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Extended right colectomy, left colectomy, or segmental left colectomy for splenic flexure carcinomas: a European multicenter propensity score matching analysis

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Abstract

Background The surgical resection of the splenic flexure carcinoma (SFC) is challenging and the optimal surgical procedure for SFCs remains a matter of debate. The present study aimed to compare in a multicenter European sample of patients the short- and long-term outcomes of extended right (ERC) vs. left (LC) vs. segmental left colectomy (SLC) for SFCs.

Methods This retrospective multicenter study analyzed the surgical and oncological outcomes of SFC patients undergoing elective curative intent surgery between 2000 and 2018. Descriptive and exploratory analyses were first conducted on the whole sample. Outcomes of the different procedures (ERC vs. LC vs. SLC) were then compared using propensity score matching for multilevel treatment. Overall (OS) and disease-free survival (DFS) were evaluated by Kaplan–Meier method.

Results From a total of 399 SFC patients, 143 (35.8%) underwent ERC, 131 (32.8%) underwent LC, and 125 (31.4%) underwent SLC. Overall, 297 (74.4%) were laparoscopic procedures. An increase in operative time, time to flatus, time to regular diet, and hospital stay was observed with the progressive extension of SFC resection. ERC was associated with significantly increased risk of postoperative ileus compared to both LC and SLC. A significantly greater number of lymph nodes were retrieved by ERC, but the objective of at least 12 retrieved lymph nodes was achieved in 85% of patients, without procedure-related differences. No differences were observed in OS or DFS between ERC, LC, and SLC.

Conclusion The present study supports the resection of SFCs by colon-sparing surgical techniques, such as SLC.

Keywords Splenic flexure carcinoma · Extended right colectomy · Left colectomy · Segmental left colectomy · Propensity score matching · Postoperative complications

Splenic flexure carcinomas (SFCs) have traditionally been defined as the tumors arising from the portion between the distal third of the transverse colon and the proximal part of the descending colon [1, 2]. More recently, some authors limited the definition to tumors located within 10 cm of the splenic flexure edge [3, 4]. SFCs represent less than 10% of all colorectal cancers [2, 5], but they have been associated with a poorer prognosis compared to other colonic locations due to the high risks of presentation as an emergency or at an advanced stage [2, 6].

Achieving a complete tumor resection with free margins and adequate lymph node retrieval can be challenging for cancers located at the splenic flexure [7]. Nonetheless, SFCs have been systematically excluded from the main randomized clinical trials (RCTs) that evaluated the use of laparoscopy for colon cancer resection [8].

In this scenario, studies specifically focusing on the surgical outcomes of SFC patients are scarce, and no clear evidence exists on the gold standard surgical approach and extent of resection [3, 4, 8–31]. Overall, three main types of surgical procedures have been described: the extended

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right colectomy (ERC), the left colectomy (LC) and the segmental left colectomy (SLC) [8]. Evidence-based criteria for assisting surgeons' decisions are lacking, and previous comparisons between ERC, LC and SLC procedures found inconclusive results. Some authors advocate for extended resections of SFCs due to the highly heterogeneous blood supply and lymphatic drainage of the splenic flexure [1], whereas others support colon-sparing options to avoid an unnecessary resection of the middle colic artery and to preserve colonic length [24, 32].

The present study aims to evaluate and compare the short- and long-term outcomes of three different surgical procedures (i.e., ERC, LC, and SLC) performed for the elective treatment of SFCs in a large, multicenter European sample of SFC patients.

Materials and Methods

Study design

The *SFC Study Group* was established in March 2017 with the aim of building a European multicenter database of SFC patients who underwent surgical resection between January 2000 and January 2018. The SFC study group comprised 11 surgical units from tertiary care centers in 6 European countries. Each participating center contributed data retrieved from prospectively maintained local databases that were input into a single common database used for the statistical analyses in the present study. Patients signed an informed consent for the use of their personal data for scientific purposes. Due to the retrospective design of the project, which was conducted exclusively on anonymous patients' records, no institutional review board was required. All personal data were treated in conformity to the principles declared to the National Commission for Data Protection and Liberties and the study was reported following the recommendations listed in the STROBE checklist for cohort and case–control studies [33].

Study population

Patients' records were selected to be included in the SFC database and were further extracted for the present statistical analyses if they met the following criteria: adults aged > 18 years; radiologically (by total body computed tomography [CT] and positron emission tomography [PET] in cases of suspected lymphatic packets), clinically, and histologically proven colon cancer located at the splenic flexure or up to 10 cm proximal towards the transverse colon or 10 cm distal towards the descending colon (as assessed on the preoperative CT scan) [4, 8, 17]; SFCs graded as AJCC TNM stage I to IV [34]; curative intent surgical resection; elective surgery setting; and one- or two-stage surgery (via temporary stoma). Patients with more than one carcinoma of the colon and polyposis coli were excluded.

Three types of surgical procedures were considered: ERC, LC, and SLC [8]. The ERC procedure consists of the resection of the terminal ileum and the right, transverse, and proximal descending colon, in which the ileocolic, right colic, middle colic, and left colic arteries are ligated, and an anastomosis between the ileum and the colon is performed [17, 20]. The LC procedure consists of the resection of the colonic segment between the left third of the transverse colon and the colorectal juncture (i.e., left half of the colon). The inferior mesenteric artery and the left branch of the middle colic artery are ligated at their origins, and a colorectal anastomosis is performed [4, 13, 20]. The SLC procedure consists of the resection of the distal part of the transverse colon, the splenic flexure and the proximal descending colon. The left colic artery and left branches of the middle colic vessels are ligated, and a colo-colonic anastomosis is performed between the transverse and descending sigmoid colon [9, 35].

Two types of surgical approaches were considered: laparoscopy and open surgery.

All patients were operated on by experienced colorectal surgeons. The perioperative care and follow-up was guided by the local multidisciplinary team in all participating centers. Adjuvant chemotherapy was considered for patients with AJCC TNM stage III/IV disease and unfavorable tumor characteristics. Follow-up was continued for at least 5 years, including blood tests (e.g., CEA levels), abdominal and chest CT scans, full colonoscopy and selective use of biopsies in case of suspected recurrence.

Study outcomes

Study outcomes included: intraoperative variables (e.g., operative time, blood loss), postoperative variables (e.g., postoperative morbidity and mortality, length of hospital stay), quality of the surgical resection (e.g., resection margin status, number of retrieved lymph nodes) and overall (OS) and disease-free survival (DFS) up to 5 years.

Conversion was defined as a premature interruption of the laparoscopic approach before the resection phase was concluded [36]. Postoperative morbidity and mortality were defined as events that occurred during the hospital stay or within 90 days after surgery. Postoperative complications were graded according to the Dindo-Clavien classification; complications graded as Dindo-Clavien III or higher were considered as severe postoperative complications [37]. Postoperative ileus was defined as the absence of bowel movements or flatus associated with intolerance of oral intake lasting more than 3 days postoperatively [38]. An R0 resection was defined as macroscopically complete removal of the tumor with a microscopically free resection margin and no peritoneal spread.

Statistical analysis

Descriptive and exploratory analyses

Statistical analyses were performed using R 3.5.1 [39]. For descriptive analyses, means (sd) and counts (%) were provided for continuous and categorical variables, respectively, and for each group of surgical procedures (ERC, LC, SLC). The first comparisons were carried out by applying Chi-squared tests for categorical variables and ANOVA tests for continuous variables. For this preliminary descriptive step, *p* values were given without any adjustment for multiple testing. In order to highlight graphical differences within the 3 groups of surgical procedures, a principle component analysis was also conducted on the continuous variables of interest.

Propensity score matching

In order to minimize the selection bias inherent in a retrospective study design, and to compare the three groups by taking into account covariates that may have potentially influenced the selection of ERC, LC or SLC procedures, we applied the propensity score matching (PSM) method for three groups, as described in Bryer et al. [40] For each group (ERC, LC, SLC), propensity scores were calculated by running logistic regression models that included the following covariates: age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, comorbidity > 1, tumor size on preoperative CT scan, tumor category (pT), node category (pN), metastasis category (pM), surgical approach (laparoscopic vs. open surgery), and year of surgery. The type of surgical procedure (LC vs. ERC, SLC vs. ERC and LC vs. SLC) was entered into the regression model as the dependent variable. Caliper matching method was used to minimize the number of retained triplets (i.e., to reduce the number of duplicate treatments units). The three matched groups were then evaluated with respect to the study endpoints. Global (respectively, Two-by-Two) comparisons between ERC, LC and SLC groups were performed using ANOVA (respectively, paired T-tests) for continuous variables and Chi-squared (respectively, McNemar) tests for categorical variables. All *p* values were adjusted for multiple comparisons using the Benjamini & Yekutieli correction [41]. In addition, for categorical variables that reached statistical significance, Odds ratios (OR) were calculated and provided with their 95% confidence interval (CI).

Survival analyses

As pointed by several authors [42–46], cox regression models applied to the entire cohort could be often more powerful tools in detecting treatment effects as compared with matched studies. Therefore, survival analyses were carried out on the whole sample. Overall Survival (OS) was defined as the time from surgery to death and was censored at the last follow-up date if no events occurred. Disease-Free Survival (DFS) was defined as the time from surgery to disease recurrence and was censored at the last follow-up date if no events occurred. First, Kaplan–Meier curves were provided for OS and DFS, with a log rank (Mantel–Cox) test for group comparisons. Then, a stepwise variable selection procedure (with iterations between the 'forward' and 'backward' steps and a control of variance inflating factors values) was used to obtain the best candidates final regression models for both OS and DFS. Adjusted HR for both best candidates was given with their 95% confidence intervals. For both models, proportional hazards assumptions were tested using the scaled Schoenfeld residuals.

Results

The present study population comprised 399 SFC patients who met the selection criteria. According to the type of surgical procedure, 143 (35.8%) patients underwent ERC, 131 (32.8%) underwent LC, and 125 (31.3%) underwent SLC. No difference in tumor location was observed between the three groups. No preemptive diversion or endoscopic stenting was performed. Overall, 297 (74.4%) patients were operated on via laparoscopic surgery.

Demographic, clinical and oncological variables of the whole study population and by surgical procedure are presented in Table 1. Compared to the other surgical procedures, ERC was most commonly performed in patients with a weight loss > 10% and presenting with more than one comorbidity. Conversely, in patients who had undergone previous abdominal surgery, SLC was performed more frequently compared to the other approaches. No significant group differences were observed for tumor characteristics, size, and differentiation and AJCC stage.

Explorative data analysis by Principal Component Analysis (Fig. 1) showed that ERC patients formed a larger cluster to the top and right as compared with others. Looking at the first two axes (that explained 68.5% of the total variability), showed that ERC are characterized by higher values for hospital stay, time to regular diet and time to flatus (x

Table 1 Demographic, clinical, imaging, and histological/oncological characteristics of SFC patients operated on by ERC, LC, and SLC

	Whole sample (*n* = 399)	ERC (*n* = 143)	LC (*n* = 131)	SLC (*n* = 125)	*p* value
Demographic and clinical variables					
Gender (M/F) [*n*]	235/164	83/60	81/50	71/54	0.692
Age (year) [median(range)]	68 (35–96.4)	68 (35–91)	68 (44–94.2)	68.2 (38–96.4)	0.852
Age > 75 (year) [*n*(%)]	112 (28.1)	36 (25.2)	44 (33.6)	32 (25.6)	0.229
BMI (kg/m^2) [median(range)]	26 (16–42)	26 (16–42)	26.3 (18–40.5)	25.4 (18–38)	0.759
Obesity (BMI ≥ 30 kg/m^2) [*n*(%)]	71 (17.8)	21 (14.7)	25 (19.1)	25 (20)	0.470
ASA score [*n*%]					0.211
I–II	281 (70.4)	93 (65)	96 (73.3)	92 (73.6)	
III–IV	118 (29.6)	50 (35)	35 (26.7)	33 (26.4)	
Weight loss > 10% [*n*(%)]	53 (13.3)	29 (20.3)	13 (9.9)	11 (8.8)	**0.008**
Preoperative serum CEA (U/mL) [mean(SD)]	19.39 (90.47)	20.85 (80.49)	22.62 (127.18)	14.95 (50.90)	0.827
Comorbidities (> 1) [*n*(%)]	121 (30.3)	52 (36.4)	29 (22.1)	40 (32)	**0.033**
Diabetes [*n*(%)]	76 (19)	34 (23.8)	16 (12.2)	26 (20.8)	**0.043**
Cardiopulmonary diseases [*n*(%)]	197 (49.4)	80 (55.9)	56 (42.7)	61 (48.8)	0.091
Kidney failure [*n*(%)]	23 (5.8)	13 (9.1)	7 (5.3)	3 (2.4)	0.062
Neurocognitive disorders [*n*(%)]	18 (4.5)	10 (7)	4 (3.1)	4 (3.2)	0.203
Smoking [*n*(%)]	53 (13.3)	20 (14)	11 (8.4)	22 (17.6)	0.091
Previous abdominal surgery [*n*(%)]	131 (32.8)	35 (24.5)	39 (29.8)	57 (45.6)	**0.001**
Preoperative treatment [*n*(%)]					
Neoadjuvant chemotherapy	10 (2.5)	1 (0.7)	3 (2.3)	6 (4.8)	0.099
Surgical procedure [*n*(%)]					0.184
Laparoscopy	297 (74.4)	108 (75.5)	103 (78.6)	86 (68.8)	
Open surgery	102 (25.6)	35 (24.5)	28 (21.4)	39 (31.2)	
Type of procedure [*n*(%)]					0.293
Primary anastomosis	390 (97.7)	142 (99.3)	127 (96.9)	121 (96.8)	
Two-step procedure via temporary ostomy	9 (2.3)	1 (0.7)	4 (3.1)	4 (3.2)	
Type of anastomosis[a] [*n*(%)]					0.555
Mechanical	277 (71)	101 (71.1)	94 (74)	82 (67.8)	
Manual	113 (29)	41 (28.9)	33 (26)	39 (32.2)	
Preoperative imaging assessment on CT scan					
Tumor size (largest dimension, cm) [mean(SD)]	4.41 (1.73)	4.31 (1.78)	4.42 (1.64)	4.50 (1.76)	0.678
Peri-colic nodal involvement [*n*(%)]	128 (32.1)	52 (36.4)	37 (28.2)	39 (31.2)	0.344
Patients with suspected extracolic organ involvement [*n*(%)]	36 (9)	17 (11.9)	13 (9.9)	6 (4.8)	0.117
Suspected synchronous metastasis [*n*(%)]	43 (10.8)	9 (6.3)	19 (14.5)	15 (12)	0.079
Histological/oncological variables					
Stage of disease AJCC [*n*(%)]					0.086
I/II	238 (59.6)	81 (56.6)	89 (61.1)	77 (61.6)	
III	103 (25.8)	45 (31.5)	25 (19.1)	33 (26.4)	
IV	58 (14.5)	17 (11.9)	26 (19.8)	15 (12)	
Lymphovascular invasion [*n*(%)]	127 (31.8)	52 (36.4)	42 (32.1)	33 (26.4)	0.233
Perineural invasion [*n*(%)]	69 (17.3)	28 (19.6)	22 (19.8)	15 (12)	0.167
Tumor size (largest dimension, cm) [mean(SD)]	4.40 (2.01)	4.63 (2.06)	4.32 (2.08)	4.21 (1.86)	0.194
Tumor grade [*n*(%)]					0.126
Well differentiated	133 (33.3)	58 (40.6)	38 (29)	37 (29.6)	
Moderately differentiated	190 (47.6)	56 (39.2)	67 (51.1)	67 (53.6)	
Poorly differentiated	76 (19)	29 (20.2)	26 (19.9)	21 (16.8)	
Adjuvant treatment [*n*(%)]	165 (41.5)	64 (44.8)	57 (43.5)	44 (35.2)	0.236

Significant *p* values are indicated in bold

AJCC American Joint Committee on Cancer, *ASA* American Society of Anesthesiology, *BMI* body mass index, *CEA* carcinoembryonic antigen, *CT* computed tomography, *ERC* extended right colectomy, *LC* left colectomy, *SLC* segmental left colectomy, *SFC* splenic flexure carcinoma

[a]Calculated for patients with a primary anastomosis

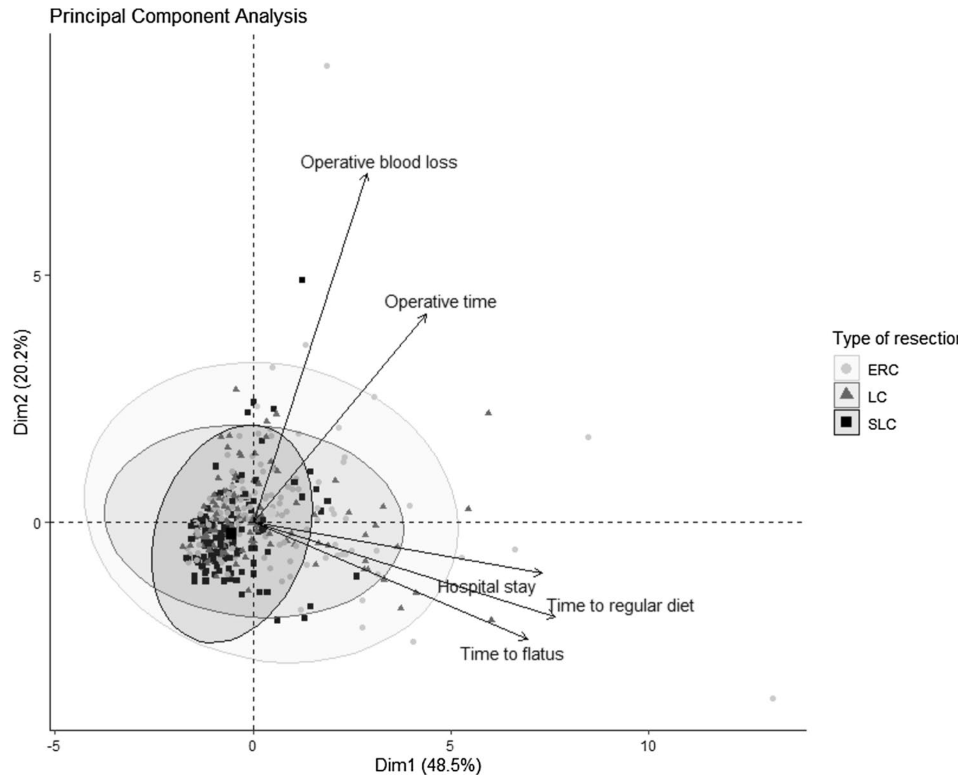


Fig. 1 Principal component analysis for the three types of surgical procedures. Extended right colectomy (ERC), left colectomy (LC), and segmental left colectomy (SLC)

axis), and also higher values for operative blood loss and operative time (y axis). These exploratory findings were confirmed with significant within-group differences after PSM (Table 2).

By applying PSM, the final matched sample was composed by 110 patients per group. No demographic, clinical and oncological variables showed a significant imbalance between the 3 groups after PSM. In addition, the multiple covariate balance plot of absolute standardized effect sizes before and after propensity score adjustment (Fig. 2) suggested reasonable balance has been achieved across all covariates and across three models since effect sizes were smaller than the unadjusted in most cases and relatively small.

Overall, conversion from laparoscopy to open surgery occurred in 32 (9.9%) patients, without procedure-related difference. Reasons for conversion included: uncontrollable bleeding during vascular pedicle dissection ($n=4$, 12.5%), impossible adhesiolysis ($n=5$, 15.6%), technical difficulties due to tumor invasion of an adjacent organ ($n=5$, 15.6%), and difficult exposure or inadequate visualization due to tumor fixation ($n=18$, 56.3%).

The rate of postoperative complications was higher among ERC patients (58.2%) compared to the SLC group (33.6%; $p<0.001$) and the LC group (43.6%; $p=0.043$), but there were no group differences in terms of severity (Dindo-Clavien classification) ($p=0.548$). Anastomotic leakage occurred in 29 (8.8%) patients, with no differences between groups. In total, 7 (6.4%) ERC patients, 12 (10.9%) LC patients, and 10 (9.1%) SLC patients presented with an anastomotic leakage. Of these, 19/29 (66%) required reoperation. Conversely, postoperative ileus was more frequently observed in ERC patients, who presented an increased risk by 8.43 times compared to the SLC group and by 3.97 times compared to the LC group. A faster recovery (time to flatus, time to regular diet and hospital stay) was observed for patients in the SLC group compared to the ERC group, with a mean difference of -1.7 days for time to flatus, -3.3 days for return to regular diet, and -5.7 days for hospital stay. No group differences were observed regarding 90 days mortality. An R0 resection was observed in 99.7% of the patients and in more than 80% of the patients at least 12 lymph nodes were retrieved during the operation, without procedure-related differences. However, a significantly higher mean number of retrieved lymph nodes was associated with the ERC procedure (Table 2).

Over a mean follow-up time of 41.74 (37.27) months, no group differences were observed in the OS or DFS rates, which are shown in Figs. 3 and 4, respectively. Disease recurrence over the entire follow-up period was observed in 77 (20%) patients: 29 (21.3%) in the ERC group, 25 (19.4%) in the LC group, and 23 (19.2%) in the SLC group ($p=0.89$). Overall, distant metastases were observed in 71 (18.4%) patients and local recurrence was observed in 10 (2.6%) patients, with no differences among the groups ($p=0.94$ and $p=0.95$, respectively). Distant recurrences included:

Table 2 Operative and postoperative outcomes in SFC patients after propensity score matching

Variables	ERC ($n=110$)	LC ($n=110$)	SLC ($n=110$)	Overall Comparison p value	Two-by-two comparisons p values (Odds Ratios, 95%CI)		
					ERC vs. LC	ERC vs. SLC	LC vs. SLC
Operative time (min) [mean(SD)]	232.8 (77.5)	225.1 (71.9)	204.7 (52.6)	**0.040**	1	**0.015**	0.093
Conversion to laparotomy[b] [n(%)]	7 (8.3)	19 (22.6)	6 (7.3)	0.133			
Operative blood loss (mL) [mean(SD)]	187 (224.7)	166.9 (111.7)	89 (94.5)	**< 0.001**	1	< 0.001	< 0.001
Number of intraoperative transfused patients [n(%)]	8 (7.3)	2 (1.8)	7 (6.4)	1			
Splenectomy for [n(%)]							
Oncological reason	7 (6.4)	8 (7.3)	4 (3.6)	1			
Hemostatic reason	1 (0.9)	5 (4.5)	0 (0.0)	0.454			
Intraoperative complication [n(%)]	4 (3.6)	13 (11.8)	3 (2.7)	0.221			
Patients with postoperative complication [n(%)]	64 (58.2)	48 (43.6)	37 (33.6)	0.056			
Anastomotic leakage[a] [n(%)]	7 (6.4)	12 (10.9)	10 (9.1)	1			
Postoperative ileus [n(%)]	36 (32.7)	12 (10.9)	6 (5.5)	**< 0.001**	**0.014** **3.97 (1.93–8.16)***	**< 0.001** **8.43 (3.38–21.04)***	1 2.12 (0.77–5.88)
Postoperative complication classified as Dindo-Clavien ≥ III [n(%)][d]	17 (26.6)	24 (50.0)	14 (37.8)	0.548			
Reoperation [n(%)]	14 (12.7)	18 (16.4)	6 (5.5)	0.536			
Time to flatus [mean(SD)]	4.6 (3.8)	3.5 (2.6)	2.9 (1.4)	**< 0.001**	0.0551	**< 0.001**	0.053
Return to regular diet [mean(SD)]	7.8 (6.1)	7.4 (5.5)	4.5 (1.8)	**< 0.001**	1	**< 0.001**	**< 0.001**
Hospital stay, days[c] [mean(SD)]	14.3 (13.3)	16.8 (20.9)	8.6 (4.6)	0.001	1	**< 0.001**	**0.002**
Mortality at 90 days [n(%)]	8 (7.3)	1 (0.9)	7 (6.4)	0.702			
Readmission within 60 days [n(%)]	15 (13.6)	4 (3.6)	4 (3.6)	0.131			
Positive resection margin [n(%)]	0	0	1 (0.9)	1			
Number of lymph nodes harvested [mean(SD)]	25.1 (12.7)	19.9 (11.1)	18.1 (8.5)	**< 0.001**	**0.017**	**< 0.001**	0.593
≥ 12 lymph nodes [n(%)]	97 (88.2)	94 (85.5)	90 (81.8)	1			

Significant p values are indicated in bold

ERC extended right colectomy, *LC* left colectomy, *SLC* segmental left colectomy, *SFC* splenic flexure carcinoma

[a]Calculated for patients with a primary anastomosis

[b]Calculated for patients operated on via laparoscopy

[c]Excluding deceased patients

[d]Calculated on patients with postoperative complications

*Adjusted odds ratio and 95% confidence interval

isolated liver metastasis ($n=33$, 46.5%), isolated pulmonary metastasis ($n=9$, 12.7%), isolated spleen metastasis ($n=1$, 1.4%), liver and pulmonary metastasis ($n=3$, 4.2%), peritoneal carcinomatosis ($n=13$, 18.3%) and systemic metastatic disease ($n=12$, 16.9%), with no differences among the three groups ($p=0.222$).

Cox regression best predictors for OS and DFS are given in Table 3. Proportional hazards were assumed for both models ($p=0.472$ for OS and $p=0.10$ for DFS) and no collinearity issues were detected, as variance-inflating factors were lower to 1.5 for all predictors included in both models. Synchronous metastasis was identified as a strong

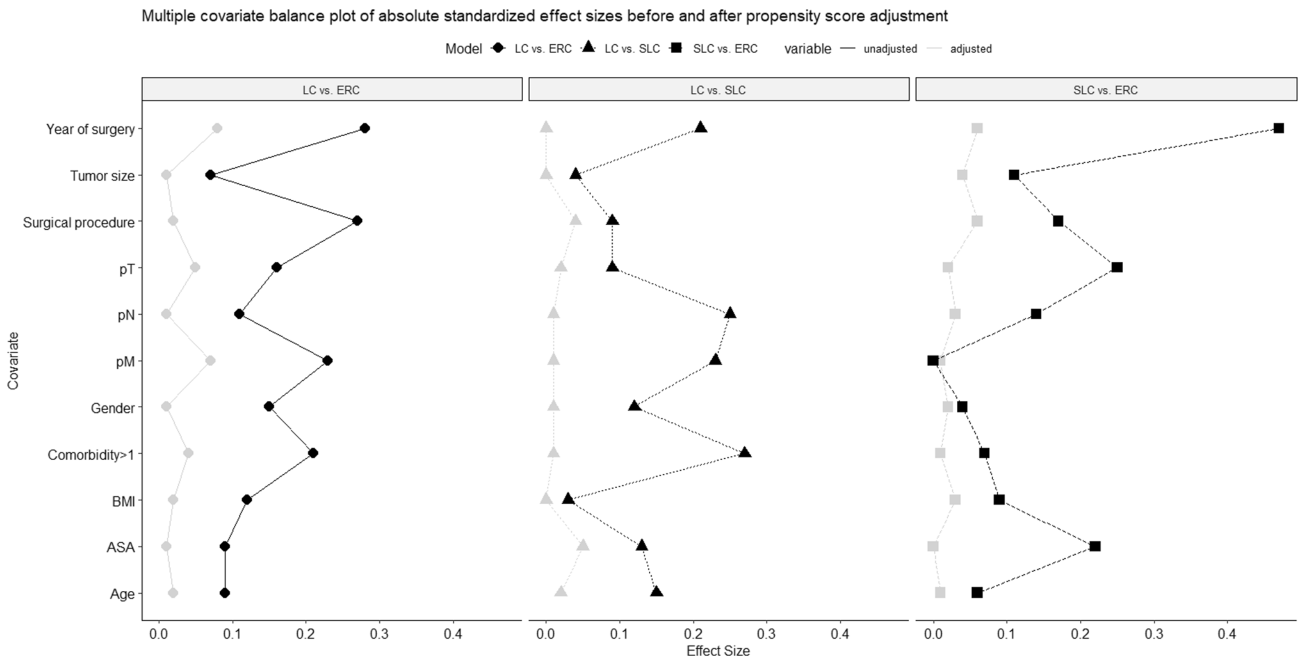
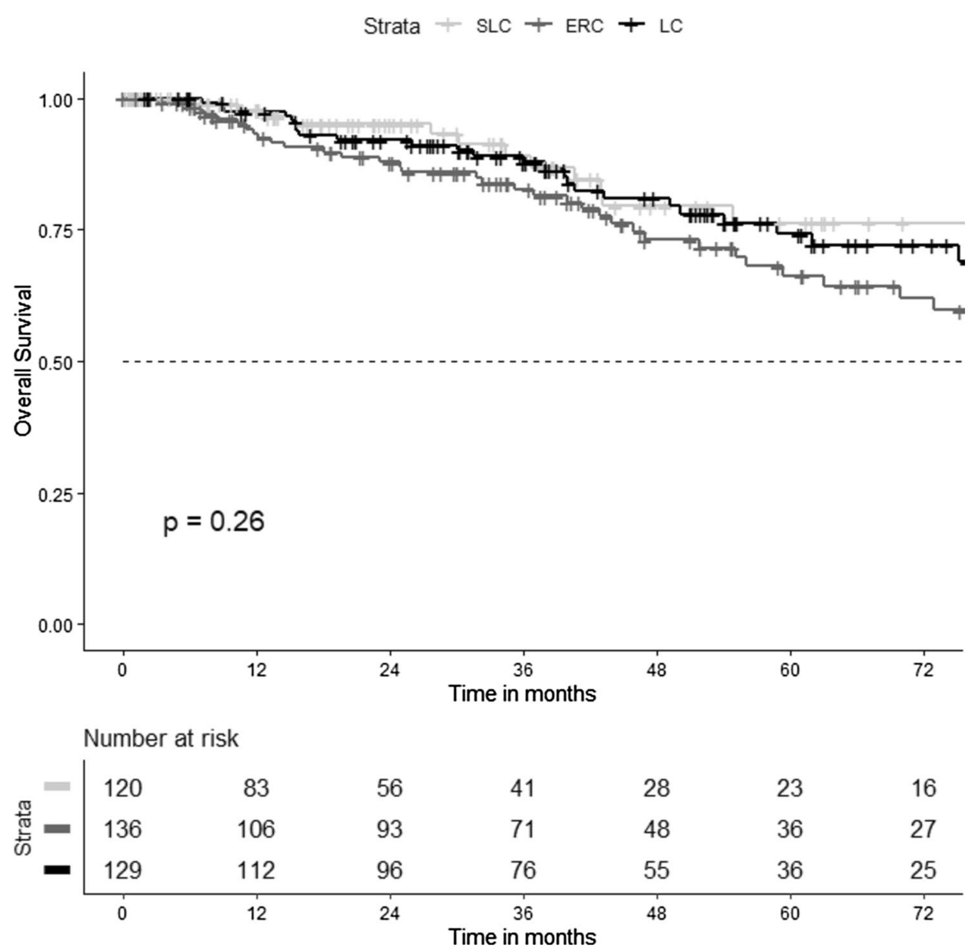


Fig. 2 Multiple covariate balance plot of absolute standardized effect sizes before and after propensity score matching

Fig. 3 Survival analyses (Kaplan–Meier Method) for overall survival (OS). The 1-, 2- and 5-year OS rates for the extended right colectomy (ERC) group were 93.3%, 87.9%, and 66.2%, respectively; for the left colectomy (LC) group, rates were 97.5%, 92.2% and 74.3%, respectively; and for the segmental left colectomy (SLC) group, rates were 97.8%, 95.2%, and 76.3%, respectively ($p = 0.26$)



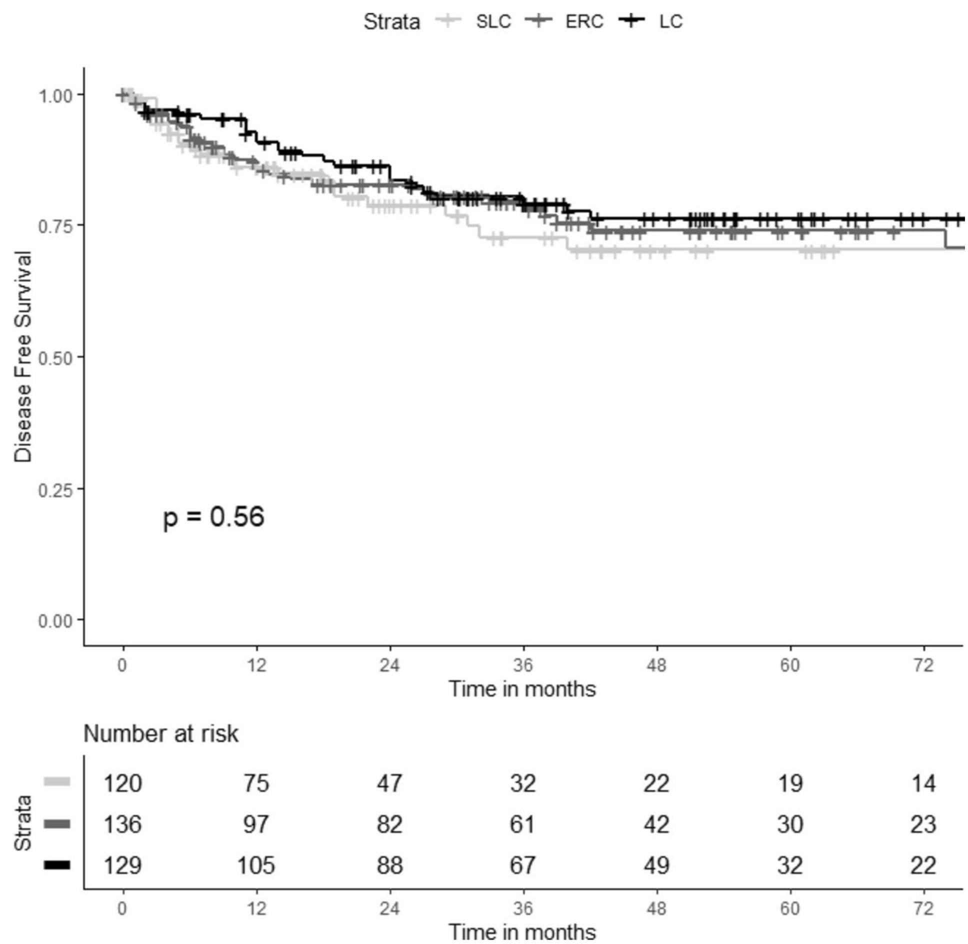


Fig. 4 Survival analyses (Kaplan–Meier Method) for disease-free survival (DFS). The 1-, 2- and 5-year DFS rates for the extended right colectomy (ERC) group were, respectively, 85.5%, 82.8%, and 73.9%; for the left colectomy (LC) group, they were 90.9%, 83.4%, and 76.3%, respectively; and for the segmental left colectomy (SLC) group, they were 86.2%, 78.8%, and 70.3%, respectively ($p=0.56$)

Table 3 Multivariate Cox regression models for overall and disease-free survival

Variables	Whole sample			
	Overall survival		Disease-free survival	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age > 75 year	3.06 (1.91–4.90)	< 0.001		
Synchronous metastasis (pM +)	3.38 (1.81–6.28)	< 0.001	4.31 (2.37–7.84)	**< 0.001**
pT4 vs. pT1-3	2.06 (1.28–3.32)	0.003	2.91 (1.81–4.69)	**< 0.001**

HR < 1 indicates an improvement in survival (positive prognostic factor); HR > 1 indicates a worse survival (negative prognostic factor). Significant *p* values are indicated in bold

HR hazards ratio, *CI* confidence interval

predictor of both OS and DFS. Neither the type of resection (ERC, SLC, LC) nor the type of surgical approach (open vs. laparoscopy) were found to have a significant effect on OS or DFS rates.

Discussion

The present results, which are based on a large multicenter European sample of SFC patients, showed an increase in operating time, time to flatus, time to resumption of oral diet, and length of hospital stay with the progressive extension of SFC resection. Moreover, patients undergone ERC procedures showed an increased incidence of postoperative complications, particularly a significant higher risk of post-operative ileus compared to both LC and SLC. Despite ERC being associated with an average greater number of retrieved lymph nodes, no group differences was observed in the rate of retrieving at least 12 lymph nodes. Concerning the long-term outcomes, no procedure-related difference was found for OS and DFS.

The published literature about the surgical treatment of SFCs is limited and heterogeneous [8, 25, 31, 47], as splenic flexure is a less common location for colon cancers, and its definition has not yet been standardized. Most of the previous studies provided pooled analyses of elective and emergency surgeries for SFCs, which makes direct comparisons difficult [4, 20, 21, 27, 29]. Odermatt et al. [29] compared 38 ERC vs. 30 LC patients, whereas Gravante et al. [21]

compared 64 ERC vs. 34 LC patients. Both studies included fewer than 15% of cases operated on by laparoscopy, as well as a high rate of emergency procedures (50% and 36.7%, respectively), which were more likely in the ERC patients. Nonetheless, no procedure-related differences were observed in regard to short- or long-term outcomes [21, 29]. Similarly, a matched case–control study by de'Angelis et al. [20] comparing 27 patients undergoing elective laparoscopic ERC vs. 27 patients undergoing elective laparoscopic LC demonstrated similar postoperative outcomes and survival in the absence of metastatic disease. However, the ERC procedure was associated with a significantly longer operative time [20]. The observational multicenter study by Beisani et al. [4] compared 68 elective subtotal colectomy (STC) vs. 76 elective LC patients and found a higher rate of overall morbidity, particularly postoperative ileus, in STC patients, but there were no differences in patient recovery, hospital stay, need for reoperation, or survival. More recently, Binda et al. [25] compared 158 ERC and 166 LC, of which 16.6% were performed in emergency settings. The authors found no significant difference concerning 30-day mortality and need for reoperation, concluding that the optimal procedure for SFC remains debatable as ERC and LC appear to achieve comparable short-term outcomes. Only a previous study, in our knowledge, considered the three surgical procedures for the treatment of SFCs, namely, ERC, LC and SLC [27]. Martin Arevalo et al. [27], however, performed only two-by-two comparisons by using PSM on 170 patients; of these, 72.4% were operated on in an elective surgery setting, and 15% via laparoscopy [27]. The results showed no pairwise differences between the surgical techniques for any of the variables being evaluated.

The present study, which represents the largest sample analyzed so far composed of only elective surgery for SFCs, demonstrates significant procedure-related differences. Indeed, the present findings suggest that the progressively extending the surgical resection has a significant impact on intraoperative and postoperative outcomes. Major differences are observed when comparing ERC to SLC, with longer operative time, more overall postoperative complications and postoperative ileus, longer time to flatus, time to regular diet and hospital stay for ERC patients. These differences may be explained by the extent of the surgical resection, considering that the larger dissection related to the ERC procedure likely requires a longer operative time and is more likely associated with a slower recovery. However, no significant difference was noted on OS or DFS up to 5 years. This was confirmed in the Cox regression models, where the type of surgery was not a significant predictor of OS and DFS. Conversely, the age at surgery > 75 years, the tumor stage (pT4), and the presence of synchronous metastasis (pM +) impact on OS, as the pT4 and the pM + predicted DFS.

In accordance with previous studies [4, 20, 21, 27, 29], the present analyses show that ERC is associated with an average greater number of lymph nodes retrieved with the surgical specimen, although all 3 procedures appear to achieve the goal of harvesting at least 12 lymph nodes at similar rates. For many authors, the number of harvested lymph nodes is essential for correct tumor staging, adjuvant chemotherapy indication, and consequently, long-term survival [17, 48]. In the case of SFCs, extensive resection of the terminal ileum and the right, transverse, and proximal descending colon is related to the vascular anatomy of the splenic flexure, which is marked by the binding, through different and variable arterial archways (i.e., Riolan's arch, Drummond and Moskowitz arteries), between the superior and inferior mesenteric vascular systems [49]. This singular area shows a triple lymphatic drainage to both mesenteric drainways with potential extramesocolic spread. The majority of lymph node metastases of SFCs are located along the para-colic arcade and the left colic artery [13, 24]. However, several reports have suggested the existence of alternative routes of lymphatic dissemination toward the root of the inferior mesenteric vein, the middle colic and superior mesenteric arteries, the spleen, the greater omentum, and the lower border of the pancreas [17, 32, 50]. Particularly, Manceau et al. [17] recently reported a single institution series of 65 patients in which nearly 10% of SFC cases had the involvement of distal lymph nodes along the right colic artery. The authors conclude that ERC is a valid oncologic procedure for SFC patients, particularly for those with synchronous resectable or potentially resectable liver metastasis. However, this justification may be debatable in light of only anecdotal evidence of middle colic and superior mesenteric artery involvement and similar oncologic outcomes and long-term survival between ERC, LC and SLC procedures. It should be considered that distal lymph node involvement could be interpreted as metastatic disease and the systemic dissemination of the primary SFC tumor [27, 32].

It is interesting to note that the rate of laparoscopy observed in the present study (74.4%) is higher than in previous ones, representing the current trends of applying minimally invasive approaches in colorectal cancer surgery. All laparoscopic procedures were safely performed, as deemed by a similar rate of conversion to laparotomy and similar rate of R0 resection. These results are in accordance with the findings of a recent systematic review and meta-analysis by Martínez-Pérez et al. [8] and support the clear trend of increasing application of laparoscopy to perform all three surgical procedures for SFCs.

The present study has the strength to analyze a large homogeneous sample of SFC patients undergoing only elective curative-intent SFC resections. The exclusion of emergency procedures is essential to correctly compare and interpret the outcomes of the 3 different surgical techniques for SFC. Moreover, we matched the 3 groups by PSM in order to minimize the selection bias related to the choice of the type of surgical procedure. As it is unlikely that a randomized controlled trial would be feasible in this area given the relative rarity of SFCs, the use of TriMatch PSM may represent the best available method to analyze and interpret the present short- and long-term data. However, due to the retrospective design, other potential selection bias, such as the exact tumor distance (cm) from the splenic flexure as assess intra-operatively, cannot be excluded. Moreover, the present study, as the current literature, did not evaluate important patient-centered outcome measures, as the quality of life, which may be drastically affected by the type of surgical resection (e.g., risk of defecatory anomalies) [8] and which need to be considered in future research to implement the evidence-based choice of the surgical procedure in case of SFCs.

In conclusion, the present findings, based on a large multlicentric experience in SFC surgical treatments, support the tendency to resect SFCs with more conservative and minimally invasive surgical techniques (e.g., SLC).

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Compliance with ethical standards

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