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Simultaneous resection of colorectal cancer and synchronous liver metastases: what determines the risk of unfavorable outcomes? An international multicenter retrospective cohort study

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Background: The use of a simultaneous resection (SIMR) in patients with synchronous colorectal liver metastases (sCRLM) has increased over the past decades. However, it remains unclear when a SIMR is beneficial and when it should be avoided. The aim of this retrospective cohort study was therefore to compare the outcomes of a SIMR for sCRLM in different settings, and to assess which factors are independently associated with unfavorable outcomes.

Methods: To perform this retrospective cohort study, patients with sCRLM undergoing SIMR (2004–2019) were extracted from an international multicenter database, and their outcomes were compared after stratification according to the type of liver and colorectal resection performed. Factors associated with unfavorable outcomes were identified through multivariable logistic regression.

Results: Overall, 766 patients were included, encompassing colorectal resections combined with a major liver resection ($n = 122$), minor liver resection in the anterolateral ($n = 407$), or posterosuperior segments ('Technically major', $n = 237$). Minor and technically major resections, compared to major resections, were more often combined with a rectal resection (29.2 and 36.7 vs. 20.5%, respectively, both $P = 0.003$) and performed fully laparoscopic (22.9 and 23.2 vs. 6.6%, respectively, both $P = 0.003$). Major and technically major resections, compared to minor resections, were more often associated with intraoperative transfusions (42.9 and 38.8 vs. 20%, respectively, both $P = 0.003$) and unfavorable incidents (9.6 and 9.8 vs. 3.3%, respectively, both $P \leq 0.063$). Major resections were associated, compared to minor and technically major resections, with a higher overall morbidity rate (64.8 vs. 50.4

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and 49.4%, respectively, both $P \leq 0.024$) and a longer length of stay (12 vs. 10 days, both $P \leq 0.042$). American Society of Anesthesiologists grades ≥ 3 [adjusted odds ratio (aOR): 1.671, $P = 0.015$] and undergoing a major liver resection (aOR: 1.788, $P = 0.047$) were independently associated with an increased risk of severe morbidity, while undergoing a left-sided colectomy was associated with a decreased risk (aOR: 0.574, $P = 0.013$).

Conclusions: SIMR should primarily be reserved for sCRLM patients in whom a minor or technically major liver resection would suffice and those requiring a left-sided colectomy. These findings should be confirmed by randomized studies comparing SIMR with staged resections.

Keywords: colorectal cancer, postoperative outcomes, simultaneous resection, synchronous colorectal liver metastases

Colorectal cancer (CRC) causes a substantial disease-burden, ranking third in incidence and second in terms of cancer-related death worldwide[1]. Around 13.5% of the patients with CRC are already affected by metastatic disease at the time of diagnosis, often limited to the liver[2,3]. In these patients with isolated synchronous colorectal liver metastases (sCRLM), multidisciplinary treatment including surgical resection improves long-term survival rates[4].

Patients with resectable CRC and sCRLM have traditionally been managed with the 'classical' two-staged approach, whereby the CRC is resected during the first stage and the sCRLM during the second stage[5]. More recently, the 'reverse' two-staged approach, with sCRLM resected first, and a simultaneous resection (SIMR) of both the CRC and sCRLM have been advocated[6,7]. Whilst there are theoretical advantages of each strategy, studies have so far shown conflicting results[5–9]. Therefore, the optimal resection timing remains a matter of debate[9].

Nevertheless, SIMRs have gained traction in recent years[10,11]. This is possibly due to improvements in surgical technique and perioperative care paralleled by the publication of comparative studies showing favorable results of the simultaneous approach, in terms of a shorter length of stay, lower costs and noninferior morbidity, mortality, and survival rates, compared to the two-staged approaches[7–9,12,13]. While one-step surgery is appealing, stringent patient selection seems to be of vital importance. Several studies have associated SIMRs performed in frail patients or in patients undergoing more extensive or challenging resections with an increased risk of morbidity and mortality[10,14–16]. However, these studies often had a relatively small sample size and lacked granularity regarding the patient, disease or procedural characteristics.

Therefore, the aim of this retrospective international multicenter study is to assess the characteristics and outcomes of patients undergoing SIMRs according to the type of resection performed, and to assess preoperative risk factors of unfavorable perioperative outcomes.

HIGHLIGHTS

- Simultaneous resections are increasingly utilized in patients with synchronous colorectal liver metastases.
- The feasibility of simultaneous resections mainly seems to depend on the type of colorectal and liver resection performed.
- Anatomically and technically major liver resections were independently associated with a higher risk of unfavorable outcomes while, conversely, left-sided colectomies were associated with a lower risk.

METHODS

This is a retrospective analysis of a multicenter database composed of the prospectively maintained databases of 17 hepatobiliary referral centers[17]. Adults who underwent an elective minimally invasive or open SIMR of their CRC and sCRLM between January 2004 and December 2019 were included, following the exclusion of patients who underwent (partially) robotic-assisted or thoracoscopic procedures, the first stage of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), or major concurrent procedures (e.g. biliary or vascular reconstructions, pancreatic, gastric, splenic, or diaphragmatic resections). Patients were stratified into three groups according to the type of liver resection that was combined with a colorectal resection, the three groups being simultaneous major liver resections, minor liver resections in the anterolateral (Segment 2, 3, 4b, 5, and 6) or posterosuperior segments (Segment 1, 4a, 7, 8; 'Technically major'). The term technically major was introduced for laparoscopic liver resections, but for the sake of consistency it was also used for open liver resections in this study[18,19]. Thereafter, patients in these three groups were subclassified according to the type of colorectal resection performed, in patients undergoing right-sided colectomies, left-sided colectomies and rectal resections (Fig. 1 for the study flowchart) The Strengthening the Reporting of Cohort Studies in Surgery (STROCSS, Supplemental Digital Content 2, http://links.lww.com/JS9/A27) guidelines were followed to write this report[20].

Definitions

Right-sided colectomies consisted of right and extended right hemicolectomies, while left-sided colectomies included left, extended left hemicolectomies and sigmoid colectomies. Rectal resections included low anterior and abdominoperineal resections. Preoperative portal vein occlusion included portal vein embolization or ligation. The Brisbane 2000 terminology was used to define the extent of a liver resection, defining a resection greater than or equal to three contiguous Couinaud's segments as major[21]. A SIMR whereby both the colorectal and liver resection were performed laparoscopically, irrespective of a possible conversion, were deemed fully laparoscopic. Intraoperative incidents were defined and graded according to the Oslo classification[22]. The Clavien–Dindo classification was used to define and grade postoperative complications until 30 days after the procedure, and complications grade 3a or higher were considered severe [23]. The ISGLS definitions of postoperative bile leak and liver failure were used[24,25]. The liver resection margin was considered microscopically free (R0) when greater than or equal

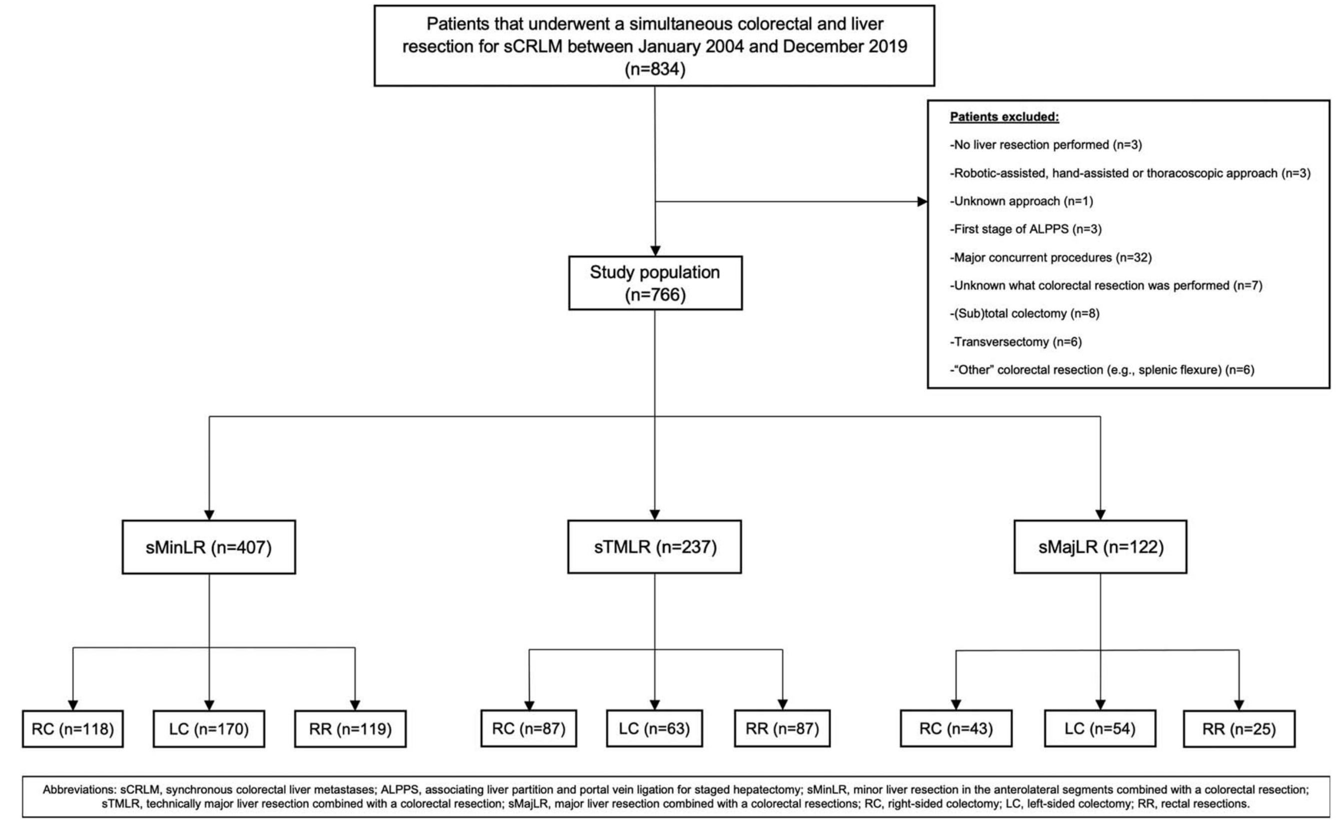

Figure 1. Study flowchart. ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; LC, left-sided colectomy; RC, right-sided colectomy; RR, rectal resections; sCRLM, synchronous colorectal liver metastases; sMajLR, major liver resection combined with a colorectal resections; sMinLR, minor liver resection in the anteriolateral segments combined with a colorectal resection; sTMLR, technically major liver resection combined with a colorectal resection.

to 1 mm. For the multivariable analyses, a prolonged length of stay was defined as a length of stay greater than or equal to 15 days. Intraoperative unfavorable events were labeled if an intraoperative incident occurred, an intraoperative transfusion was required, or blood loss was greater than or equal to 1000 ml.

Preoperative assessment

Patients underwent routine laboratory tests and imaging with thoracoabdominal computed tomography scans and, if indicated, magnetic resonance imaging with contrast. The indication for surgery was determined during a multidisciplinary meeting with hepatologists, oncologists, radiologists, and surgeons. Preoperative portal vein occlusion was generally performed in case of a future liver remnant volume of less than 20–25% in a healthy liver, 30% in a liver injured by chemotherapy or in obese patients, and 40% in cirrhotic patients or patients that had received an extensive treatment with neoadjuvant chemotherapy (more than six cycles).

Statistical analysis

Categorical variables were reported as counts and their respective percentages, and compared between groups using a χ^2 or Fisher's exact test, when appropriate. Continuous normally distributed variables were reported as the mean with its standard deviation and compared between groups using an unpaired *t* test. Continuous, not normally distributed variables were expressed as the median with its range and compared between groups using a Kruskal–Wallis test. Normality was assessed by visual inspection of histograms and Q–Q plots.

Multivariable logistic regression analyses were performed to assess which preoperatively known factors were associated with intraoperative unfavorable events, surgical morbidity, severe morbidity, and a prolonged length of stay (dependent variables). Possible confounders were identified using a directed acyclic graph, and entered into the model as independent variables (Supplementary Fig. 1, Supplemental Digital Content 1, http://links.lww.com/JS9/A0) The surgical approach (fully laparoscopic vs. hybrid/open) was forced into the model in order to investigate its impact. Missing data was present in some of the independent variables in a missing at random pattern (Supplementary Fig. 2, Supplemental Digital Content 3, http://links.lww.com/JS9/A28). Therefore, imputed data was utilized in these regression analyses. Using the mice package, five multiply imputed datasets with 30 iterations each were created using predictive mean matching for continuous, polynomial regression for ordinal and logistic regression for binary variables[26]. Multivariable logistic regression models were applied to the imputed datasets and final estimates were obtained by pooling the five estimates applying Rubin's rules[26]. The dependent variables of interest were not imputed. Additionally, a sensitivity analysis was performed wherein age was entered as a dichotomized variable (<70 vs. ≥ 70 y) in order to assess the associated risks in elderly patients. This cutoff was chosen since previous studies have shown that an age of 70 years and older is associated with increasing frailty and worsening perioperative outcomes[27]. All analyses were performed following the intention-to-treat principle, a two-sided P value less than 0.05 was considered statistically significant. In the unadjusted analyses, the Bonferroni correction for multiple testing was applied when the P value was lower than 0.05 in the initial analyses. This was done by multiplying the initial P values by three, since three comparisons were performed. Data were analyzed using R for Mac OS X version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, 766 patients that underwent a SIMR were included and stratified into the different groups of interest (Fig. 1).

Complete cohort

Baseline characteristics

In the complete cohort, 407 (53%) patients underwent a minor liver resection, 237 (31%) a technically major liver resection, and only 122 (16%) a major liver resection. The liver resection was combined with a right-sided colectomy in 248 patients (32.4%), a left-sided colectomy in 287 patients (37.5%) and a rectal resection in 231 patients (30.2%). A comparison of patients' baseline characteristics according to the type of liver resection performed showed that patients that underwent major liver resections, compared to minor and technically major liver resections, were younger (both $P \leq 0.084$), more frequently affected by larger (both $P = 0.003$), bilobar sCRLM (both $P = 0.003$) and underwent a staged hepatectomy (both $P = 0.003$), while they less often underwent fully laparoscopic procedures (both $P = 0.003$). Patients that underwent technically major liver resections less frequently underwent left-sided colectomies (both $P = 0.003$) and anatomical liver resections (both $P = 0.003$). The rates of treatment with neoadjuvant chemotherapy were comparable between the three groups, and ranged between 52.3 and 56.6% (all $P \geq 0.518$) (Table 1).

Perioperative outcomes

When assessing perioperative outcomes, technically and anatomically major liver resections, compared to minor liver resections, were associated with higher rates of intraoperative blood transfusion (both $P = 0.003$) (Supplementary Table 1, Supplemental Digital Content 4, http://links.lww.com/JS9/A29). In patients who underwent technically major liver resections, compared to minor liver resections, the intraoperative blood loss (median 200 vs. 150 mL, respectively, $P = 0.003$), and rates of conversion (25.9 vs. 8.3%, respectively, $P = 0.003$) were significantly higher. In addition, major liver resections, compared to minor and technically major liver resections, were associated with a longer length of stay (both $P \leq 0.042$), higher rates of overall and surgical morbidity (both $P \leq 0.024$ and $P \leq 0.015$, respectively) (Supplementary Table 1, Supplemental Digital Content 4, http://links.lww.com/JS9/A29).

Subgroup analysis of patients who underwent minor liver resections

Among patients undergoing a minor liver resection, those who underwent a right-sided colectomy, compared to a left-sided colectomy, were older (median 69 vs. 64 y, respectively, $P = 0.006$) and more frequently had a history of extrahepatic abdominal surgery ($P = 0.045$). Patients who underwent rectal resections were, compared to both patients that underwent right-sided and left-sided colectomies, more often treated with neoadjuvant chemotherapy (73.7 vs. 42.4 and 50.6%, respectively, both $P = 0.003$) (Table 2).

Concerning perioperative outcomes, right-sided colectomies, compared to left-sided colectomies, were associated with a higher rate of overall (58.5 vs. 45.3%, respectively, $P = 0.111$) and severe morbidity (19.5 vs. 9.4%, respectively, $P = 0.066$), although these differences did not reach statistical significance after the correction for multiple testing. These increased morbidity rates mainly seemed to be caused by prolonged gastric and bowel dysfunction (12.7 vs. 4.1%, respectively, $P = 0.042$), pulmonary complications (15.3 vs. 6.5%, respectively, $P = 0.078$), and sepsis (5.1 vs. 0.6%, respectively, $P = 0.123$) (Table 2, and Supplementary Table 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A29). Rectal resections were associated with a longer operative time (both $P = 0.003$) (Table 2).

Subgroup analysis of patients who underwent technically major liver resections

In the technically major liver resection group, patients undergoing right-sided colectomies, compared to left-sided colectomies, were more often operated with a fully laparoscopic approach, although this difference was not statistically significant (29.9 vs. 12.7%, respectively, $P = 0.066$). In this subgroup, patients undergoing rectal resections were more often treated with neoadjuvant chemotherapy (62.4 vs. 42.5%, respectively, $P = 0.042$) (Table 3). The perioperative outcomes in the technically major liver resections groups were mostly comparable; the only exceptions regarded, for patients undergoing a rectal resection, significantly longer operative times (both $P \leq 0.039$) (Table 3).

Subgroup analysis of patients who underwent major liver resections

Patients who underwent a major liver resection combined with a rectal resection, compared to a left-sided colectomy, were more often operated with a fully laparoscopic approach (16 vs. 0%, respectively, $P = 0.042$). Treatment with neoadjuvant chemotherapy was more common when a major liver resection was combined with a rectal resection, compared to right-sided colectomies (80 vs. 39.5%, respectively, $P = 0.009$) (Table 4). Regarding perioperative outcomes, blood loss was higher, although not significant, when a major liver resection was combined with a right-sided colectomy, compared to a left-sided colectomy (median 270 vs. 150 mL, respectively, $P = 0.075$). Furthermore, the incidence of intraoperative incidents was significantly higher in case of combined rectal resections, compared to left-sided colectomies (25 vs. 0%, respectively, $P = 0.024$) (Table 4).

Table 1

Comparison of characteristics of operated patients stratified according to the type of liver resection performed

Characteristics	Overall (n = 766)	sALR (A) (n = 407)	sTMR (B) (n = 237)	sAMR (C) (n = 122)	P (A vs. B)	P (A vs. C)	P (B vs. C)
Sex, male	457 (59.7)	243 (59.7)	147 (62)	67 (54.9)	0.619	0.403	0.235
Age, years	65 [56,72]	65 [55.3, 72.9]	66 [58.9, 72]	62 [52.7, 68]	0.228	0.084*	0.006*
Median BMI, kg/m^2 [IQR]	25.4 [22.9, 28.4]	25.5 [23.1, 28.9]	24.9 [22.3, 27.7]	26.2 [22.3, 29.1]	0.111*	0.819	0.228
ASA score 3 and 4	282 (39)	154 (39.6)	90 (41.7)	38 (32.2)	0.68	0.18	0.114
Cirrhosis	9 (1.2)	2 (0.5)	7 (3)	0	0.075*	1	0.128
Previous extrahepatic surgery	247 (32.4)	141 (34.7)	68 (28.9)	38 (31.4)	0.156	0.57	0.719
Previous hepatic surgery	30 (3.9)	16 (3.9)	12 (5.1)	2 (1.7)	0.62	0.352	0.194
Neoadjuvant chemotherapy	415 (54.4)	223 (54.9)	123 (52.3)	69 (56.6)	0.582	0.831	0.518
Preoperative portal vein occlusion					0.054	0.102	0.855
PVE	54 (7.2)	20 (4.9)	23 (9.7)	11 (10.5)			
PVL	10 (1.3)	5 (1.2)	4 (1.7)	1 (1)			
Two-stage hepatectomy					0.122	0.003*	0.003*
First stage	58 (9.4)	28 (9.1)	29 (14.5)	1 (1)			
Second stage	6 (1)	1 (0.3)	0	5 (4.8)			
Disease characteristics (liver)							
Median tumor size, mm [IQR]	30 [18,45]	28 [15.3, 40]	25 [16,35]	50 [35,80]	0.129*	0.003*	0.003*
Median number of lesions [IQR]	2 [1, 4]	2 [1, 3]	2 [1, 4]	3 [1, 6]	0.003*	0.003*	0.260
Bilobar distribution	145 (19.5)	74 (19)	26 (11.3)	45 (36.9)	0.045*	0.003*	0.003*
Operative characteristics							
Laparoscopic approach	156 (20.4)	93 (22.9)	55 (23.2)	8 (6.6)	0.995	0.003*	0.003*
Type of liver resection					0.003*	0.003*	0.003*
Nonanatomical	452 (59.0)	275 (67.6)	177 (74.7)	0			
Anatomical	226 (29.5)	107 (26.3)	31 (13.1)	88 (72.1)			
Nonanatomical/anatomical	88 (11.5)	25 (6.1)	29 (12.2)	34 (27.9)			
Type of colorectal resection					0.003*	0.137	0.003*
Right-sided colectomy	248 (32.4)	118 (29)	87 (36.7)	43 (35.2)			
Left-sided colectomy	287 (37.5)	170 (41.8)	63 (26.6)	54 (44.3)			
Rectal resection	231 (30.2)	119 (29.2)	87 (36.7)	25 (20.5)			
Creation of stomy					0.003*	0.604	0.042*
Ileostomy	102 (17.8)	54 (16.3)	35 (25.2)	13 (12.9)			
Colostomy	52 (9.1)	23 (6.9)	20 (14.4)	9 (8.9)			
Unknown type of stomy	2 (0.3)	0	2 (1.4)	0			
Concurrent thermal ablation	37 (4.8)	26 (6.4)	9 (3.8)	2 (1.6)	0.223	0.068	0.423

Values are expressed in counts (percentages) or in medians [IQR].
ALR indicates, anatomically minor liver resection in the anterolateral segments combined with a colorectal resection; ASA, American Society of Anesthesiologists; PVE, portal vein embolization; PVL, portal vein ligations; sAMR, anatomically major resection combined with a colorectal resection; sTMR, technically major resection combined with a colorectal resection.
*$P < 0.05$ in initial analyses, reported value with Bonferroni correction.

Preoperative factors associated with unfavorable perioperative outcomes

Results of the multivariable analyses are shown in Table 5. In these multivariable analyses, American Society of Anesthesiologists (ASA) grades 3 or 4 [adjusted odds ratio (aOR): 1.477, 95% CI: 1.005–2.170; $P = 0.047$), larger liver lesions (aOR: 1.009, 95% CI: 1.001–1.017; $P = 0.020$), technically (aOR: 2.448, 95% CI: 1.662–3.606; $P < 0.001$) and anatomically major liver resections (aOR: 2.968, 95% CI: 1.694–5.199; $P < 0.001$) were independently associated with a higher intraoperative unfavorable event rate. Conversely, a greater number of lesions was independently associated with a reduced intraoperative unfavorable event rate (aOR: 0.921, 95% CI: 0.865–0.980; $P = 0.009$).

A history of abdominal surgery (aOR: 1.623, 95% CI: 1.162–2.268; $P = 0.005$) and undergoing an anatomically major liver resection (aOR: 1.837, 95% CI: 1.144–2.952; $P = 0.012$) was independently associated with a higher surgical morbidity rate. Specifically looking at factors independently associated with severe morbidity, patients with ASA grades 3 or 4 (aOR: 1.671, 95% CI: 1.106–2.524; $P = 0.015$) or undergoing a major liver resection (aOR: 1.788, 95% CI: 1.009–3.170; $P = 0.047$) had an increased severe morbidity risk, while patients undergoing a liver resection combined with a left-sided colectomy had a reduced risk of severe morbidity (aOR: 0.547, 95% CI: 0.340–0.882; $P = 0.013$). Factors independently associated with a prolonged length of stay were older age (aOR: 1.017, 95% CI: 1.001–1.033; $P = 0.043$), ASA grades 3 or 4 (aOR: 1.585, 95% CI: 1.088–2.309; $P = 0.017$), and undergoing surgery for a greater number of lesions (aOR: 1.066, 95% CI: 1.011–1.123; $P = 0.018$). In the sensitivity analysis, an age greater than or equal to 70 years was independently associated with a higher risk of surgical morbidity (aOR: 1.453, 95% CI: 1.014–2.082; $P = 0.042$) and a prolonged length of stay (aOR: 1.695, 95% CI: 1.170–2.456; $P = 0.005$) (Supplementary Table 3, Supplemental Digital Content 4, http://links.lww.com/JS9/A29).

DISCUSSION

This retrospective international multicenter study indicates that at the present time, in selected patients and in experienced centers,

Table 2

Comparison of the characteristics and outcomes of patients who underwent anatomically minor liver resections combined with the different colorectal resections

	Anatomically minor RC (A)	Anatomically minor LC (B)	Anatomically minor RR (C)			
Characteristics	(n = 118)	(n = 170)	(n = 119)	P (A vs. B)	P (A vs. C)	P (B vs. C)
Sex, male	69 (58.5)	96 (56.5)	78 (65.5)	0.828	0.323	0.153
Median age, years [IQR]	69 [59.3, 75]	64 [53, 71.6]	62 [51, 70.1]	0.006*	0.003*	0.298
Median BMI, kg/m^2 [IQR]	25.7 [23.5, 28]	25.8 [23.1, 30]	25.1 [22.9, 28.3]	0.57	0.384	0.151
ASA score 3 and 4	51 (44)	55 (33.7)	48 (43.6)	0.108	1	0.127
Cirrhosis	0	1 (0.6)	1 (0.8)	1	1	1
Previous extrahepatic surgery	52 (44.1)	50 (29.4)	39 (33.1)	0.045*	0.109	0.598
Previous hepatic surgery	3 (2.5)	7 (4.1)	6 (5.1)	0.696	0.497	0.92
Neoadjuvant chemotherapy	50 (42.4)	86 (50.6)	87 (73.7)	0.21	0.003*	0.003*
Preoperative portal vein occlusion	3 (2.5)	12 (7.1)	10 (8.4)	0.217	0.076	0.186
Two-stage hepatectomy				0.126	0.068	0.609
First stage	4 (4.1)	12 (10.6)	12 (12.2)			
Second stage	0	1 (0.9)	0			
Disease characteristics (liver)						
Median tumor size, mm [IQR]	28 [16,40]	30 [17,45]	24.5 [15,40]	0.312	0.365	0.111*
Median number of lesions [IQR]	2 [1,3]	2 [1,4]	2 [1,3]	0.359	0.738	0.507
Bilobar distribution	22 (19)	34 (21.2)	18 (15.9)	0.753	0.666	0.344
Operative characteristics						
Laparoscopic approach	28 (23.7)	40 (23.5)	25 (21)	1	0.729	0.717
Type of liver resection				0.114	0.259	0.457
Nonanatomical	83 (70.3)	108 (63.5)	84 (70.6)			
Anatomical	32 (27.1)	48 (28.2)	27 (22.7)			
Nonanatomical/anatomical	3 (2.5)	14 (8.2)	8 (6.7)			
Creation of stomy	5 (5.1)	10 (7.4)	62 (63.2)	0.117*	0.003*	0.003*
Concurrent thermal ablation	9 (7.6)	7 (4.1)	10 (8.4)	0.309	1	0.204
Intraoperative outcomes						
Median operative time, minutes [IQR]	256.5 [154.5, 302.8]	292.5 [204, 399.3]	394.5 [300.5, 483.8]	0.031	0.003*	0.003*
Median intraoperative blood loss, mL [IQR]	100 [52.3, 300]	150 [100, 350]	150 [100, 300]	0.231	0.177	0.811
Intraoperative blood transfusion	27 (24.3)	28 (17.2)	22 (19.8)	0.195	0.517	0.692
Pedicle clamping	18 (16.1)	38 (24.4)	28 (24.8)	0.135	0.146	1
Intraoperative incidents	2 (2.2)	4 (3.1)	4 (4.7)	1	0.175	0.069
Conversion to laparotomy (in case of lap, approach)	2 (7.1)	4 (11.8)	1 (4.5)	0.856	1	0.656
Postoperative outcomes						
Overall complications	69 (58.5)	77 (45.3)	59 (49.6)	0.111*	0.214	0.549
Surgical	37 (31.4)	42 (24.9)	35 (29.7)	0.28	0.888	0.442
Anastomotic leak	6 (5.1)	12 (7.1)	11 (9.2)	0.665	0.323	0.649
Abdominal collection	13 (11)	14 (8.2)	9 (7.6)	0.555	0.489	1
Prolonged ileus/DGE/SBO	15 (12.7)	7 (4.1)	7 (5.9)	0.042*	0.117	0.679
Hemorrhage	7 (5.9)	6 (3.6)	5 (4.2)	0.505	0.767	1
Bile leakage	2 (1.7)	3 (1.8)	2 (1.7)	1	1	1
Posthepatectomy liver failure	1 (0.8)	1 (0.6)	4 (3.4)	1	0.366	0.185
SSI	3 (2.5)	4 (2.4)	2 (1.7)	1	1	1
Nonsurgical	32 (27.1)	29 (17.2)	27 (22.9)	0.06	0.548	0.293
Severe complications (CD ≥ 3)	23 (19.5)	16 (9.4)	21 (17.6)	0.066*	0.843	0.06
90-day or in-hospital mortality	1 (0.9)	0	1 (0.8)	0.852	1	0.862
Median LOS, days [IQR]	10 [7, 15]	9 [8, 12]	11 [8, 15]	0.645	0.333	0.129*
R0 resection margin (liver)	29 (25.4)	37 (22)	22 (19)	0.602	0.306	0.634
Readmission	2 (1.9)	4 (2.7)	1 (1)	0.984	1	0.655

Values are expressed in counts (percentages) or in medians [IQR].

ASA indicates, American Society of Anesthesiologists; CD, Clavien–Dindo; DGE, delayed gastric emptying; LC, left-sided colectomy; LOS, length of stay; PVE, portal vein embolization; PVL, portal vein ligation; RC, right-sided colectomy; RR, rectal resections; SBO, small bowel obstruction; SSI, surgical site infection.

*$P < 0.05$ in initial analyses, reported value with Bonferroni correction.

SIMRs can be performed with acceptable results regardless of the extent and complexity of both the colorectal and liver resection. In particular, the observed mortality rates of 0.5, 1.7, and 2.5% following colorectal resections combined with minor, technically major, and anatomically major liver resections, respectively, reflect the rates commonly reported following liver resections alone[28–31]. However, the type of liver resection performed was strongly associated with the feasibility of a SIMR in our study. The risk of unfavorable intraoperative outcomes seems to increase when a colorectal resection is combined with a technically complex or

Table 3

Comparison of the characteristics and outcomes of patients who underwent technically major liver resections combined with the different colorectal resections

Characteristics	Technically major RC (A) (n = 87)	Technically major LC (B) (n = 63)	Technically major RR (C) (n = 87)	P (A vs. B)	P (A vs. C)	P (B vs. C)
Sex, male	47 (54)	39 (61.9)	61 (70.1)	0.426	0.126*	0.380
Median age, years [IQR]	68 [61.4, 74.1]	66 [55.1, 71]	65 [58,70]	0.114*	0.114*	0.964
Median BMI, kg/m^2 [IQR]	24.7 [22.5, 27.3]	25 [22.2, 28.1]	24.8 [22.4, 28]	0.457	0.658	0.721
ASA score 3 and 4	39 (50)	20 (36.4)	31 (37.3)	0.167	0.145	1
Cirrhosis	3 (3.5)	3 (4.8)	1 (1.2)	1	0.630	0.421
Previous extrahepatic surgery	20 (23.3)	20 (31.7)	28 (32.6)	0.333	0.234	1
Previous hepatic surgery	4 (4.7)	3 (4.8)	5 (5.8)	1	1	1
Neoadjuvant chemotherapy	37 (42.5)	33 (52.4)	53 (62.4)	0.304	0.042*	0.295
Preoperative portal vein occlusion	9 (10.3)	8 (12.7)	10 (11.5)	0.323	0.964	0.392
Two-stage hepatectomy				0.702	0.708	1
First stage	9 (12.2)	9 (16.1)	11 (15.7)			
Second stage	0	0	0			
Disease characteristics (liver)						
Median tumor size, mm [IQR]	24 [15,40]	25 [16.3, 36.5]	22 [16.8, 30]	0.598	0.609	0.177
Median number of lesions [IQR]	2 [1,4]	2 [1, 4.8]	3 [1, 4]	0.897	0.404	0.558
Bilobar distribution	9 (10.5)	7 (11.7)	10 (11.8)	1	0.978	1
Operative characteristics						
Laparoscopic approach	26 (29.9)	8 (12.7)	21 (24.1)	0.066*	0.495	0.123
Type of liver resection				0.499	0.766	0.829
Nonanatomical	62 (71.3)	49 (77.8)	66 (75.9)			
Anatomical	14 (16.1)	6 (9.5)	11 (12.6)			
Nonanatomical/anatomical	11 (12.6)	8 (12.7)	10 (11.5)			
Creation of stomy	5 (12.9)	7 (20)	45 (69.3)	0.314	0.003*	0.003*
Concurrent thermal ablation	6 (6.9)	1 (1.6)	2 (2.3)	0.259	0.278	1
Intraoperative outcomes						
Median operative time, minutes [IQR]	253 [195, 310]	270 [238, 330]	365 [286.8, 480]	0.215	0.003*	0.039*
Median intraoperative blood loss, mL [IQR]	200 [105, 370]	204.5 [122.5, 500]	210 [100, 445]	0.512	0.967	0.579
Intraoperative blood transfusion	32 (39)	16 (27.1)	40 (46.5)	0.196	0.41	0.087*
Pedicle clamping	34 (40)	22 (34.9)	31 (35.6)	0.647	0.665	1
Intraoperative incidents	8 (10.4)	5 (10.2)	7 (9.1)	0.731	0.243	0.655
Conversion to laparotomy (in case of lap, approach)	6 (23.1)	3 (37.5)	5 (25.0)	0.726	1	0.843
Postoperative outcomes						
Overall complications	43 (49.4)	28 (44.4)	46 (52.9)	0.662	0.762	0.393
Surgical	26 (30.6)	12 (19.4)	28 (32.6)	0.178	0.91	0.11
Anastomotic leak	1 (1.2)	1 (1.6)	6 (7)	1	0.127	0.253
Abdominal collection	12 (14)	7 (11.1)	11 (12.8)	0.791	1	0.955
Prolonged ileus/DGE/SBO	3 (3.5)	3 (4.8)	5 (5.8)	1	0.717	1
Hemorrhage	2 (2.3)	0	2 (2.3)	0.626	1	0.626
Bile leakage	4 (4.7)	2 (3.2)	5 (5.7)	0.975	1	0.73
Posthepatectomy liver failure	4 (4.7)	1 (1.6)	2 (2.3)	0.583	0.678	1
SSI	5 (5.8)	2 (3.2)	3 (3.5)	0.734	0.717	1
Nonsurgical	29 (33.7)	15 (24.2)	25 (29.1)	0.285	0.622	0.637
Severe complications (CD ≥ 3)	19 (21.8)	8 (12.7)	20 (23)	0.221	1	0.166
90-day or in-hospital mortality	2 (2.4)	0	2 (2.3)	0.622	1	0.634
Median LOS, days [IQR]	10 [7.5, 17]	10 [8,12]	11 [8,18]	0.782	0.206	0.09
R0 resection margin (liver)	27 (31.8)	19 (31.7)	24 (28.9)	1	0.857	0.866
Readmission	3 (6.4)	0	2 (3.6)	0.419	0.91	0.758

Values are expressed in counts (percentages) or in medians [IQR].

ASA indicates, American Society of Anesthesiologists; CD, Clavien–Dindo; DGE, delayed gastric emptying; LC, left-sided colectomy; LOS, length of stay; PVE, portal vein embolization; PVL, portal vein ligation; RC, right-sided colectomy; RR, rectal resections; SBO, small bowel obstruction; SSI, surgical site infection.

*$P < 0.05$ in initial analyses, reported value with Bonferroni correction.

anatomically major liver resection, while the risk of unfavorable postoperative outcomes seems to be uniquely affected by the liver resection extent. Surprisingly, and against general beliefs, left-sided colectomies, compared to right-sided colectomies, were independently associated with a lower severe morbidity rate.

Several studies comparing the different treatment sequences in patients with sCRLM have highlighted the reluctancy of surgeons to perform a SIMR in case of extensive disease requiring a challenging liver resection or in case of patients with an indication for a liver resection combined with a rectal resection[10,11,16,32–34].

Table 4

Comparison of the characteristics and outcomes of patients who underwent anatomically major liver resections combined with the different colorectal resections

Characteristics	Anatomically major RC (A) (*n* = 43)	Anatomically major LC (B) (*n* = 54)	Anatomically major RR (C) (*n* = 25)	*P* (A vs. B)	*P* (A vs. C)	*P* (B vs. C)
Sex, male	28 (65.1)	25 (46.3)	14 (56)	0.1	0.626	0.575
Median age, years [IQR]	64.4 [4,7,57,68]	59.1 [49.8, 68]	62 [56, 69.5]	0.103	0.675	0.255
Median BMI, kg/m^2 [IQR]	25.4 [23.4, 27.9]	26.1 [21.7, 30.4]	26.9 [22.5, 29.5]	0.831	0.548	0.806
ASA score 3 and 4	12 (28.6)	18 (35.3)	8 (32)	0.64	0.984	0.978
Cirrhosis	0	0	0	NA	NA	NA
Previous extrahepatic surgery	14 (32.6)	15 (28.3)	9 (36)	0.82	0.981	0.671
Previous hepatic surgery	0	2 (3.8)	0	0.569	NA	0.829
Neoadjuvant chemotherapy	17 (39.5)	32 (59.3)	20 (80)	0.084	0.009*	0.121
Preoperative portal vein occlusion	2 (5.4)	6 (13.1)	4 (18.2)	0.435	0.261	0.57
Two-stage hepatectomy				0.472	1	0.739
First stage	0	1 (2.2)	0			
Second stage	1 (2.7)	3 (6.5)	1 (4.5)			
Disease characteristics (liver)						
Median tumor size, mm [IQR]	50 [30,80]	60 [40,80]	45 [30,65]	0.326	0.468	0.148
Median number of lesions [IQR]	3 [1,4]	3 [1,6]	3 [2,6]	0.387	0.204	0.497
Bilobar distribution	14 (32.6)	24 (44.4)	7 (28)	0.326	0.904	0.252
Operative characteristics						
Laparoscopic approach	4 (9.3)	0	4 (16)	0.076	0.663	0.042*
Type of liver resection				0.874	0.663	0.43
Nonanatomical	0	0	0			
Anatomical	31 (72.1)	37 (68.5)	20 (80)			
Nonanatomical/anatomical	12 (27.9)	17 (31.5)	5 (20)			
Creation of stomy	5 (14.7)	4 (8.6)	13 (61.9)	0.671	0.003*	0.003*
Concurrent thermal ablation	1 (2.3)	1 (1.9)	0	1	1	1
Intraoperative outcomes						
Median operative time, minutes [IQR]	310 [248, 349]	337.2 [285, 438]	360 [270, 444]	0.096	0.141	0.847
Median intraoperative blood loss, mL [IQR]	270 [187.5, 850]	150 [85, 387.5]	200 [100, 450]	0.075*	0.192	0.502
Intraoperative blood transfusion	17 (50)	20 (42.6)	8 (33.3)	0.661	0.321	0.62
Pedicle clamping	11 (26.8)	15 (28.8)	5 (20)	1	0.74	0.581
Intraoperative incidents	3 (10.7)	0	5 (25)	0.140	0.083	0.024*
Conversion to laparotomy (in case of lap, approach)	1 (25)	0	1 (25)	NA	1	NA
Postoperative outcomes						
Overall complications	30 (69.8)	35 (64.8)	14 (56)	0.766	0.378	0.616
Surgical	22 (51.2)	22 (41.5)	9 (36)	0.461	0.338	0.829
Anastomotic leak	3 (7)	6 (11.1)	2 (8)	0.73	1	0.98
Abdominal collection	5 (11.6)	8 (15.1)	1 (4)	0.846	0.531	0.293
Prolonged ileus/DGE/SBO	5 (11.6)	4 (7.5)	3 (12)	0.741	1	0.828
Hemorrhage	2 (4.7)	4 (7.5)	4 (12)	0.874	0.524	0.828
Bile leakage	3 (7)	5 (9.3)	2 (8)	0.973	1	1
Posthepatectomy liver failure	4 (9.3)	4 (7.5)	0	1	0.3	0.39
SSI	1 (2.3)	0	0	0.916	1	NA
Nonsurgical	10 (23.3)	18 (34)	5 (20)	0.357	0.993	0.319
Severe complications (CD ≥ 3)	13 (30.2)	12 (22.2)	4 (16)	0.508	0.309	0.735
90-day or in-hospital mortality	3 (7.1)	0	0	0.171	0.449	NA
Median LOS, days [IQR]	11 [9,15]	11 [9,19]	12 [10,17]	0.732	0.354	0.474
R0 resection margin (liver)	13 (30.2)	18 (35.3)	9 (36)	0.129*	0.916	0.24
Readmission	2 (6.9)	0	0	0.348	0.642	NA

Values are expressed in counts (percentages) or in medians [IQR].

ASA indicates, American Society of Anesthesiologists; CD, Clavien–Dindo; DGE, delayed gastric emptying; LC, left-sided colectomy; LOS, length of stay; PVE, portal vein embolization; PVL, portal vein ligation; RC, right-sided colectomy; RR, rectal resections; SBO, small bowel obstruction; SSI, surgical site infection

*$P < 0.05$ in initial analyses, reported value with Bonferroni correction.

Delving deeper into this selection process, our study results suggest that not only disease characteristics, but also patient-related factors may play an important role in surgeons' choice to combine certain types of procedures, as indicated by the younger age of patients undergoing a major liver resections and by the rare association of a major liver resection with a rectal resection. This cautious selection reflects the available evidence, which shows that the perioperative risks increase with the complexity of the colorectal resection and the

Table 5

Multivariable analyses for intraoperative unfavorable incidents, surgical morbidity, severe morbidity (CD ≥ 3), and prolonged length of stay

	Intraoperative unfavorable incidents		Surgical morbidity		Severe morbidity		Prolonged length of stay	
Term	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P	aOR (95% CI)	P
Minimally invasive approach	1.119 (0.728–1.719)	0.608	1.001 (0.660–1.520)	0.995	1.048 (0.646–1.698)	0.850	0.992 (0.643–1.531)	0.972
Age at operation	0.990 (0.974–1.006)	0.225	1.010 (0.995–1.025)	0.198	1.004 (0.986–1.022)	0.680	**1.017 (1.001–1.033)**	**0.043**
ASA score								
I/II	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
III/IV	**1.477 (1.005–2.170)**	**0.047**	1.173 (0.828–1.661)	0.369	**1.671 (1.106–2.524)**	**0.015**	**1.585 (1.088–2.309)**	**0.017**
Previous abdominal surgery	0.993 (0.690–1.431)	0.972	**1.623 (1.162–2.268)**	**0.005**	1.025 (0.681–1.541)	0.907	1.250 (0.878–1.777)	0.216
Size largest liver lesion	**1.009 (1.001–1.017)**	**0.020**	1.004 (0.997–1.011)	0.250	1.005 (0.998–1.013)	0.171	1.005 (0.998–1.012)	0.205
Number of lesions	**0.921 (0.865–0.98)**	**0.009**	1.041 (0.988–1.097)	0.131	0.962 (0.894–1.036)	0.309	**1.066 (1.011–1.123)**	**0.018**
Bilobar distribution	0.710 (0.438–1.152)	0.165	1.119 (0.736–1.702)	0.598	0.798 (0.455–1.401)	0.431	1.128 (0.725–1.756)	0.592
Type of colorectal resection								
Right-sided colectomy	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Left-sided colectomy	0.895 (0.583–1.375)	0.614	0.701 (0.476–1.032)	0.072	**0.574 (0.340–0.882)**	**0.013**	0.710 (0.469–1.074)	0.104
Rectal resection	1.118 (0.722–1.730)	0.617	0.963 (0.647–1.433)	0.851	0.944 (0.597–1.493)	0.806	1.346 (0.895–2.024)	0.154
Type of liver resection								
Minor	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Technically major	**2.448 (1.662–3.606)**	**< 0.001**	0.992 (0.685–1.435)	0.964	1.337 (0.865–2.064)	0.191	1.216 (0.833–1.777)	0.311
Major	**2.968 (1.694–5.200)**	**< 0.001**	**1.837 (1.144–2.952)**	**0.012**	**1.788 (1.009–3.170)**	**0.047**	1.494 (0.898–2.486)	0.122

aOR, indicates adjusted odds ratio; ASA, American Society of Anesthesiologists; CD, Clavien–Dindo.
statistical significance in the multivariable model, with a $P \leq 0.05$ values are in bold.

extent of the liver resection, and was probably pertinent in achieving the excellent perioperative outcomes reported in this study[10,15].

The severe morbidity (14.7–23.8%) and mortality rates (0.5–2.5%) in this study are broadly consistent with most recent literature on the topic, while higher rates were reported in the only published randomized clinical trial (severe morbidity 49% and mortality 7.4%)[12,16,32,35]. Additionally, in comparison with the existing literature, improved results were seen in the major liver resection group, possibly reflecting the extensive liver surgical experience in the participating centers[10,36,37]. Nevertheless, the type and extent of the performed liver resection was still the main factor influencing the perioperative course in this study, in terms of the risk of intraoperative unfavorable events, severe morbidity and a prolonged length of stay. Several studies have reported a similar association between perioperative outcomes and the liver resection extent, while other studies have presented different findings[10,16,38,39]. In our study the ASA score was also independently associated with several postoperative outcomes, in line with an earlier report[16].

To our knowledge this is the first study investigating the feasibility and safety of SIMRs for sCRLM, in which the subdivision of minor liver resections in the anterolateral and posterosuperior segments is utilized. As expected, the patients who underwent a minor liver resection for lesions located in the anterior 'easy' segments showed the best perioperative outcomes and, as such, acted as a reference parameter for further comparison. In this setting, resections in the posterosuperior segments, compared to resections in the anterolateral segments, were independently associated with worse intraoperative but similar postoperative outcomes. This may be related to the intrinsic surgical difficulty of technically major liver resections, leading to an increased risk of bleeding or conversion. However, the limited liver resection extent may justify the similarity of postoperative outcomes between the two groups of patients. In contrast, patients undergoing a major liver resection showed the worst intraoperative and postoperative outcomes.

Interestingly, undergoing a left-sided colectomy was independently associated with a lower severe morbidity rate, when compared to a right-sided colectomy. This finding is in contrast with the concept that patients with an indication for a right hemicolectomy and a minor hepatectomy would be the most proper candidates for a SIMR, and is inconsistent with the literature regarding colectomies solely, reporting a similar risk of postoperative morbidity for right and left-sided colectomies[40,41]. A possible explanation for this finding may concern the anatomical location, as both resections are, in case of a right-sided colectomy, performed in the right upper quadrant of the abdomen. During a simultaneous left-sided colectomy the resections are performed in two different quadrants, which may dilute the areas of inflammation leading to a less severe inflammatory response and guarantees a certain distance between the two operative fields, reducing the risk of cross-contamination. Furthermore, the anastomotic site and technique may have an impact. The anastomotic technique during a left hemicolectomy often consists of a colorectal mechanical anastomosis with a circular stapler, only requiring a small opening of the proximal colon for the introduction of a circular stapler with minimal field contamination due to the dense fecal consistency. In contrast, when a right hemicolectomy is performed the anastomosis requires the opening of not only the colon, but also the small bowel with intra-abdominal manipulation of the opened anastomotic access. Theoretically, this may lead to a higher risk of gut flora dispersion in the paramesocolic space, with a subsequent increased risk for (ascending) infectious complications. Obviously, selection bias could have had an influence on these results. Surgeons may widen the indications for a SIMR when a right colectomy is needed. However, an adjustment for known confounding factors was made by using multivariable analyses.

A clear benefit of the laparoscopic approach during SIMR, as extensively described separately for colorectal and liver resections and, to a lesser extent, for SIMR, was not found in this study[42–44]. This could be due to the fact that a large proportion of the included procedures was performed partially laparoscopic and partially open. Furthermore, the benefits of minimally invasive surgery could decrease in more extensive procedures, since the damage to the abdominal wall then constitutes a more limited fraction of the overall surgical trauma.

This study has various limitations that should be acknowledged. First, the retrospective and multicenter design of this study has its obvious shortcomings, including the risk of selection bias and differences in the surgical techniques between participating centers. However, the large sample size decreases the likelihood of type 2 errors. Second, while multivariable logistic regression models were used to adjust for measured confounders, unmeasured and unknown confounders may still play an important role. Only a large randomized trial could mitigate these effects. Third, as the study period is relatively long, the perioperative outcomes could have improved over the years investigated due to the developments in perioperative care and surgical techniques occurring during this period.

CONCLUSION

SIMRs for CRC with sCRLM can be performed with acceptable morbidity and mortality rates in experienced centers. The feasibility of this procedure is however mainly dependent on the type of colorectal and liver resection performed. Anatomically and technically major liver resections are associated with a higher risk of intraoperative unfavorable incidents, while only anatomically major liver resections are associated with a higher risk of surgical and severe morbidity, conversely, left-sided colectomies are associated with a lower risk of severe morbidity.

Ethical approval

The medical ethical committee of Brescia approved this study and waived the need to obtain informed consent due to its retrospective nature and the use of pseudonymized data. (Judgement's reference number: NP 5467).

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Author contribution

J.P.S., G.Z., M.A.H.: study conception and design, analysis and interpretation of data, and drafting of manuscript. Acquisition of data and critical revision done by all authors.

Conflicts of interest disclosure

The authors have no related conflicts of interest to declare.

Research registration unique identifying number (UIN)

1. Name of the registry: https://www.clinicaltrials.gov/
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Data statement

The data that support the findings of this study are available from the corresponding author, M.A.H., upon reasonable request. The data are not publicly available since this could compromise the privacy of research participants.

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