Journal of Crohn's and Colitis, 2022, **16**, 954–962
https://doi.org/10.1093/ecco-jcc/jjab215
Advance access publication 13 December 2021
Original Article

Long-term Oncological Outcome of Segmental Versus Extended Colectomy for Colorectal Cancer in Crohn's Disease: Results from an International Multicentre Study

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Abstract

Background and Aims: Crohn's disease increases colorectal cancer risk, with high prevalence of synchronous and metachronous cancers. Current guidelines for colorectal cancer in Crohn's disease recommend pan-proctocolectomy. The aim of this study was to evaluate oncological outcomes of a less invasive surgical approach.

Methods: This was a retrospective database analysis of Crohn's disease patients with colorectal cancer undergoing surgery at selected European and US tertiary centres. Outcomes of segmental colectomy were compared with those of extended colectomy, total colectomy, and pan-proctocolectomy. Primary outcome was progression-free survival. Secondary outcomes included overall survival, synchronous and metachronous colorectal cancer, and major postoperative complications.

Results: Ninety-nine patients were included: 66 patients underwent segmental colectomy and 33 extended colectomy. Segmental colectomy patients were older [$p = 0.0429$], had less extensive colitis [$p = 0.0002$] and no preoperatively identified synchronous lesions [$p = 0.0109$].

Median follow-up was 43 [31–62] months. There was no difference in unadjusted progression-free survival [$p = 0.2570$] or in overall survival [$p = 0.4191$] between segmental and extended colectomy. Multivariate analysis adjusting for age, sex, ASA score, and AJCC staging, confirmed no difference for progression-free survival (hazard ratio [HR] 1.00, $p = 0.9993$) or overall survival [HR 0.77, $p = 0.6654$]. Synchronous and metachronous cancers incidence was 9% and 1.5%, respectively. Perioperative mortality was nil and major complications were comparable [7.58% vs 6.06%, $p = 0.9998$].

Conclusions Segmental colectomy seems to offer similar long-term outcomes to more extensive surgery. Incidence of synchronous and metachronous cancers appears much lower than previously described. Further prospective studies are warranted to confirm these results.

Key Words: Crohn's disease; colorectal cancer; surgery

1. Introduction

Crohn's disease [CD] is an inflammatory bowel disease [IBD] producing intermittent transmural inflammation affecting the whole gastrointestinal tract, with a prevalence ranging from 1.5 to 318 persons per 100 000 depending on the geographical region, with higher incidence in northern Europe and North America.[1,2] Patients with CD are at increased risk for developing colorectal cancer [CRC].[3,4] Recent studies have raised concern for the possibility of a 'field effect' of CD, similar to ulcerative colitis [UC], and therefore of patients being at risk of developing multiple CRCs.[5,6] The concept of field cancerisation was proposed by Slaughter *et al.*, and CD inflamed mucosa might represent a model of preconditioned epithelium activated over an area in which multiple

Received: August 3, 2021. **Revised:** October 11, 2021. **Accepted:** November 22, 2021

cell groups undergo a process of irreversible change towards cancer.[7]

No effect on prognosis has ever been demonstrated for this phenomenon. Nonetheless, the theoretical risk of synchronous and/or metachronous lesions have prompted experts to recommend pan-proctocolectomy [PPC] for all CD patients with CRC.[8–10] PPC in CD patients requires creation of a permanent stoma in most instances, as a restorative procedure involving an ileal pouch-anal anastomosis [IPAA] is not feasible in most circumstances.[11] PPC with permanent ileostomy can be quite life-changing, particularly in patients who do not have major bowel symptoms associated with Crohn's disease.[12] Total colectomy [TC] represents a more conservative option to preserve sphincter function, but functional results are still less than optimal.[13,14] Oncological segmental colectomy [SC] is the accepted standard of care for sporadic CRC, with optimal results from both the oncological and the functional perspective, but is not recommended in cases of CD-associated CRC [CD-CRC].

Little evidence exists on the real impact of SC as opposed to extended colectomy [EC] on long-term oncological outcomes of CD-CRC patients. The aim of this study is to compare the effects of SC and EC on long-term prognosis of patients with CRC arising in the background of CD.

2. Methods

This study included patients who underwent surgery for CD-CRC at selected tertiary referral IBD centres across five countries in Europe and the USA. Patients were identified retrospectively through individual centres' hospital databases, and clinical data were registered in a dedicated database. The study was approved by the promoting centre's independent ethical committee and then by the local institutional review board at each participating centre. The study was registered at ClinicalTrial.Gov [NCT04654494].

2.1. Patients

Patients with a diagnosis of CD undergoing surgery for CRC were eligible for inclusion in the study. Patients with small bowel disease only, colitis in remission or active at the time of cancer diagnosis, were included in the study. Patients with final diagnosis other than adenocarcinoma were excluded, along with those affected by UC or indeterminate colitis.

All consecutive patients with available follow-up, operated on between January 1, 2010, and December 31, 2020, were evaluated for inclusion.

2.2. Study design

This was a retrospective multicentre study comparing the short- and long-term outcomes of different surgical operations in patients with CD-CRC. The study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] Statement.[15]

Patients who underwent SC were compared with patients who underwent EC, including TC and PPC. Choice of surgical operation was taken by the individual surgeon-patient combination. In consideration of the importance of long-term oncological outcomes, patients were classified in the two groups based on the extent of remaining colon after the index cancer operation, irrespective of the extent of the operation itself. For example, patients who had previously undergone right hemicolectomy for CD and subsequently underwent completion colectomy for CRC, were considered as having undergone EC rather than SC. Surgery was performed following universally accepted oncological principles independently of the extent of resection.

Oncological therapy modality and regimens were chosen by individual centres, following current practice guidelines and ensuring the best possible therapy for each patient. Follow-up was independently structured in all centres, but universally included physical examination, carcinoembryonic antigen [CEA], and thoraco-abdominal-pelvic CT every 6–12 months for the first 5 years. Additionally, colonoscopy/proctoscopy was performed at 1 year and thereafter every 12-36 months for most patients with remaining colon/rectum.

2.3. Outcome measures

Primary outcome was progression-free survival [PFS], defined as the length of time elapsed between date of index operation and disease progression or death, whichever occurred first. Disease progression was defined as appearance of new lesions or significant growth of existing lesions, according to RECIST criteria.[16]

Secondary outcomes were overall survival [OS], synchronous and metachronous CRC, and major postoperative complications. OS was defined as length of time elapsed between date of index operation and death from any cause. Synchronous neoplasia was defined as histologically confirmed co-existence of two or more neoplastic lesions on the surgical specimen, and it was assessed only in patients who underwent EC. Metachronous lesions were defined as CRC arising on a patients' residual colon or rectum, diagnosed during follow-up after surgery. Major postoperative complications were defined as Clavien-Dindo category ≥IIIB.

2.4. Study variables

Preoperative data included age, gender, American Society of Anaesthesiologists [ASA] score, CD history, Montreal Classification, history of previous surgery, cancer history, diagnosis, and CRC location and staging. The extent of CD colitis was classified into anatomical segments and its eventual presence in each segment was recorded. CRC was staged according to the American Joint Committee on Cancer [AJCC] classification.

Intraoperative details included operation performed, setting, operative approach, and intraoperative complications.

Postoperative information included complications, mortality, length of stay [LOS], unscheduled re-admission, and histopathological evaluation.

Follow-up included tumour recurrence/progression, mortality, and metachronous cancer diagnosis.

2.5. Statistical analysis

A non-parametric approach was preferred in the statistical analysis, due to relatively limited sample size. Continuous variables were described by median, first and third quartiles; categorical variables were summarised by absolute frequencies and percentages. Group comparison were performed using the chi square test for categorical variables [or Fisher's exact test in the case of sparse tables] and Wilcoxon rank-sum test for continuous variables. Unadjusted survival curves were calculated using the Kaplan–Meier method. The Wilcoxon test was used to compare groups. Cancer-specific mortality

was analysed in the framework of competing risk analysis. Cumulative incidence curves were reported for both cancer-specific and non-cancer specific events. Groups were compared using Gray's test.

Multivariate analysis was performed using the Cox model. Hazard ratios [HR] were estimated by maximum partial likelihood method and tested using the Wald chi square statistic. Profile likelihood-based confidence intervals were reported. Continuous variables were represented in the Cox model as a linear effect. This assumption was verified by plots of deviance residuals against covariate values; no evidence of non-linear effects was observed. Possible violations of proportionality were evaluated by plots and test statistics based on Schoenfeld residuals. No time-dependent effect was detected.

All analyses were performed using SAS version 9.4 and R.

3. Results

A total of 110 patients were operated on for CRC arising in CD between 2010 and 2020. Eleven patients were excluded, 99 satisfied all criteria and were included in the analysis [Figure 1].

A total of 66 patients underwent segmental colectomy [SC] and 33 patients underwent extended colectomy [EC]. Details of procedures performed are reported in Table 1.

3.1. Patients' demographics

Baseline characteristics of the two groups are summarised in Table 2.

Patients were diagnosed with CD a median of 184 [22–365] vs 132 [206–304] months before CRC diagnosis in SC and EC, respectively [$p = 0.4198$]. Seventeen SC vs 14 EC patients

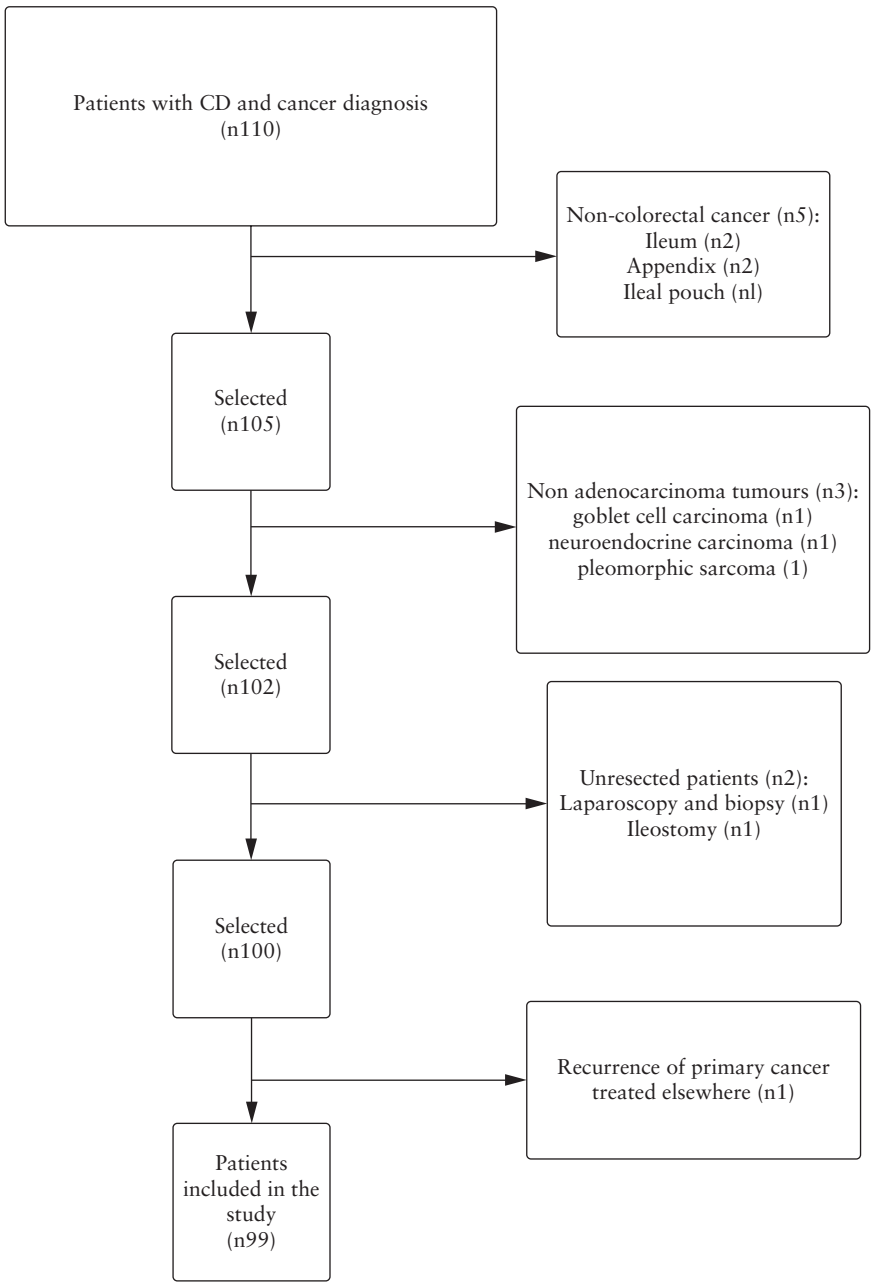

Figure 1. Patient selection.

Table 1. Surgical procedures.

Segmental colectomy	**Ileocaecal resection**	**1**
	Right colectomy	16
	Extended right colectomy	10
	Transverse colectomy	1
	Left colectomy	3
	Extended left colectomy	3
	Sigmoidectomy	3
	Anterior resection	11
	Abdominoperineal resection	9
	Pelvic exenteration	8
	Right hemicolectomy and sigmoid resection	1
Extended colectomy	Pan-proctocolectomy	12
	Ileal pouch-anal anastomosis	1
	Pelvic exenteration and panproctocolectomy	2
	Subtotal colectomy	7
	Total colectomy	6
	Extended left colectomy [completing TC]	1
	Pelvic exenteration [completing PPC]	1
	Abdominoperineal excision [completing PPC]	3

TC, total colectomy; PPC, pan-proctocolectomy.

had previously undergone a total of 48 intra-abdominal operations for CD [$p = 0.0997$] [Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online]. Patients were significantly older in the SC group: 59 [51–68] vs 54 [40–60] years, $p = 0.0495$. Other characteristics, including sex distribution and ASA score, were comparable between groups. Colitis distribution was significantly different in patients undergoing SC vs EC [$p = 0.0002$]: in the SC group, 45.45% and 12.13% of patients were free from Crohn's colitis and had pan-proctocolitis, respectively, whereas this occurred in 18.18% and 48.49% in the EC group, respectively. Overall, in 62.12% [SC] vs 27.27% [EC] of patients, CRC arose on non-CD-inflamed colonic/rectal segments.

Right colon cancer was present in 36% vs 15.15% of patients:, 7.58% vs 18.18% had transverse colon cancer, 19.70% vs 24.24% had left/sigmoid colon cancer, and 36.36% vs 42.43% had rectal cancer, in SC and EC, respectively [$p = 0.1011$].

Cancer staging distribution did not differ between SC and EC groups [$p = 0.3043$]. In the SC group, 15.15% of patients had metastatic disease at diagnosis, as compared with 3.03% in the EC group [$p = 0.0939$].

No patient had synchronous neoplastic lesions suspected or clinically diagnosed before SC, whereas 12% of patients [4/33] in the EC group were diagnosed at preoperative colonoscopy with synchronous neoplasia, including one low-grade dysplasia [LGD], one high-grade dysplasia [HGD], and two CRCs [$p = 0.0109$].

3.2. Surgical management and perioperative outcomes

Perioperative outcomes are summarised in Table 3. Surgical operations were performed in the elective setting in 87.88% vs 93.94% in SC vs EC, respectively [$p = 0.4886$].

A laparoscopic approach was prevalent and undertaken in 59.09% vs 69.70% patients [$p = 0.3038$], including three robotic-assisted cases. Two patients required conversion from minimally invasive to open surgery. In the SC group, 3.17% of patients had R1 resections, vs 6.06% of patients in the EC group [$p = 0.6055$].

No difference was detected in major complications [7.58% after SC and 6.06% after EC, $p = 0.9998$]. No 30-day mortality was registered. LOS was also similar with a median of 11 [6–20] days in SC and 9 [7–12] days in EC [p=0.2289].

3.3. Survival

At a median follow-up of 43 [31–62] months, 33.33% of patients had disease progression in the SC group and 24.24% in the EC group. There was no difference in unadjusted PFS between SC and EC [$p = 0.2570$] [Figure 2A]. Estimated PFS at 1- and 3-year follow-up was 0.82 (standard error [s.e.] 0.05) and 0.68 [s.e. 0.06] in the SC group, and 0.97 [s.e. 0.03] and 0.70 [s.e. 0.10] in the EC group.

During follow-up, death occurred in 24.24% after SC and 15.15% after EC. There was no difference in unadjusted overall survival in SC and EC groups [$p = 0.4191$] [Figure 2B]. Estimated overall survival at 1 and 3 years was 0.90 [s.e. 0.04] and 0.80 [s.e. 0.05] in the SC group, 0.97 [s.e. 0.03] and 0.83 [s.e. 0.08] in the EC group. Cancer-specific survival was also similar [Supplementary Figure 1 and Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online].

Multivariate analysis was performed both for PFS and OS, adjusting for known factors affecting oncological outcomes, namely age, sex, ASA score, and stage. Results from the Cox models [Table 4] confirmed differences between EC and SC to be non-significant. The only significant predictor was CRC stage: stages III and IV were associated with an increased risk of death and progression as compared with stage I, whereas no significant difference was detected for stage II. Reduction of risk was observed over time in both models although it was not significant.

In both models, no significant departure from proportionality was observed, and residual analysis supported the assumption of a linear effect for age.

3.4. Synchronous and metachronous disease

Characteristics of patients with synchronous and metachronous CRC are summarised in Supplementary Tables 1 and 2, available as Supplementary data at *ECCO-JCC* online.

Synchronous neoplastic lesions were identified in 24.24% of pathology reports among the 33 patients who had undergone EC. LGD was detected in 12.12% of cases [4/33], HGD in 3.03% [1/33], and adenocarcinoma in 9.09% of cases [3/33]. In particular, only 25% [1/4] of low-grade dysplastic lesions were identified preoperativel,y whereas HGD was identified at preoperative biopsy; 66% [2/3] of synchronous cancers were histologically diagnosed preoperatively and the remaining were identified as a highly suspicious lesion at preoperative colonoscopy. All three patients underwent EC [one PPC, one subtotal colectomy, and one TC] accordingly. Two patients progressed and died after 9 and 25 months and the third patient is alive and disease-free after 23 months.

Overall, including all patients at risk for developing new lesions [i.e. SC + 13 EC patients who maintained the rectum], one patient developed a metachronous CRC [1.26%]. This patient was diagnosed with transverse colon cancer 6 months after abdominoperineal resection for low rectal cancer [SC

Table 2. Baseline demographics of patients.

Variable		Segmental colectomy [*n* = 66]		Extended colectomy [*n* = 33]		
		n or median	% orQ1-Q3	*n* or median	% orQ1-Q3	*p*-value
Age		59	51-68	54	40-60	0.0495
Sex						0.8832
	M	41	62.12%	21	63.64%	
	F	25	37.88%	12	36.36%	
ASA						0.2241
	I/II	42	63.64%	25	75.76%	
	III/IV	24	36.36%	8	24.24%	
CD duration [months]		184	22-365	132	206-304	0.4198
Perianal disease						0.9163
	Yes	21	32.31%	10	31.25%	
	No	44	67.69%	22	68.75%	
	NA	2		1		
Extent of CD colitis						0.0002
	No colitis	30	45.45%	6	18.18%	
	Segmental colitis/ proctitis	28	42.42%	11	33.33%	
	Pan-proctocolitis	8	12.13%	16	48.49%	
Previous intrabdominal surgery for CD						0.0997
	No	47	71.21%	18	54.55%	
	Yes	19	28.79%	15	45.45%	
Cancer location						0.1011
	Right	20	36.36%	5	15.15%	
	Tranverse	5	7.58%	6	18.18%	
	Left/sigmoid	13	19.70%	8	24.24%	
	Rectum	24	36.36%	14	42.43%	
Synchronous dysplasia/cancer						0.0109
	No	66	100.00%	29	87.88%	
	Yes	0	0.00%	4	12.12%	
AJCC staging						0.3043
	I	16	24.24%	11	33.33%	
	II	24	36.36%	13	39.39%	
	III	16	24.24%	8	24.24%	
	IV	10	15.16%	1	3.04%	
pM						0.0939
	0	56	84.85%	32	96.97%	
	I	10	15.15%	1	3.03%	
Year of treatment						
	2010–2015	34	51.52%	12	36.36%	0.1542
	2016–2020	32	48.48%	21	63.64%	
Preoperative use of 20 mg prednisolone or equivalent for >6 weeks						0.7457
	No	57	86.36%	30	90.91%	
	Yes	9	13.64%	3	9.09%	
Preoperative anti-TNF use						0.8505
	No	55	83.33%	27	81.82%	
	Yes	11	16.67%	6	18.18%	

CD, Crohn's disease; ASA, American Society of Anaesthesiologists; AJCC, American Joint Committee on Cancer; pM, Pathological Metastases Stage.

group]. He underwent transverse colectomy but developed lung metastases 6 months later. He was alive at latest contact 30 months after index operation. Another patient was diagnosed with multifocal dysplasia 84 months after extended right hemicolectomy, did not undergo further procedures, did not develop recurrence, and was alive at latest contact after

Table 3. Operative and perioperative outcomes.

Variable		Segmental colectomy[$n = 66$]		Extended colectomy [$n = 33$]		
	n or median	% orQ1-Q3	*n* or median	% orQ1-Q3		*p*-value
Setting						0.4886
	Elective	58	87.88%	31	93.94%	
	Emergency	8	12.12%	2	6.06%	
Approach						0.3038
	Open	27	40.91%	10	30.30%	
	Laparoscopic	39	59.09%	23	69.70%	
Resection margin						0.6055
	R0	61	96.83%	31	93.94%	
	R1	2	3.17%	2	6.06%	
	R2	0	0.00%	0	0.00%	
	Missing	3				
Clavien–Dindo class						0.9998
	0/I/II/IIIa	61	92.42%	31	93.94%	
	IIIb/IV/V	5	7.58%	2	6.06%	
Haemorrhage		2	3.03%	0	0.00%	0.5510
Superficial surgical site infection		15	22.73%	5	15.15%	0.4369
30 days reoperation		5	7.58%	2	6.06%	0.9998
30-day mortality		0	0.00%	0	0.00%	
Length of stay		11	6-20	9	7-12	0.2289
Readmission		6	9.09%	2	6.06%	0.7152

M, male; F, female; NA, not available.

9 years of follow-up. Rates of metachronous disease development did not significantly differ [Supplementary Figure 2 and Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online].

4. Discussion

The present study compared the short- and long-term outcomes of patients undergoing SC with those of patients undergoing EC for CD-CRC. PFS and OS were similar after a median of 43 months of follow-up. Furthermore, the incidence of synchronous and metachronous CRC was lower than previously reported. The current study represents one of the largest series to date to focus on surgery for CD-CRC. It was designed to provide evidence to better inform clinical guidelines which are currently based on data from studies focusing on less impacting endpoints.[17]

Guidelines from Europe and the USA recommend PPC for CD patients with diagnosis of CRC.[8,9] Current recommendations are based primarily on two studies: Kiran *et al.* reported a 40% rate of distant dysplasia in 10 patients with CRC, undergoing EC.[5] Maser *et al.* reported a 39% rate of metachronous cancers in 64 patients after SC or TC[6]; many of these metachronous cancers were very early relapse or anastomotic recurrences, and could actually represent synchronous cancers or cancer persistence due to suboptimal index surgery. Furthermore, most CRCs [88%] were early stage [I/II] and metachronous-specific survival was not reported.[6]

Bogach *et al.*, in a recent population-based study from Ontario, Canada, also investigated survival rates of patients with IBD [both CD and UC] and cancer.[18] They gathered 366 patients with CD operated on for CRC between 2007 and 2015, and compared the OS of patients undergoing SC vs TC vs PPC, detecting no long-term differences. Unfortunately, these results have relevant limitations. First, data came from hospitals of all levels, with as many as 10% of patients operated in rural areas, possibly affecting the quality of surgery and, as matter of fact, 45.6% of UC patients with CRC underwent SC.[19] Furthermore, data were extrapolated from an administrative database, with a very large amount of relevant information [e.g., disease staging, disease-specific survival, and disease progression data] being incomplete or missing.

Nevertheless, results of the Canadian study are in line with findings of the current study, suggesting that extending surgery beyond what is needed for conventional CRC may not provide any long-term advantage also in CD patients. Therefore, EC might represent an over-treatment for most patients, with significant associated morbidity.[8,9] In fact, even though similar postoperative complication rates were found [in line with previous reports[20]], quality of life is significantly invalidated after EC, especially after PPC[12,13,20] and particularly in CD, as in most patients IPAA is not an option.[21]

Another significant finding of present study is represented by the rates of synchronous and metachronous CRCs. Overt adenocarcinoma was found in 9.09% of patients—a much lower rate than previously reported [e.g., 40%, four out of 10 in Kiran's series[5]]. In addition, metachronous CRC developed in only 1.26% patients. One factor that may have affected previously reported rates of synchronous and metachronous CRC is that Kiran *et al.* referred to their monocentric experience, dating back to 1987, and Maser *et al.* analysed data of patients treated starting from 1970.[5,6] Data feeding the present study solely focused on the latest 10 years of activity, representing a reliable and up-to-date picture of referral centres'

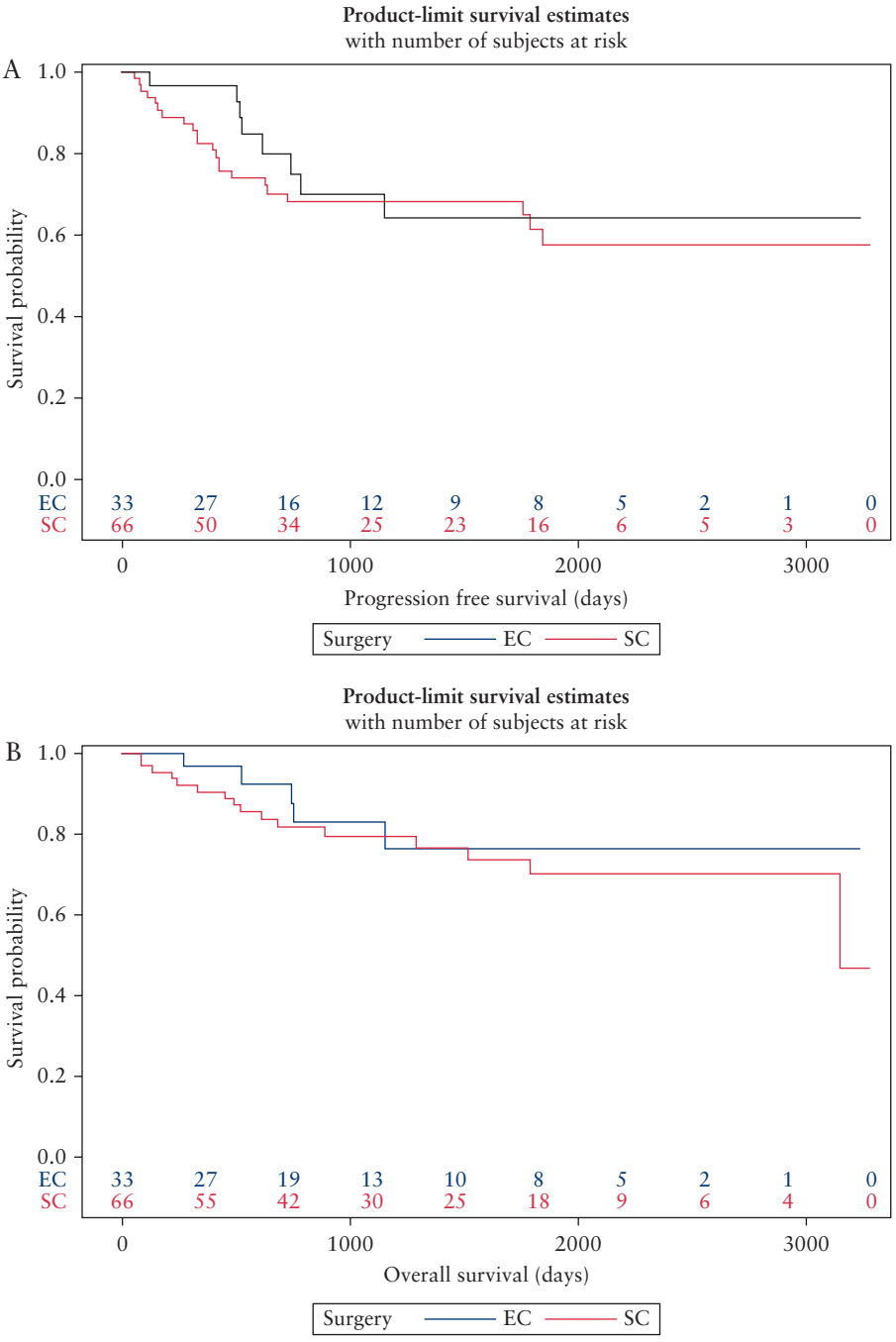

Figure 2. Kaplan–Meier curves for: A] progression-free survival; and B] overall survival for CRC in CD patients treated with SC or EC. CRC, colorectal cancer; CD, Crohn's disease; SC, segmental colectomy; EC, extended colectomy.

management of CD-CRC. The radically different medical therapy that is currently administered to CD patients may well have had an impact on inflammation duration, intensity, and consequences,[22] and therefore on development of CRC, likely decreasing incidence of synchronous and metachronous lesions, should they have ever been as high as previously reported.[23]

The current study has some limitations. The length of follow-up [median 43 months] can be regarded as the main limitation of the analysis, as it may not have been long enough for metachronous CRC to appear or affect survival. Nonetheless in the largest study on the subject, out of 25 metachronous CRC 50% were diagnosed within 2 years and 75% within 4 years.[6] Therefore, the length of follow-up seems adequate to detect most metachronous CRC, based on contemporary literature. Still, progression and overall survival are similar despite a higher incidence of metastatic disease in the SC group, and this could also be due to the limited follow-up. Other weaknesses include the relatively small sample size [there was nearly 10% difference in PFS between the two groups, which was not statistically significant with this sample size, but may be clinically significant with increased numbers] and the retrospective design of the study. Most patients were Caucasian from Europe and North America, and this might also impact on the generalizability of results. Moreover the study is multicentric, possibly

Table 4. Predictors of survival at Cox analysis.

	Progression-free survival			Overall survival		
Variable	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Surgery [EC vs SC]	1.00	[0.39, 2.58]	0.9946	0.76	[0.23, 2.54]	0.6508
Sex[female vs male]	1.71	[0.76, 3.81]	0.1925	2.04	[0.75, 5.52]	0.1608
ASA score[III/IV vs I/II]	0.98	[0.41, 2.33]	0.9623	1.36	[0.48, 3.86]	0.5646
Stage			<0.0001			0.0006
II vs I	0.63	[0.18, 2.25]	0.4729	0.79	[0.13, 4.93]	0.7968
III vs I	5.00	[1.75, 14.29]	0.0027	8.28	[1.76, 38.87]	0.0074
IV vs I	6.02	[1.64, 22.17]	0.0069	9.34	[1.54, 56.76]	0.0152
Age [linear effect, x 10 years]	1.05	[0.78, 1.43]	0.7390	1.16	[0.80, 1.70]	0.4279
Year [linear effect x year]	0.93	[0.80, 1.09]	0.3704	0.89	[0.73, 1.08]	0.2269

HR, hazard ratio; CI, confidence interval; EC, extended colectomy; SC, segmental colectomy; ASA, American Society of Anaesthesiologists.

introducing heterogeneity in clinical practice pre-, intra-, and postoperatively, but this may well represent one of its major strengths due to the fact that all participant centres are referral institutions for IBD surgery.

Patients in the SC group were twice as many as those in the EC group, despite much of the study period being successive to the publication of official guidelines. Differences between study groups could represent another potential source of bias. On the other hand, this may mirror some scepticism by expert IBD surgeons as to the effective need for EC, or it may be subsequent to patients' unwillingness to undergo extensive surgery, especially when sphincter function is threatened, or it may stem from a combination of the two. Furthermore, the two groups had very similar preoperative characteristics with few significant differences, each of which may reflect a preoperative selection process made by the operating surgeon and [probably] by patients themselves [shared decision making]. One such difference is that patients in the EC group were younger compared with their SC counterparts, even though age was accounted for in multivariate analysis. The reason for this difference could be ascribed to a perceived higher risk of metachronous CRC given the longer life expectancy on the one hand, and to a better probability of withstanding extended surgery on the other hand. Also, the extent of CD colitis was different, with more patients without colitis in the SC group and more patients with pancolitis in the EC group. This was easily predictable, considering that extensive colitis could be a justifiable indication per se for extensive surgery. On the contrary, it is with much greater concern that surgeons would remove healthy bowel in CD patients. All patients with synchronous lesions detected on preoperative colonoscopy biopsy underwent EC: remote synchronous disease represented a valid indication for extended surgery. However, it is interesting to note that overall, despite the clear existence of an important selection bias due to a tailored approach to surgery, based on multiple reasons, this does not affect survival.

Finally all patients with concomitant CD and CRC, irrespective of the presence of active CD colitis, have been included and it could be argued that in the absence of florid colitis, the indication to extensive surgery has a weaker rationale. Yet, there are numerous arguments in favour of including these patients. CRC risk is increased in all CD patients, suggesting the presence of a carcinogenic mechanism that may be independent of overt colonic inflammation.[22] Kiran *et al.* reported that 20% of CRC had no active colitis, and Maser *et al.* found that 11% of included patients were affected solely by ileal disease.[5,6] Among these, 38% developed metachronous CRC, in line with the reported rates for the rest of their cohort of patients with active colitis. Last, American guidelines recommend PPC for all CD-CRC patients whereas European guidelines, under the heading of 'Cancer and Crohn's disease', address CRC and Crohn's colitis but do not specify if an alternative treatment exists for CRC in CD patients without active colitis.[8,9]

A prospective randomised study is needed to confirm the findings of the current study. Yet the difficulty of randomisation due to the extremely multifaceted nature of each patient's disease, personal beliefs, and ethical issues, makes it difficult to plan such a complex trial.

In conclusion, SC appears to offer similar long-term oncological outcomes compared with EC, while providing functional benefits. In addition, the incidence of synchronous and metachronous CD-CRC appears to be much lower than previously estimated. Further prospective studies are needed to confirm these findings and clarify the impact of surgery on prognosis of these patients. Meanwhile, current guidelines for the treatment of CRC in CD patients may need to be reconsidered.

The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

Supplmentary Data

Supplementary data are available at *ECCO-JCC* online.

Funding

The authors have no funding sources to declare.

Conflict of Interest

Authors have no conflict of interest to disclose.

Acknowledgments

MIUR Excellence, Department Project awarded to the Department of Mathematics, University of Rome Tor Vergata.

Author Contributions

BS: design of the study and analysis and interpretation of data, drafting the article, final approval of the version to be submitted. GSS: concept and design of the study and analysis and interpretation of data, drafting and critical revision of the article for important intellectual content, final approval of the version to be submitted. AN: analysis and interpretation of data, critical revision of the article for important intellectual content, final approval of the version to be submitted. JK, JW, AS, KZ, YP, GS, AF, EGG, EEB, TK, LS, SS, VB, MC, EA, AF, MA, MF, MMG, GP: acquisition of data, critical revision of the article for important intellectual content, final approval of the version to be submitted.

Results from this study have been presented orally at the Virtual Ecco'21 Congress on Thursday July 8, 2021.

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