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The impact of synchronous liver resection on the risk of anastomotic leakage following elective colorectal resection. A propensity score match analysis on behalf of the *iCral* study group

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ABSTRACT

Introduction: how best to manage patients with colorectal cancer and synchronous liver metastasis is still controversial, with specific concerns of increased risk of postoperative complications following combined resection. We aimed at analyzing the influence of combined liver resection on the risk of anastomotic leak (AL) following colorectal resection.

Methods: we reviewed the iCral prospectively maintained database to compare the relative risk of AL of patients undergoing colorectal resection for cancer to that of patients receiving simultaneous liver and colorectal resection for cancer with isolated hepatic metastases. The incidence of AL was the primary outcome of the analysis. Perioperative details and postoperative complications were also appraised.

Results: out of a total of 996 patients who underwent colorectal resection for cancer, 206 receiving isolated colorectal resection were compared with a matched group of 53 patients undergoing simultaneous liver and colorectal resection. Combined surgery had greater operative time and resulted in longer postoperative hospitalization compared to colorectal resection alone. The proportion of overall morbidity following combined resection was significantly higher than after isolated colorectal resection (56.6% vs. 37.9%, $p = 0.021$). Overall, the two groups of patients did not differ neither on the rate of major postoperative complications, nor in terms of AL (9.4% vs. 6.3%, $p = 0.381$). At specific multivariate analysis, the duration of surgery was the only risk factor independently associated with the likelihood of AL.

Conclusions: combining hepatic with colorectal resection for the treatment of synchronous liver metastasis from colorectal cancer does not increase significantly the incidence of AL.

Introduction

Approximately 15–25% of colorectal cancer (CRC) patients present with metastatic disease at diagnosis, whereby 50–80% have disease dissemination confined to the liver [1–3]. In such circumstances, liver and colorectal tumor resection is considered the best treatment option, leading to 5-year overall survival rates approaching 50% [1,3–6].

In case of resectable synchronous colorectal liver metastasis (CRLM), whether liver resection should be performed as a staged operation or in combination with excision of the primary malignancy is still a matter of debate [6–11]. Recent years have seen a growing interest in simultaneous resections [3,6,11–13], and recent evidence including some comprehensive meta-analyses suggested some clinical advantages favoring combined resection over staged surgery [8,12,14]. Beside the obvious advantage of a single operation, combined resection may result in improved long-term survivals, avoiding the risk of hepatic and/or extrahepatic disease progression during the interval period [3,4,9]. Nevertheless, synchronous resections can be associated with a higher risk of

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perioperative morbidity related to both colorectal and hepatic procedures, particularly in the case of primary rectal malignancy and when major hepatectomy is undertaken [15–17]. With reference to colorectal resection, anastomotic leakage (AL) is one of the most serious postoperative complications, which not only conditions the immediate postoperative course, but may also affect negatively long-term oncological outcomes, mainly due to failure to return to intended adjuvant therapies [1,2,15,18,19]. In the setting of simultaneous resection of CRLM, this risk becomes even more important due to the increased complexity of the procedure, and the presence of advanced disease [6,18–20]. Despite previous demonstrations that overall complication rates do not significantly differ, a number of retrospective analyses on simultaneous resection of primary colorectal malignancy and liver metastases have reported increased incidence of AL as compared to staged colorectal resection and hepatectomy [1–3,15]. Actually, whether performing simultaneous liver resection may impair surgical outcomes of colorectal resection is still unclear [3,5,6].

The present study aimed to evaluate whether the combination with CRLM resection may influence the postoperative outcomes of CRC patients receiving surgery by analyzing a prospective nationwide multicenter observational database using propensity score matching analysis [21,22].

Material and methods

Data were collected from a prospective maintained database of consecutive patients undergoing colorectal resection from 19 Italian surgical centers participating in the *iCral* observational study from September 2017 to February 2020 [21]. The study protocol was approved by the regional ethics committee (Comitato Etico Regionale delle Marche - *CERM*) and registered at *ClinicalTrials.gov* (Identifier: NCT03560180) [21,22].

The database was retrospectively analyzed for all cases with diagnosis of adenocarcinoma submitted to elective colorectal resection with curative intent. Patients were thus divided into a group including patients who underwent isolated colorectal resection (CRR) and a group of patients with synchronous metastatic disease confined to the liver who received colorectal resection in combination with liver resection (CRLR). Exclusion criteria included the presence of proximal stoma diversion, *trans*-anal surgery, pregnancy, ongoing infections before surgery and surgery performed in association with hyperthermic intraperitoneal chemotherapy (HIPEC). Any type of surgical approach (conventional open, laparoscopic, robotic) was included, and outcomes of interest were primarily assessed according to an *intention to treat* principle of analysis.

Incidence of AL was the primary endpoint of the analysis. Secondary outcomes of interest included operative time, length of postoperative hospital stay (LOS), overall and major postoperative complications.

Due to the likelihood of significant differences on baseline characteristics between the two groups of patients, data were compared using propensity score matching (PSM).

Preoperative assessment featured triphasic contrast-enhanced total body computed tomography with or without abdominal magnetic resonance imaging (MRI). For each patient, indication for surgery was discussed in a multidisciplinary team meeting which included surgeons, oncologists, radiologists, endoscopists and radiation therapists.

Postoperatively, no routine imaging was performed and patients were followed by each surgical team. Postoperative morbidity was recorded and graded according to the classification proposed by *Dindo* et al. [23], with grade III-IV events being defined as major complications. Particularly, the diagnosis of AL [21] was defined as any of the following occurrence:

- *Clinical:* evidence of purulent or enteric liquid in abdominal drains
- *Radiological:* presence of perianastomotic collection in CT scan or leakage of contrast during enema studies
- *Surgical:* evidence of anastomotic dehiscence at reoperation

All ALs were considered regardless of their clinical significance. Major hepatectomy was defined as the resection of three or more *Couinaud* segments [24]. Mortality was defined as death while in the hospital service or within the first month following surgery.

Statistical analysis

Statistical analysis was performed using the SPSS version 24.0 for Windows (IBM, Armonk, NY, USA). According to the recommendations of *Lonjon* et al. [25], propensity score match analysis was performed between the two groups (CRR *vs*. CRLR) to minimize the risk of selection bias. The PSM analysis was performed in a 1:4 match using the nearest-neighbor matching method with no replacement to diminish the biases from the different distribution of covariables. Matching was done when the difference in the logit of PSM between nearest neighbors was within a caliper-width equal to 0.2 times the SD of the logit of the PSM. The two groups were thus matched for the following variables: age, gender, ASA, BMI, diabetes, chronic renal failure, dialysis, cirrhosis, use of steroids, neoadjuvant chemotherapy, associated surgical procedures, surgical approach, type of colorectal resection and anastomosis technique (Table 1).

Continuous variables with normal distribution are reported as mean ± standard deviation and compared using 2-sided Student t tests, whereas categorical variables are expressed as the number with percentage. Non-normally distributed continuous data are reported as median (InterQuartile Range, IQR) values and compared with the Mann-Whitney *U* test. The distribution of variables was analyzed using the Kolmogorov–Smirnov test. The comparison of categorical variables was performed using the χ^2 test with the Yates correction or Fisher's exact test when appropriate.

To identify variables that were independent predictors of outcome, a logistic regression analysis with backward stepwise selection was constructed employing those variables with a significant level of $p < 0.20$ at univariate analysis. Receiver operating curve (ROC) analysis was also undertaken to identify an operating time cutoff value for predicting anastomotic leakage. Statistical significance was set at $p < 0.05$.

Results

Out of 1609 patients enrolled in the study, 996 patients (61.9%) met the inclusion criteria and entered the analysis, whereby 69 received CRLR and 927 underwent only CRR. Baseline characteristics of the included patients are given in Table 1.

Before PSM, in the CRLR group there was a significantly higher rate of patients with ASA score III-IV (65.2% *vs.* 41.2%, p < 0.001), cirrhosis (7.2 *vs.* 1%, p < 0.001), and prior neoadjuvant chemotherapy (21.7% *vs.* 2.4%, p < 0.001), whereas the proportion of patients with impaired renal function was not significantly lower as compared to the CRR group (0% *vs.* 5.7% $p = 0.202$). With regard to perioperative details, significant differences between CRLR and CRR were present as for the rate of open surgical approach (58 *vs.* 20.5%, $p < 0.001$), and associated surgical procedures (5.8% *vs.* 0.9% $p = 0.002$). The two groups did not differ significantly on the type of colorectal resection ($p = 0.304$), and anastomotic technique ($p = 0.170$). After PSM, 53 patients in the CRLR group and 206

Table 1
Baseline characteristics of included patients before and after propensity score matching (PSM). CRLR: ColoRectal and Liver Resection; CRR: ColoRectal Resection.

	Pre PS match			Post PS match		
	CRLR Group (n.° = 69)	CRR Group (n.° = 927)	p	CRLR Group (n.° = 53 pz)	CRR Group (n.° = 206 pz)	p
Age	69.29 (59–79)	72.8 (64–80)	0.093	70.08 (64–79)	73.91 (63–81)	0.448
Sex (Male)	39 (56.5%)	504 (54.4%)	0.825	33 (62.3%)	114 (55.3%)	0.437
BMI	25.80 (22.42–28.98)	25.36 (22.86–28.13)	0.645	25.01 (23.40–28.40)	25.65 (22.65–28.60)	0.899
ASA class			<0.001			>0.999
I-II	24 (34.8%)	545 (58.8%)		20 (37.7%)	77 (37.4%)	
III-IV	45 (65.2%)	382 (41.2%)		33 (62.3%)	129 (62.6%)	
Diabetes	6 (8.7%)	144 (15.5%)	0.175	6 (11.3%)	23 (11.2%)	>0.999
Chronic renal failure	0	53 (5.7%)	0.202	0	0	NA
Dialysis	0	1 (0.1%)	>0.999	0	0	NA
Cirrhosis	5 (7.2%)	9 (1.0%)	<0.001	2 (3.8%)	5 (2.4%)	0.634
Steroids	0	21 (2.3%)	0.956	0	0	NA
Neoadjuvant Chemotherapy	15 (21.7%)	22 (2.4%)	<0.001	3 (5.7%)	16 (7.8%)	0.772
Initial Open approach	40 (58.0%)	190 (20.5%)	<0.001	27 (50.9%)	74 (35.9%)	0.066
Colorectal resection			0.304			0.991
Right Hemicolectomy	31 (45.0%)	468 (50.5%)		26 (49.1%)	94 (45.6%)	
Left Hemicolectomy	19 (27.5%)	232 25.0%)		12 (22.6%)	51 (24.8%)	
Anterior Rectal Resection	16 (23.2%)	153 (16.5%)		12 (22.6%)	50 (24.3%)	
Splenic flexure resection	2 (2.9%)	39 (4.2%)		2 (3.8%)	8 (3.9%)	
Transverse resection	1 (1.4%)	25 (2.7%)		1 (1.9%)	3 (1.5%)	
Other	0	10 (1.1%)		0	0	
Additional procedures(s)	4 (5.8%)	8 (0.9%)	0.002	3 (5.7%)	4 (1.9%)	0.153
Stapled anastomosis	59 (85.5%)	794 (85.7%)	0.021	45 (84.9%)	175 (85.0%)	>0.999
Anastomosis technique			0.170			0.952
Side-to-Side isoperistaltic	35 (50.7%)	402 (43.4%)		28 (52.8%)	105 (51.0%)	
End-to-End	33 (47.9%)	339 (36.6%)		24 (45.3%)	96 (46.6%)	
Side-to-Side antiperistaltic	0	72 (7.8%)		0	0	
Side-to-End	1 (1.4%)	70 (7.6%)		1 (1.9%)	5 (2.4%)	
End-to-Side	0	44 (4.7%)		0	0	

patients in the CRR group were eventually analyzed. The two study groups were well-balanced with a mean difference for each covariable of less than 0.25. According to the surgical technique the patient were originally approached (intention to treat) the two groups did not differ significantly ($p = 0.066$, see Table 1).When initial open and laparoscopic procedures converted to open surgery were combined, the CRLR had significantly lower procedures completed in a minimally invasive fashion as compared to the CR group ($p = 0.01$, see Table 2).

For all CRLR surgeries, the same surgical team performed both the colorectal and the hepatic step of the procedure. The mean number of hepatic lesions was 3 ± 4.4 per patient (median: 1, IQR 1–3). A minor hepatectomy was performed in the vast majority of patients (92.5%), mostly as single or multiple wedge resection. Of note, nearly a half of the procedures included at least one resection in the posterosuperior segments (i.e. S7 or S8).

As for associated surgical procedure, in the CRR group there were 2 patients receiving bowel resections, 1 patient receiving partial bladder resection and 1 patient receiving unilateral oophorectomy, while in the CRLR group there were 3 patients receiving unilateral oophorectomy. 49.1% of patients received surgery with a minimally invasive approach in the CRLR group, while

Table 2
Operative and post-operative characteristics of included patients after PSM. Variables are reported as values (with percentages), median (with IQR), or mean (with standard deviation). CRLR: ColoRectal and Liver Resection; CRR: ColoRectal Resection.

	Post PS match		
	CRLR Group (n:° = 53)	CR Group (n.° = 206)	p
Duration of surgery	268 (200–355)	150 (120–200)	<0.001
Initial Laparoscopy	260 (180–360)	162 (131–216)	<0.001
Initial Open	270 (237–336)	135 (105–176)	<0.001
Conversions (% on laparoscopy)	7 (26.9%)	15 (11.4%)	0.058
Open Approach (initial or laparoscopic converted)	34 (64.2%)	89 (43.2%)	0.010
Liver resection			
Wedge resection	27 (50.9%)	–	–
Multiple wedge resection	17 (32.1%)	–	–
Segmentectomy	5 (9.4%)	–	–
Major hepatectomy	4 (7.5%)	–	–
Mean number of hepatic lesions per patient	3 (±4.4)	–	–
Posterosuperior segments	27 (50.9%)	–	–
Perioperative transfusion	12 (22.6%)	40 (19.4%)	0.741
Overall Complications	30 (56.6%)	78 (37.9%)	0.021
Major Complications	7 (13.2%)	21 (10.2%)	0.702
Anastomotic leakage	5 (9.4%)	13 (6.3%)	0.381
Re-operation	4 (7.5%)	19 (9.2%)	0.910
Mortality	1 (1.9%)	4 (1.9%)	>0.999
Hospital stay	8 (6–12.5)	7 (5–8)	0.001

this proportion was 64.1% in the CRR group ($p = 0.066$). The conversion rate to open surgery was 11.4%, with no statistical difference between CRR and CRLR (11.4% *vs.* 26.9%, $p = 0.058$). The perioperative transfusion rate in the two groups was similar.

Simultaneous liver and colorectal resection was associated with a significantly longer median operative time (268 min, IQR 200–355) as compared to isolated CRR (150 min, IQR 120–200) for both open and laparoscopic surgeries ($p < 0.001$).

Overall, 108 patients (41.7%) experienced postoperative complications, of which 78 (37.9%) in the CRR group and 30 (56.6%) in the CRLR group, with a significant difference ($p = 0.021$). The overall incidence of major postoperative morbidity was 10.8% (28 patients), and it was not significantly higher following CRLR as compared to CRR alone ($p = 0.702$). The incidence of AL was slightly higher in the CRLR group (9.4% *vs.* 6.3%), although this difference did not reach statistical significance ($p = 0.381$). The management of AL did differ significantly between the two groups, with higher proportion of radiological treatment (i.e. percutaneous drainage) in the CRLR group (60%) and higher rate of surgical treatment (i.e. re-intervention) in the CR group (92.3%, $p = 0.008$).

Median LOS was significantly longer following CRLR (8 days, IQR 6–13) than after CRR (7 days, IQR 5–8, $p = 0.001$). Overall mortality was identical for the two groups (1.9%). Perioperative data, including operative details and main outcomes are summarized in Table 2.

Specific univariate analysis revealed that sex, diabetes, cirrhosis, open surgical approach, duration of surgery, as well as combined surgery were not specific risk factor for AL ($p = 0.078$, Table 3). According to the logistic regression model, on the multivariate analysis the duration of the surgery was the only independent risk factor of AL (OR 1.008, 95% CI 1.003–1.013; $p = 0.001$, Table 4). At the analysis of the ROC curve, an operative time greater than 237 min was associated with an OR of 4.28 (CI 1.593–11.497; $p = 0.004$) of developing AL.

Table 4
Risk factors for anastomotic leakage (AL): multivariate analysis. Only variables with a significant level of $p < 0.20$ at univariate analysis have been included. OR: Odd Ratio (with 95% Confidence Interval).

	OR (95% CI)	p
Sex (Male)	2.119 (0.640–7.018)	0.219
Diabetes	1.544 (0.393–6.065)	0.533
Cirrhosis	6.396 (0.889–45.993)	0.065
Neoadjuvant chemotherapy		
Approach		
Open	0.497 (0.122–2.030)	0.330
Laparoscopic	0.382 (0.097–1.507)	0.169
Open or converted	2.322 (0.806–6.689)	0.118
Duration of surgery	1.008 (1.003–1.013)	0.001

Discussion

The management of CRC patients with synchronous liver metastasis is challenging and the only chance of curative-intent treatment implies surgical extirpation of both sites of disease. However, the optimal timing and sequence of each procedure is still controversial [1,3,7,9]. In the case of CRC presenting with resectable, isolated hepatic metastasis, simultaneous resection reduces the risk of disease progression and presents the evident advantage of requiring a single procedure [3,4,6,9]. On the other hand, it may result in higher incidence of postoperative complications, and particularly anastomosis-related morbidity, which generally accounts for the vast majority of surgical morbidity and re-operation rate following combined resection [5,14,16]. Despite the recent

Table 3
Risk factors for anastomotic leakage (AL): univariate analysis. Variables are reported as values (with percentages) or median (with IQR).

	AL (n:° = 18)	No AL (n.° = 241)	p
Age	69.3 (63–77)	73 (63–81)	0.606
Sex (Male)	14 (77.8%)	133 (55.2%)	0.105
BMI	24.9 (22.0–28.9)	25.6 (22.9–28.5)	0.601
ASA class			0.531
I-II	5 (27.8%)	92 (38.2%)	
III-IV	13 (72.2%)	149 (61.8%)	
Diabetes	4 (22.2%)	25 (10.4%)	0.127
Cirrhosis	2 (11.1%)	5 (2.1%)	0.078
Neoadjuvant chemotherapy	1 (5.6%)	18 (7.5%)	>0.999
Approach			
Open	8 (44.4%)	93 (38.6%)	0.055
Laparoscopic	6 (33.3%)	130 (53.9%)	
Converted	4 (22.2%)	18 (7.5%)	
Open or converted	12 (66.7%)	111 (46.1%)	0.149
CRLR Group	5 (27.8%)	48 (19.9%)	0.381
Colorectal resection			0.637
Right Hemicolectomy	7 (38.9%)	113 (46.9%)	
Left Hemicolectomy	4 (22.2%)	59 (24.5%))	
Anterior Rectal Resection	5 (27.8%)	57 (23.7%)	
Splenic flexure resection	1 (5.6%)	9 (3.7%)	
Transverse resection	1 (5.6%)	3 (1.2%)	
Additional procedures	–	7 (2.9%)	>0.999
Stapled anastomosis	17 (94.4%)	203 (84.2%)	0.490
Anastomosis technique			0.638
Side-to-Side isoperistaltic	9 (50%)	124 (51.5%)	
End-to-End	8 (44.4%)	112 (46.5%)	
Side-to-End	1 (5.6%)	5 (2.1%)	
Duration of surgery (minutes)	242 (157–353)	160 (129–228)	0.078
Perioperative transfusion	3 (16.7%)	28 (11.7%)	0.463

diffusion of simultaneous surgery for stage IV CRC, the actual burden of the risk of AL following simultaneous CRLR has rarely been examined in detail. Currently available evidence is mainly limited by its retrospective nature, the lack of considerable caseload and the presence of several selection biases, largely due to the fact that the choice of proceeding with sequential resection is more likely for patients with advanced *T-stage* and extended metastasis burden in the liver [1,3,6,9,13]. Accordingly, we aimed at evaluating a large cohort of patients from a prospectively maintained database, from which unselected patients undergoing simultaneous resection were compared to a corresponding, well balanced group of patients undergoing isolated CRR with comparable baseline and perioperative characteristics. Of note, the two study groups were matched on the proportion of neoadjuvated patients, type of initial surgical approach, type of colorectal procedure and anastomosis technique. Our primary endpoint was to determine whether the risk of AL following CRC resection is influenced by concomitant resection of liver metastasis. Interestingly, while there was significant difference in terms of methods of diagnosis and management, the relative incidence of anastomotic leaks differed without statistical significance between the two groups.

This finding is consistent with that observed by *Boudjema* et al., who recently published the results of a timely and elegant prospective, randomized controlled trial comparing simultaneous versus delayed resection for resectable synchronous colorectal cancer liver metastasis [3]. The primary outcomes of interest were the incidence of major postoperative morbidity occurring at both colorectal and liver sites, while secondary outcomes included overall and disease-free survival. The authors pooled a total of 105 patients and found that there were no statistically significant differences between the two groups of patients in terms of major complications. Interestingly, with the incidence of digestive complications in particular, the occurrence of anastomotic-related events, such as peritonitis, intra-abdominal abscess and AL was more frequently observed in the group of patients receiving simultaneous resection as compared to those patient undergoing surgery with a staged approach, although this difference did not elicit statistical significance ($p = 0.08$).

The largest evidence upon the topic is that published by *Synder and colleagues,* who recently investigated the available data on isolated resection of primary CRC, isolated resection of CRLM, and simultaneous CRLR from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) [16]. Between 2014 and 2017, on a total of more nearly 31 000 procedures identified, there were more than 23 000 isolated CRRs and nearly 600 combined CRLRs. Overall, both medical and surgery-related postoperative complications occurred with higher incidence within the group of patients receiving CRLR compared to colectomy or hepatectomy alone. Similarly, the percentage of patients with major complication was significantly higher following CRLR (29.9%) compared to isolated CRR (22.2%) or hepatectomy alone (17.1%). Interestingly, the risk of AL, as well as also that of postoperative ileus increased significantly following simultaneous CRLR (7.9% *vs.* 3.8%, and 36.4% *vs.* 19.1%, respectively). Specific adjusted analyses were performed after controlling for potential confounding factors affecting the risk of postoperative complications, and patients receiving CRLR were still associated with increased rates of overall and major morbidity. Unfortunately, patients were analyzed and compared regardless of type of colonic and liver resection, use of portal clamping, baseline characteristics, medication, surgical approach and anastomotic technique (including the presence of diverting stoma). Hence, data concerning the risk of AL were likely to be biased by unbalanced, inhomogeneous groups of comparison [6,16].

The predictive risk of AL following simultaneous CRLR of metastatic CRC patients was investigated also by *Nakajima* et al., who retrospectively reviewed the medical records of 86 patients undergoing CRLR and compared their outcomes to those of nearly 1700 patients receiving isolated CRR [6]. Interestingly, in the CRLR group, 64% of patients went on to develop complications, compared to 32% in the CRR group. Particularly, 21% of patients had leakage following combined resection, while only 7% of patients had leakage following isolated CRR. At the same time, similar to our results, multivariate analyses revealed that longer operative time was the only independent predictive factor for AL following CRLR. Particularly, the incidence of AL was 50% in patients who had operative time >8 h, while it was 13% in patients with operation time equal or less than 8 h. However, besides the specific merits of including an impressive caseload and the accuracy of the analysis, the generalizability of results was mainly limited by unbalanced groups of comparison and the presence of specific confounding factors in the evaluation of the risk of AL, such as the inclusion of patients with diversion stoma.

In our analysis about 64% and 50% of patients in the CRR and CRLR group received surgery with a minimally invasive approach, respectively. This finding reflects the general trend of diffusion of MIS, which is broadly adopted in colorectal surgery and is being increasingly embraced for liver surgery and in the setting of synchronous disease to carry out a simultaneous CRLR [1,11,26]. Actually, data from large databases and recent meta-analyses shows that a minimally invasive approach is as appropriate as traditional open surgery for simultaneous CRLR, with distinct advantages in terms of blood loss and abbreviated postoperative hospitalization [26–29]. At the same time, the rate of postoperative complications, as well as oncological long-term outcomes showed no significant differences between the two approaches [29–31]. However, even in experienced centers with dedicated surgical teams, careful patients selection is crucial, and recent studies indicate that MIS is still deemed suitable mostly for cases that do not require extensive hepatectomy [1,26,27,29].

To our knowledge, our study is the first large clinical, matched analysis specifically focusing on the impact of liver resection on the risk of AL following synchronous surgical management of patients with stage IV CRC. By employing propensity score matching, we have been able to compare two well-matched groups of patients and provide reliable evidence of clinical practice. Despite the relative proportions of patients who eventually received an open procedure (initial open or laparoscopic converted) were significantly different, the two groups of patients were similar according to the intention to treat principle, as the rates of minimally invasive surgical approach were similar between the CRLR and CR group. In our analysis, secondary outcomes of interest included the relative incidence of postoperative overall and major morbidity between the CRR and CLCR group. Our analysis also demonstrated that the relative rates of overall morbidity in the postoperative course were sensibly higher following combined resections, while the proportion of patients experiencing severe complications did not discord significantly between CRR and CRLR. At this regard, our results are still consistent with findings of previous meta-analyses published upon the argument [6,8,12,13,16], although the vast majority of previous reports did compare the outcomes of simultaneous resection to those of staged surgery for patients with metastatic disease, while this was not the case in our analysis and this implies a substantial difference with respect to previous reports.

A number of risk factors for AL following colorectal surgery have been investigated by various reports [19]' [-22,20]' [32,33]. There are several factors such as obesity, level of anastomosis, prior chemoradiation, urgent/emergent surgery and coronary heart disease, which have been overtly demonstrated to negatively affect the incidence of AL [32,33]. The *iCral* study group recently investigated specific risk factors for adverse events following colorectal surgery by prospectively enrolling > 1500 patients receiving elective colorectal surgery with anastomosis [22]. Overall, the rate of AL was 4.9%. Multivariate analysis revealed that perioperative blood transfusion was the only independent risk factor affecting the incidence of AL, with a specific OR of 8.15.

Conversely, the effect of associating liver resection to CRR in the setting of malignancy has been studied only limitedly so far, generally with the limits derived from the lack of a control group or unmatched comparison. Traditionally, concerns have been raised that portal clamping by the *Pringle* maneuver during liver parenchymal transection may predispose to a higher risk of AL owing to venous engorgement and bowel edema. However, the general policy of performing intermittent clamping of the hepatic pedicle is demonstrated to protect intestinal microcirculation from ischaemic sufferance [5]. Actually, even in the case of major hepatectomy, an increased anastomotic-related complications has not be reported, provided no clinical liver failure develops postoperatively [5,34]. Still, specific investigations on the argument are still lacking [3,9,11]. Indeed, even in the setting of a randomized controlled trial, such as that published by *Boudjema* et al., unbalances in the distribution of site of primary malignancy and extent of hepatectomy were acknowledged [3]. This reflects the intrinsic difficulty of running reliable analyses comparing combined CRLR with a control procedure. Nevertheless, our analysis has specific merits, essentially due to the use of a propensity score for matching the two groups of patients and the prospective nature of our database, which together increase the reliability of data collection and analysis. Given the increasing diffusion of combined CRLR for CRC with synchronous liver metastasis, our findings may provide useful data with important clinical implications [7,9,11,34–36]. In particular, our analysis confirms that careful patient selection is crucial in identifying candidates to concomitant CRLR. Preoperative therapies or other factors increasing the likelihood of postoperative liver insufficiency should be considered as relative contraindications. Also, extensive liver disease, as well as unfavorable anatomic accessibility which may likely determine complex and longer procedures should be carefully evaluated. This is particularly true in the case of primary rectal cancer, when the colorectal procedure may require more intricate and prolonged dissections. Finally, possible intraoperative difficulties encountered during colorectal or liver resection should lead to consideration of switching the procedure to a single resection, postponing the hepatic or colorectal phase of the procedure to staged surgery.

The findings of the present analysis should be interpreted with the caution due to the presence of several specific limitations. First, our study has a non-randomized design, and despite propensity score matching, a number of selection biases could not be avoided. Actually, although our findings are derived by analyzing the data of multiple institutions, combined resections were mainly performed in few centers dedicated to hepatobiliary and advanced oncological surgery. Second, the relatively low caseload, especially with regard to the CRLR group, limits the generalizability of our findings. Finally, perioperative management pathways were not standardized among institutions [37], and the general outcomes may have been influenced by this issue, at least in part.

Conclusions

Our results suggest that although simultaneous resection may be associated with higher incidence of postoperative morbidity, the rates of major complications and AL in particular are comparable to that of patients receiving CRR alone.

The Italian Colorectal Anastomotic Leakage (iCral) Study Group members

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CRediT authorship contribution statement

Francesco Guerra: Project administration, Writing – original draft, Writing – review & editing, Final approval. **Filippo Petrelli:** Data acquisition, Writing – original draft, Writing – review & editing, final approval. **Paola Antonella Greco:** Data acquisition, Writing – original draft, Writing – review & editing, Final approval. **Valerio Sisti:** Data acquisition, Writing – original draft, Writing – review & editing, Final approval. **Marco Catarci:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing, Final approval. **Roberto Montalti:** Project administration, Data acquisition, Formal analysis, Writing – original draft, Writing – review & editing, Final approval. **Alberto Patriti:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing, final approval.

Declaration of competing interest

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