $p = 0.198$), using monoclonal agents in 112 patients ($p = 0.698$). Fourteen patients had a complete radiological response in the liver after the neoadjuvant treatment (7.4%) and 16 patients had progression of liver metastases (8.4%, $p = 0.505$) (Table 1).

Operative characteristics

One hundred and fifty-nine patients (77.9%) had both their primary and liver tumours resected. Among the patients who underwent the staged strategies, 34 patients underwent only the primary surgery (26.4% of PF) and 11 patients only the liver surgery (42.3% of LF, $p < 0.001$). The distribution of the procedures was not homogeneous: anterior resections were performed in a high percentage of LF (46.2%) and SR (61.2%), whilst right and extended right hemicolectomies were performed preferably in PF (30.2%, 9.3% respectively) and SR (20.5%, 10.3% respectively) approaches ($p < 0.001$).

Thirty-five patients (17.5%) were operated in an emergency setting using a PF approach (28.0% of PF) due to oncoming emergency symptoms (obstruction, bleeding, perforation).

The liver resection burden was comparable among the three groups. Among the patients who received a liver resection surgery, 104 patients had minor liver resections (61.5%), 65 patients had major liver resections (38.5%, $p = 0.212$) and one patient of the PF group did not receive any liver resection due to non-resectability of the liver disease. In the SR group, 17 patients underwent major liver resections (34.7%). There was no difference in the primary and liver access technique used (open, laparoscopic or robotic, $p = 0.172$ and $p = 0.505$, respectively). The distribution of patients that underwent percutaneous lung ablation ($p = 0.961$) and lung surgery ($p = 0.892$) was comparable between the three groups (Table 2).

Intraoperative and postoperative outcomes

Intraoperative adverse events occurred in 7 patients (3.5%): 5 in PF (3.9%), 1 in LF (4.2%) and 1 in SR group (2.0%), respectively ($p = 0.814$). These events consisted of four intraoperative bleedings, one bile leak, one anastomotic leak and one bowel perforation.

There was no significant difference in the amount of intraoperative blood loss and the number of red blood cell (RBC) transfusions when the three groups were compared ($p = 0.074$ and $p = 0.191$, respectively). The median cumulative overall operative time (OT) was 330 min (95% CI 275–390 min), with no significant difference among the groups (median of 310, 235 and 360 min respectively, $p = 0.362$). The median cumulative overall stay in the intensive care unit (ICU) was 2.0 days ($p = 0.914$) and the median cumulative length of hospital stay (LOS) was 14.0 days (PF 15.0 days, LF 13.0 days and SR 13.5 days respectively, $p = 0.627$). There was no statistical difference in OT, length of ICU stay and LOS when the three groups were compared.

The postoperative mortality rate was 2.5% ($n = 5$): 3 patients in PF (2.3%) and 2 in SR (4.1%) respectively ($p = 0.547$). The overall morbidity rate was 34.4%, including Clavien-Dindo grade 1–2 ($n = 45$, 22.1%) and grade 3–4 ($n = 25$, 12.3%). The severity of complications was equally distributed among the three surgical groups ($p = 0.409$), revealing no statistically significant difference in mortality and morbidity. There was also no difference in postoperative RBC transfusions ($p = 0.637$).

Table 1 Baseline and preoperative characteristics

	Total	Primary first	Liver first	Simultaneous resections	*p*-value
Baseline characteristics					
Total number of patients, No. (%)	204 (100)	129 (63.2)	26 (12.8)	49[a] (24.0)	–
Gender, No. (%), Male/Female	130/74 (63.7/36.3)	78/51 (60.5/39.5)	19/7 (73.1/26.9)	33/16 (67.3/32.7)	0.396
Age, median (95% CI), years	61 (57–63)	62 (59–65)	57 (54-65)	57 (50–64)	0.230
BMI, median (95% CI), Kg/cm^2	26 (25.2–26.8)	25.9 (24.8–27.2)	25.4 (22.7–27.5)	26.5 (24.8–27.7)	0.592
Preoperative characteristics					
Primary tumour site, No. (%)					
Right colon[b]	53 (26.0)	41 (31.8)	2 (7.7)	10 (20.4)	< 0.001
Left colon	20 (9.8)	10 (7.8)	5 (19.2)	5 (10.2)	
Sigmoid	86 (42.1)	57 (44.1)	6 (23.1)	23 (46.9)	
Rectum	45 (22.1)	21 (16.3)	13 (50.0)	11 (22.5)	
Number of liver metastases at the diagnosis, No. (%)					
1	59 (29.1)	43 (33.6)	2 (7.7)	14 (28.6)	0.254
2	34 (16.7)	19 (14.8)	5 (19.2)	10 (20.4)	
3	19 (9.4)	11 (8.6)	2 (7.7)	6 (12.2)	
4	27 (13.3)	16 (12.5)	4 (15.4)	7 (14.3)	
≥5	64 (31.5)	39 (30.5)	13 (50.0)	12 (24.5)	
Size of the biggest metastasis (cm), No. (%)					
< 2	51 (25.9)	34 (27.4)	3 (12.0)	14 (29.2)	0.411
2–5	108 (54.8)	69 (55.7)	16 (64.0)	23 (47.9)	
>5	38 (19.3)	21 (16.9)	6 (24.0)	11 (22.9)	
Number of liver segments involved by metastases, No. (%)					
1	50 (25.6)	39 (32.0)	1 (4.2)	10 (20.4)	0.080
2	50 (25.6)	29 (23.8)	7 (29.2)	14 (28.6)	
3	21 (10.8)	9 (7.4)	4 (16.7)	8 (16.3)	
4	22 (11.3)	16 (13.1)	2 (8.3)	4 (8.2)	
≥ 5	52 (26.7)	29 (23.7)	10 (41.6)	13 (26.5)	
Liver metastases lobar distribution, No. (%)					
Monolobar	98 (49.0)	65 (52.0)	10 (38.5)	23 (46.9)	0.430
Bilobar	102 (51.0)	60 (48.0)	16 (61.5)	26 (53.1)	
Extra-hepatic disease (EHD), No. (%)					
No EHD	170 (83.3)	103 (79.8)	21 (80.8)	46 (93.9)	0.075
EHD	34 (16.7)	26 (20.2)	5 (19.2)	3 (6.1)	
CEA (ng/ml), No. (%)					
< 200	154 (84.6)	100 (87.0)	13 (61.9)	41 (89.1)	0.009
≥ 200	28 (15.4)	15 (13.0)	8 (38.1)	5 (10.9)	
CA19.9 (U/ml), No. (%)					
< 37	82 (58.6)	49 (56.3)	8 (44.4)	25 (71.4)	0.132
≥ 37	58 (41.4)	38 (43.7)	10 (55.6)	10 (28.6)	
Preoperative percutaneous liver ablation (pre-PLA), No. (%)					
No pre-PLA	182 (89.6)	112 (87.5)	25 (96.2)	45 (91.8)	0.697
1 pre-PLA	16 (7.9)	12 (9.4)	1 (3.8)	3 (6.1)	
>1 pre-PLA	5 (2.5)	4 (3.1)	0 (0)	1 (2.1)	
Neoadjuvant chemotherapy (nCT), No. (%)					
No nCT	13 (6.4)	11 (8.6)	0 (0)	2 (4.1)	0.198
nCT	190 (93.6)	117 (91.4)	26 (100)	47 (95.9)	

The primary local histopathological stage ($p = 0.001$) and grade ($p = 0.007$) were different between groups, with a greater distribution on the highest values. There were no differences in nodal involvement ($p = 0.075$), vascular deposits ($p = 0.092$) and radicality of the resection (0.449) of the primary tumour. The RAS mutated ratio was 36.5%

Table 1 (continued)

	Total	Primary first	Liver first	Simultaneous resections	*p*-value
Metastatic radiological response, No. (%)					
Complete	14 (7.4)	10 (8.5)	1 (3.8)	3 (6.4)	0.505
Partial	153 (80.5)	89 (76.1)	24 (92.4)	40 (85.0)	
Stable	7 (3.7)	5 (4.3)	0 (0)	2 (4.3)	
Progression	16 (8.4)	13 (11.1)	1 (3.8)	2 (4.3)	
ASA score, No. (%)					
1	7 (3.6)	3 (2.5)	2 (7.7)	2 (4.3)	0.015
2	124 (63.9)	81 (66.9)	9 (34.6)	34 (72.3)	
3	63 (32.5)	37 (30.6)	15 (57.7)	11 (23.4)	
Performance status, No. (%)					
0	56 (29.8)	30 (26.1)	6 (24.0)	20 (41.7)	0.488
1	121 (64.4)	78 (67.8)	18 (72.0)	25 (52.0)	
2	10 (5.3)	6 (5.2)	1 (4.0)	3 (6.3)	
3	1 (0.5)	1 (0.9)	0 (0)	0 (0)	
Preoperative blood test result, median, (95% CI)					
Hg (g/dl)	12.6 (12.2–13.0)	12.5 (12.1–13.0)	11.9 (11.1–13.2)	13.0 (12.2–13.3)	0.410
Bilirubin (umol/l)	12.0 (11.0–13.0)	12.0 (11.0–13.0)	11.0 (9.0–15.0)	12.0 (11.0–13.0)	0.478
Albumin (g/l)	38.0 (38.0–39.0)	38.0 (37.0–39.0)	38.0 (35.0–40.0)	39.0 (37.0–41.0)	0.184
INR	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.310

[a]One patient of the simultaneous resection group underwent the primary surgery associated with one of the two stages of the two-stage hepatectomy

[b]Two patients with primary right colon cancer had a synchronous sigmoid colon cancer

within the cohort. The percentage of wild-type RAS patients was higher in the SR group (80%) compared to PF and LF (57.4% and 63.2% respectively, $p=0.040$). In terms of liver histopathology, there was no difference in the number of liver metastases ($p=0.499$), size of the biggest metastasis ($p=0.419$), and radicality of the resection between the strategies ($p=0.580$). There was no difference between the groups in adjuvant chemotherapy administration ($p=0.563$) (Table 3).

Survival analysis

The overall median follow-up time was 29 months. The total 1-year, 3-year and 5-year OS was 91%, 70%, 54%, respectively. The 1-year OS was 94% in PF, 74% in LF and 91% in SR, the 3-year OS was 72% in PF, 54% in LF and 74% in SR, and the 5-year OS rates were 53% in PF, 36% in LF and 63% in SR respectively. When groups were pairwise compared, there was a significant difference in OS between PF and LF groups at the log-rank test ($p=0.040$). Because the three survival Kaplan–Meier curves intersected quite early in the graph (Fig. 2a), showing a change in trending, the Tarone-Ware test was performed to pairwise compare the groups [9]. According to the aforementioned test, a difference in OS was found even between LF and SR groups ($p=0.047$).

The LF versus PF group OS-hazard ratio (HR) was 2.033 (95% CI 1.017–4.064, $p=0.045$). This was statistically significant, indicating a worse survival outcome in patients undergoing the LF approach of about two times compared with the PF approach. The LF versus SR group OS-HR was 2.276 (95% CI 0.972–5.327, $p=0.058$) and the PF versus SR group OS-HR was 1.290 (95% CI 0.693–2.400, $p=0.421$). The Cox regression analysis showed a better OS outcome of the SR group, followed by the PF and LF groups, respectively (Fig. 2b).

The total 1-year, 3-year and 5-year DFS rates were 33%, 17% and 14%, respectively. The 1-year DFS rates were 31% in the PF, 21% in the LF and 45% in the SR. The 3-year DFS rates were 15%, 9%, 28% and the 5-year DFS rates were 10%, 9%, 28%, respectively, for PF, LF and SR groups. The pairwise log-rank tests were significant for SR versus both PF and LF ($p=0.005$, $p=0.008$). The LF versus SR group DFS-HR was 1.993 (95% CI 1.133–3.505, $p=0.017$), and the PF versus SR group DFS-HR was 1.660 (95% CI 1.118–2.465, $p=0.012$). This suggests that the DFS was significantly better in the SR group, followed by the PF and LF groups (Fig. 2c, d, Table S5 in the *Supplementary material 2*).

The survival analysis was carried out also for the subgroups of patients without EHD at the diagnosis and who underwent non-emergency procedures. The outcomes were

Table 2 Operative characteristics

	Total	Primary first	Liver First	Simultaneous resections	*p*-value
Not completed surgeries, No. (%)					
Primary and liver surgeries	159 (77.9)	95 (73.6)	15 (57.7)	49 (100)	< 0.001
Only primary surgery	34 (16.7)	34 (26.4)	0 (0)	0 (0)	
Only liver surgery	11 (5.4)	0 (0)	11 (42.3)[a]	0 (0)	
Primary surgery, No. (%)					
No primary surgery[a]	11 (5.4)	0 (0)	11 (42.3)	0 (0)	< 0.001
Right hemicolectomy	50 (24.5)	39 (30.2)	1 (3.8)	10 (20.5)	
Extended right hemicolectomy/ subtotal colectomy	19 (9.3)	12 (9.3)	2 (7.7)	5 (10.3)	
Left hemicolectomy	7 (3.4)	6 (4.6)	0 (0)	1 (2.0)	
Sigmoid resection	11 (5.4)	10 (7.8)	0 (0)	1 (2.0)	
Anterior resection	84 (41.2)	42 (32.6)	12 (46.2)	30 (61.2)	
Hartmann procedure	16 (7.8)	15 (11.6)	0 (0)	1 (2.0)	
Beyond TME surgery (bTME)[b]	6 (3.0)	5 (3.9)	0 (0)	1 (2.0)	
Elective/emergency procedures, No. (%)					
Elective	165 (82.5)	90 (72.0)	26 (100)	49 (100)	< 0.001
Emergency	35 (17.5)	35 (28.0)	0 (0)	0 (0)	
Liver surgery[c], No. (%)					
No liver surgery	34 (16.7)	34 (26.4)	0 (0)	0 (0)	< 0.001
Left hepatectomy	10 (4.9)	5 (3.9)	0 (0)	5 (10.2)	
Right hepatectomy	34 (16.6)	20 (15.5)	9 (34.6)	5 (10.2)	
Central hepatectomy	1 (0.5)	0 (0)	1 (3.8)	0 (0)	
Two-stage hepatectomy	4 (2.0)	2 (1.5)	1 (3.8)	1 (2.0)	
Extended left hepatectomy	2 (1.0)	1 (0.8)	0 (0)	1 (2.0)	
Extended right hepatectomy	8 (3.9)	3 (2.3)	2 (7.7)	3 (6.1)	
Left lateral sectionectomy	9 (4.4)	4 (3.1)	2 (7.7)	3 (6.1)	
Right lateral sectionectomy	2 (1.0)	2 (1.5)	0 (0)	0 (0)	
Segmentectomy	52 (25.5)	33 (25.6)	3 (11.6)	16 (32.7)	
Wedge/atypical resection	47 (23.0)	24 (18.6)	8 (30.8)	15 (30.7)	
Unresectable	1 (0.5)	1 (0.8)	0 (0)	0 (0)	
Liver resection burden[d], No. (%)					
Minor (< 3 segments)	104 (61.5)	60 (63.8)	12 (46.2)	32 (65.3)	0.212
Major (≥ 3 segments)	65 (38.5)	34 (36.2)	14 (53.8)	17 (34.7)	
Intraoperative radiofrequency ablation (iRFA), No. (%)					
No iRFA	163 (97.0)	89 (95.7)	25 (96.2)	49 (100)	0.344
iRFA	5 (3.0)	4 (4.3)	1 (3.8)	0 (0)	
Primary surgery technique					
Open	157 (87.2)	99 (84.6)	14 (100)	44 (89.8)	0.172
Laparoscopic	22 (12.2)	18 (15.4)	0 (0)	4 (8.2)	
Robotic	1 (0.6)	0 (0)	0 (0)	1 (2.0)	
Liver surgery technique					
Open	158 (92.9)	86 (90.5)	26 (100)	46 (93.9)	0.505
Laparoscopic	6 (3.5)	4 (4.2)	0 (0)	2 (4.1)	
Robotic	6 (3.5)	5 (5.3)	0 (0)	1 (2.0)	

[a]One unresectable primary

[b]One patient had a right hemicolectomy in addition to the bTME

[c]Additional liver procedures:

In one left hepatectomy (LHE), one segment resection was also performed; in one LHE, one wedge resection was performed; both the procedures were in the SR group.

In three right hepatectomies, one wedge resection was performed; two of these were in the PF group and one in the SR group.

Table 2 (continued)

In one extended left hepatectomy of the SR group, one wedge resection was also performed.

In one extended right hepatectomy of the LF group, one wedge resection was also performed.

In four left lateral sectionectomies, at least one wedge resection was performed; one of these was in the PF, one in the SR and two in the LF group.

In one right lateral sectionectomy of the PF group, one wedge resection was performed.

In sixteen segment resections, at least one (1–6) wedge resection was also performed; of these, ten were in the PF, one in the LF and five in the SR group.

One liver lesion in the PF group was unresectable; it was considered in the total calculation.

In the central hepatectomy procedure, one wedge resection was also performed.

[d]Within patients that underwent liver surgery

comparable: the LF group resulted in a worse OS and the SR in a better DFS compared to the other groups, respectively (Tables S6–S9 in the *Supplementary material 2*).

Univariate survival analysis was performed on possibly impacting preoperative factors. In our series, the factors impacting significantly both the OS and DFS were the surgical strategy, the number of liver metastases, the size of the largest metastasis, the number of liver segments involved in the metastases and the CEA level. The multivariate analysis was calculated including these factors in the model. It showed that there was no significant difference between the three surgical strategies in terms of OS (PF vs SR OS-HR 1.090, 95% CI 0.544–2.186, $p = 0.808$; LF vs SR OS-HR 1.582, 95% CI 0.586–4.268, $p = 0.365$). Instead, the PF approach was found to have significantly worse DFS compared with the SR approach at the multivariate analysis (PF vs SR DFS-HR 1.803, 95% CI 1.172–2.774, $p = 0.007$; LF vs SR DFS-HR 1.252, 95% CI 0.660–2.375, $p = 0.492$) (Table 4).

Discussion

The treatment of CRC with SCRLM has always been challenging for the MDT and, even today, it is not clear the best surgical resection sequence for patients with resectable disease [3, 6]. The inclusion criteria and protocol of this study allow having practical results, as all patients with a surgical decision were considered, even those who did not undergo the second surgery in the sequential approaches. In the current literature, there are studies that compare the sequential with the simultaneous strategy [10–18], and one primary study comparing the PF, LF and SR approaches [19]. Even due to a lack of effective stratifying and prognostic factors [20, 21], randomised controlled trials are difficult to be performed to date. This is a single-tertiary centre study that aims to provide the MDT with effective previsions on patients with CRC and SCRLM and an indication for curative surgery. The biases of the study are related to its retrospective nature: selection bias due to the surgical indications eventually forced by the neoadjuvant treatment response and the stage of the disease at the time of the first surgery. In our series, the primary site seems to have influenced the surgical strategy adopted: 50% of LF strategies were used for rectal cancers and only 7.7% for right colon cancers ($p = 0.001$). This could be explained by the fact that the LF approach allows the removal of metastases while rectal cancer is controlled by neoadjuvant therapy [22]. Another limitation of this study is the small number of patients undergoing the LF strategy. This is due to the fact that the LF approach is recent, and the PF approach is still the most used by the MDT.

Moreover, the data analysis from this study was made difficult by the heterogeneity of the data collected. Some patients treated with a staged approach received their first surgery at another hospital and were referred to our tertiary centre only afterwards. This has led to a lack of some intraoperative and short-term postoperative data and possibly an underestimation of postoperative events in patients undergoing the staged approaches.

The choice of adopting the PF approach, often called the conventional approach, is sometimes conditioned by the state of emergency resulting from the colorectal lesion, and sometimes preferred as it allows to evaluate the response of the CRLM to neoadjuvant chemotherapy to select the patients who could benefit from liver surgery [3, 23]. In our series, 35 patients (17.5%) underwent a PF approach due to oncoming emergency symptoms. For these reasons, the PF represents the largest group in this study. Since the SR approach was demonstrated safe [24, 25], even with a large burden of hepatic resections in some retrospective studies [11, 13, 26], it has been increasingly considered for the resectable disease over the past few years in high-volume institutions. However, if the SR is safe is still unclear, as recent retrospective studies showed the SR having higher postoperative mortality (6% vs 1%) [12] and morbidity rates (52% vs 36%) [13–15] compared to the staged approach, even when a lower burden of liver resection was performed in the SR group. Recently, the first randomised controlled trial comparing the SR with the delayed resection of the SCRLM was published (METASYNC study): the complication rate was equal in both groups (28% vs 13% of colorectal

Table 3 Intraoperative and postoperative outcomes

	Total	Primary first	Liver first	Simultaneous resections	*p*-value
Intraoperative outcomes					
Intraoperative blood loss (ml), No. (%)					
< 500	21 (16.4)	14 (20.0)	2 (12.5)	5 (11.9)	0.074
500–1000	54 (42.2)	24 (34.3)	5 (31.2)	25 (59.5)	
> 1000	53 (41.4)	32 (45.7)	9 (56.3)	12 (28.6)	
Intraoperative blood transfusions (red cells units), No. (%)					
No transfusions	145 (75.9)	96 (79.3)	15 (62.5)	34 (73.9)	0.191
≤ 2	34 (17.8)	20 (16.6)	5 (20.8)	9 (19.6)	
> 2	12 (6.3)	5 (4.1)	4 (16.7)	3 (6.5)	
Intraoperative adverse events, No. (%)					
No adverse events	193 (96.5)	122 (96.1)	23 (95.8)	48 (98.0)	0.814
Adverse events	7 (3.5)	5 (3.9)	1 (4.2)	1 (2.0)	
Duration of surgery, median (95% CI), min	330 (275–390)	310 (190–445)	235 (90–770)	360 (320–405)	0.362
Postoperative outcomes					
Length of ICU stay, median (95% CI), days	2.0 (2.0–2.0)	2.0 (2.0–3.0)	2.0 (1.0–6.0)	2.0 (2.0–3.0)	0.914
Length of hospital stay, median (95% CI), days	14.0 (13.0–15.0)	15.0 (13.0–16.0)	13.0 (9.0–26.0)	13.5 (12.0–16.0)	0.627
In-hospital/30-days mortality and morbidity, No. (%)					
Mortality	5 (2.5)	3 (2.3)	0 (0)	2 (4.1)	0.547
Clavien-Dindo grade 1–2 complications	45 (22.1)	25 (19.4)	5 (19.2)	15 (30.6)	0.409
Clavien-Dindo grade 3–4 complications	25 (12.3)	15 (11.6)	5 (19.2)	5 (10.2)	
Postoperative blood transfusions, No. (%)					
No transfusion	171 (89.1)	109 (90.1)	21 (91.3)	41 (85.4)	0.637
Transfusions	21 (10.9)	12 (9.9)	2 (8.7)	7 (14.6)	
Primary histopathology report (AJCC 8th edition), No. (%)					
pT0	3 (1.7)	0 (0)	1 (6.7)	2 (4.2)	0.001
pT1	4 (2.2)	1 (0.8)	1 (6.7)	2 (4.2)	
pT2	10 (5.5)	4 (3.4)	1 (6.7)	5 (10.4)	
pT3	110 (60.8)	65 (55.1)	11 (73.3)	34 (70.8)	
pT4	54 (29.8)	48 (40.7)	1 (6.7)	5 (10.4)	
pN0	46 (25.4)	26 (22.2)	7 (46.7)	13 (26.5)	0.075
pN1	86 (47.5)	53 (45.3)	5 (33.3)	28 (57.2)	
pN2	49 (27.1)	38 (32.5)	3 (20)	8 (16.3)	
pEMVI −	50 (30.3)	25 (24.3)	6 (42.9)	19 (39.6)	0.092
pEMVI +	115 (69.7)	78 (75.7)	8 (57.1)	29 (60.4)	
Grade 1	2 (1.1)	0 (0)	0 (0)	2 (4.1)	0.007
Grade 2	146 (84)	89 (80.9)	11 (73.3)	46 (93.9)	
Grade 3	26 (14.9)	21 (19.1)	4 (26.7)	1 (2)	
R0 resection	164 (91.6)	105 (91.3)	15 (100)	44 (89.8)	0.449
R1 resection	15 (8.4)	10 (8.7)	0 (0)	5 (10.2)	
RAS wild type	106 (63.5)	62 (57.4)	12 (63.2)	32 (80.0)	0.040
RAS mutated	61 (36.5)	46 (42.6)	7 (36.8)	8 (20.0)	
Liver histopathology report, No. (%)					
No residual tumour	7 (4.2)	4 (4.2)	0 (0)	3 (6.2)	0.499
1 metastasis	64 (38.3)	37 (39.4)	6 (24.0)	21 (43.8)	
2 metastases	38 (22.7)	22 (23.4)	8 (32.0)	8 (16.7)	
3 metastases	24 (14.4)	15 (16.0)	4 (16.0)	5 (10.4)	
4 metastases	15 (9.0)	9 (9.6)	3 (12.0)	3 (6.2)	
≥ 5 metastases	19 (11.4)	7 (7.4)	4 (16.0)	8 (16.7)	

Table 3 (continued)

	Total	Primary first	Liver first	Simultaneous resections	*p*-value
Liver metastatic size < 2 cm	50 (32.1)	27 (30.0)	6 (24.0)	17 (41.5)	0.419
Liver metastatic size 2–5 cm	86 (55.1)	51 (56.7)	14 (56.0)	21 (51.2)	
Liver metastatic size > 5 cm	20 (12.8)	12 (13.3)	5 (20.0)	3 (7.3)	
R0 resection	134 (81.2)	75 (81.5)	18 (72.0)	41 (85.4)	0.580
R1 resection	28 (17.0)	15 (16.3)	6 (24.0)	7 (14.6)	
R2 resection	3 (1.8)	2 (2.2)	1 (4)	0 (0)	
Adjuvant chemotherapy (aCT), No. (%)					
No aCT	31 (16.5)	19 (16.2)	6 (23.1)	6 (13.3)	0.563
aCT	157 (83.5)	98 (83.8)	20 (76.9)	39 (86.7)	

complications, 15% vs 17% of liver complications, respectively), with a worse OS in the delayed resection group [18]. Another recent study by Giuliante et al. showed that the three strategies had comparable mortality and morbidity rates, with comparable survival outcomes in patients with solitary and unilobar SCRLM, while the LF approach was associated with a survival advantage in patients with multiple bilobar metastases [19]. In our study, the mortality rates for the PF, LF and SR were 2.3%, 0% and 4.1%, respectively, with no statistical difference between them ($p=0.547$) and with no difference in the liver burden resected ($p=0.212$). According to some recent studies [11, 12], the overall morbidity rates were comparable between the three approaches PF, LF and SR: 31.0%, 38.4% and 40.8%, respectively ($p=0.409$). Even if the SR was the group with the highest ratio of complications, it was the group with fewer major ones, as the Clavien-Dindo 3–4 grade complication rates were 11.6%, 19.2% and 10.2%, respectively.

A network metanalysis of thirty-two retrospective studies comparing the three surgical approaches [27] concluded that there were no differences in terms of morbidity and long-term survival outcomes: the LF approach ranked first in the relative ranking based on 5-year OS outcomes and postoperative complication rate, PF was the second and SR the third one. A recent retrospective study of She et al. [28] showed a worse OS for patients undergoing SR with an equal burden of liver resection compared to the staged approach (75.0% vs 90.7% of 1-year OS, $p=0.003$). However, the cohort included was quite dated, therefore difficult to compare with the current means and technologies of care. Also, in the population-based cohort study by Bogach et al. [12] the SR approach was found to have poorer survival outcomes compared with the staged resection approach (median OS of 40 vs 78 months), but the SR group received less chemotherapy than the staged resection group. All retrospective studies comparing staged and simultaneous approaches have selection bias due to two main factors: first, the MDT choice of adopting one strategy is given by the disease stage and setting; second, the inclusion of patients undergone both primary and liver surgeries in the staged resection group. This can lead to a confusing interpretation of the results because the MDT is not able to determine if patients undergoing the staged strategies will complete the second surgery in the future. The indication for curative surgery should be considered the starting point for evaluating the resection strategies. To the best of our knowledge, this is one of the largest single-centre series comparing PF, LF and SR strategies in patients with CRC and SCRLM, and the only one considering as inclusion criteria the indication for a curative approach independently from the completion of the staged strategies. Indeed, it is noticeable that in our cohort, 77.9% of all patients with an indication for surgery completed both the resections on the primary and CRLM, with 22.1% of them not being able to complete it (26.4% of PF and 42.3% of LF, $p<0.001$). Certainly, these percentages do not consider patients who have received a PF or LF approach in another hospital and have not undergone the second surgery. However, these rates should be considered by the MDT in deciding on staged resection strategies.

In our analysis, the OS of the LF approach was significantly worse compared to the other approaches (HR 2.033 vs PF, HR 2.276 vs SR). The SR group achieved the best long-term OS, even if it was not demonstrated to be better than PF (5-year OS: PF 53%, LF 36%, SR 63%). The SR group was found to have a significantly better DFS, followed by the PF and LF. However, at the multivariate analysis there was no difference in OS between the three strategies and the SR had better DFS compared with the PF approach (Table 4). These findings contrast with the study of de Haas et al. [10], which

Table 4 Univariate and multivariate overall survival and disease-free survival analysis using the Cox proportional hazard model

	Overall survival						Disease-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Surgical strategy												
PF	1.289	0.693–2.397	0.423	1.090	0.544–2.186	0.808	1.671	1.126–2.481	0.011	1.803	1.172–2.774	0.007
LF	2.566	1.114–5.912	0.027	1.582	0.586–4.268	0.365	1.921	1.105–3.339	0.021	1.252	0.660–2.375	0.492
SR	1.000		0.072	1.000		0.639	1.000		0.021	1.000		0.023
Age	0.991	0.971–1.011	0.379				0.998	0.985–1.011	0.734			
Gender												
Male	0.827	0.510–1.341	0.441				1.247	0.897–1.733	0.189			
ASA score												
1	1.000		0.071				1.000		0.692			
2	1.641	0.392–6.869	0.498				1.469	0.597–3.615	0.403			
3	2.828	0.660–12.115	0.161				1.490	0.592–3.747	0.397			
Primary tumour site												
Right colon	1.140	0.753–1.725	0.536				0.958	0.722–1.271	0.764			
Left colon	1.448	0.850–2.467	0.173				0.991	0.655–1.497	0.964			
Sigmoid	1.000		0.305				1.000		0.889			
Rectum	0.746	0.469–1.187	0.216				1.109	0.828–1.485	0.487			
No. liver metastases												
1	1.000		0.023	1.000		0.095	1.000		0.001	1.000		0.137
2	1.208	0.542–2.694	0.644	1.250	0.391–3.995	0.707	0.970	0.581–1.621	0.908	0.858	0.398–1.851	0.697
3	0.667	0.226–1.973	0.464	1.158	0.186–7.196	0.875	0.794	0.419–1.504	0.479	0.714	0.256–1.991	0.520
4	2.140	1.002–4.569	0.049	6.384	1.203–33.864	0.029	1.664	0.998–2.774	0.051	1.968	0.723–5.362	0.185
≥5	2.334	1.247–4.368	0.008	4.979	1.061–23.377	0.042	2.048	1.361–3.082	0.001	1.970	0.745–5.210	0.172
Size of the biggest metastases (cm)												
< 2	1.000		0.004	1.000		0.033	1.000		0.024	1.000		0.188
2–5	2.056	1.046–4.041	0.037	1.621	0.731–3.595	0.234	1.343	0.907–1.988	0.141	1.007	0.629–1.612	0.976
≥ 5	3.670	1.704–7.902	0.001	3.267	1.294–8.248	0.012	1.967	1.210–3.200	0.006	1.587	0.853–2.953	0.145
No. of liver segments involved by metastases												
1	1.000		0.080	1.000		0.189	1.000		< 0.001	1.000		0.544
2	1.377	0.677–2.799	0.377	1.006	0.348–2.908	0.991	1.139	0.717–1.809	0.582	1.297	0.617–2.727	0.492
3	1.408	0.571–3.471	0.458	0.395	0.069–2.257	0.296	1.085	0.594–1.983	0.790	0.956	0.326–2.803	0.935
4	1.068	0.411–2.777	0.892	0.119	0.018–0.798	0.028	1.166	0.638–2.132	0.618	0.726	0.240–2.196	0.570
≥ 5	2.523	1.269–5.020	0.008	0.363	0.070–1.867	0.225	2.502	1.602–3.907	<0.001	1.191	0.416–3.407	0.745
CEA (ng/ml)												
≥ 200	2.239	1.208–4.149	0.010	1.264	0.622–2.569	0.518	1.832	1.184–2.834	0.007	1.120	0.667–1.881	0.669

Table 4 (continued)

	Overall survival						Disease-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Liver resection burden												
Major (≥ 3 segments)	1.190	0.687–2.060	0.535				1.138	0.796–1.628	0.479			

concluded that the SR has a negative impact on progression-free survival.

In the subgroups of patients with no EHD at the diagnosis and that did not undergo emergency procedures, the results were comparable with the previous ones: the LF approach had the worst OS outcome, and the SR approach had the best DFS outcome.

In relation to the cumulative OT, length of ICU stay and LOS, no significant differences were found between the three surgical approaches in this study. These results contrast with other retrospective series, in which they were found to be lower in the SR group compared with the staged strategy [11–14, 17, 24, 28]. This can be explained with the inclusion in our study of patients that started the treatment pathway in one of the staged strategies and did not undergo the second surgery, therefore lowering the cumulative OT, length of ICU stay and LOS in the staged approaches. These findings provide a more realistic figure on the probability of OT and LOS that patients would have at the beginning of each surgical treatment. Indeed, these variables could represent confounding factors in the choice of the best strategy to adopt.

However, the findings of this study should be taken with caution because of several variables playing a role in the comparison of the three approaches. Factors that would lead the choice between the strategies are still to be identified, and they could be necessary for designing randomised controlled trials.

Conclusions

According to this single-tertiary centre retrospective cohort study, the three surgical strategies PF, LF and SR for the treatment of patients with CRC and SCRLM were safe, with comparable mortality and morbidity rates.

The three surgical approaches had comparable OS outcomes. The PF strategy was associated with worse DFS than SR, while the LF approach was associated with a high failure rate to progress to the second stage (primary tumour resection). Assessing the best surgical approach to patients with primary tumour and simultaneous hepatic metastases remains challenging because many variables play a role. In future, randomised controlled trials should aim to clarify it.

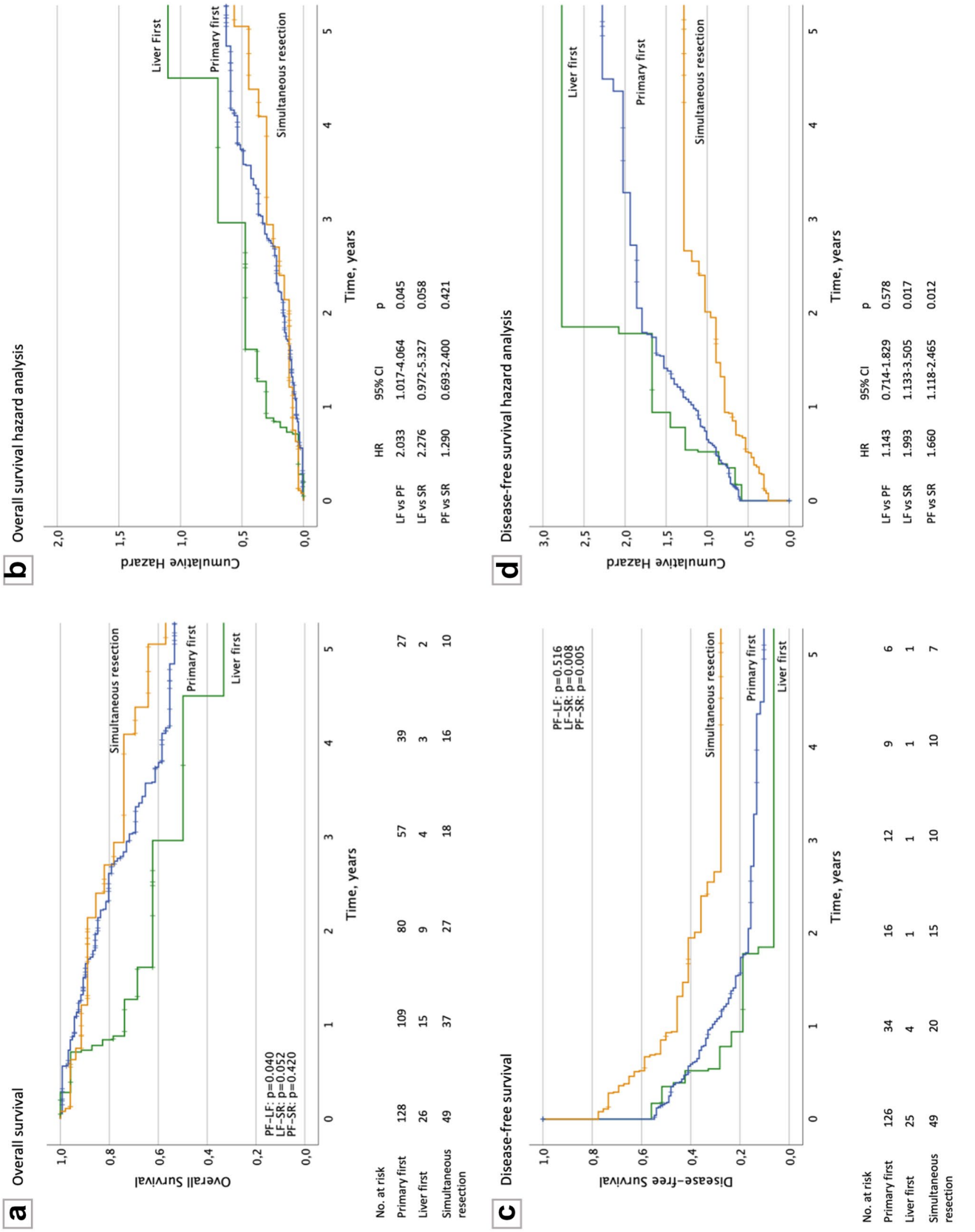

Fig. 2 Kaplan–Meier and Cox regression analysis for overall survival and disease-free survival. **a** Overall survival. **b** Overall survival hazard. **c** Disease-free Survival. **d** Disease-free survival hazard. PF: primary first; LF: liver first; SR: simultaneous resection

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Declarations

Conflicts of interest The authors do not have any conflict of interest.

Ethical approval This research was conducted following good ethical and scientific principles. Ethical committee approval was not required.

Research involving human participants and/or animals This study was performed according to the Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not required for this type of study.

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