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Comparison of functional recovery and surgical outcomes of Crohn's and Cancer patients undergoing right colectomy following an Enhanced Recovery Pathway

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ABSTRACT

Introduction. Crohn's disease (CD) is a transmural, chronic and autoimmunity disease that can affect any segment of the digestive tract. With 58%, the ileocecal segment is the most prevalent primary location of the disease and may require ileocecal resection for disease control. Formal right colectomy is the standard approach to right-sided colon cancer, in which a central resection with high ligation of the ileocolic axis is mandatory for complete removal of tumor-draining lymphovascular tissue. Conversely, CD typically needs less radical resection of lymphovascular structures and is mainly guided by the extent of the inflammatory process. The aim of this study is to compare functional recovery and surgical outcomes of patients undergoing ileocecal resection for CD to patients with right-sided colon cancer undergoing oncological right colectomy within a standardized enhanced recovery pathway.

Methods. This is a retrospective cohort study with data deriving from the ERAS database of the CHUV. 195 patients (n=153 (78%) with cancer and n=42 (22%) with CD) were included. We collected demographic and surgical information, functional outcomes (postoperative pain level, opioid use, time from surgery to return to flatus and stool, postoperative oral intake of fluids, postoperative weight change and postoperative mobilization), postoperative complications and some specific assessments for oncological and Crohn's patients, including total number of resected lymph nodes.

Results. Oncological patients were older, sicker (ASA score) and had higher BMI scores. Crohn's group experienced significantly more pain at POD 0-3, and significant differences were observed in intraoperative EDA use and postoperative opioid use within 48 hours. Return of flatus and stool was similar in both groups and no difference was seen in surgical outcome. Oncological patients gained significantly more weight and had a larger lymph node yield than the CD group.

Conclusion. This study did not reveal differences in functional and surgical outcome in CD and cancer patients undergoing mesentery-sparing or oncological right colectomy, respectively. Based on these data, more extensive resection in CD patients to prevent disease recurrence may be warranted and will most likely not negatively impact functional recovery.

Keywords. Crohn's disease – Right colectomy – Functional outcome – Surgical outcome – Postoperative recurrence

INTRODUCTION

Crohn's disease (CD) is a transmural, chronic and autoimmunity disease that can affect any segment of the digestive tract[1]. Despite being a non-curative disease, more than half of patients need surgical treatment[2] for medically refractory inflammation leading to acute (i.e. perforation) or chronic (i.e. stricture) complications. With 58%, the ileocecal segment is the most prevalent primary location[3] of the disease and may require ileocecal resection for disease control[2,4]. Formal right colectomy is the standard approach to right-sided colon cancer, in which a central resection with high ligation of the ileocolic axis is mandatory for complete removal of tumor-draining lymphovascular tissue. Conversely, CD typically needs less radical resection of lymphovascular structures and is mainly guided by the extent of the inflammatory process.

Assuming that the Abbreviated Injury Scale (AIS) for mesenteric injury in traumatology increases the risk of small bowel obstruction[5], central resection of the ileocolic pedicle and its neurovascular structures may have an impact on functional recovery including postoperative ileus (POI), which occurs in up to 24% after right colectomy[6.]

The aim of this study was to compare functional recovery and surgical outcomes of patients undergoing ileocecal resection for CD to patients with right-sided colon cancer undergoing oncological right colectomy within a standardized enhanced recovery pathway.

METHODS

This is a retrospective cohort study with data deriving from the enhanced recovery after surgery (ERAS) database of the Centre Hospitalier Universitaire Vaudois, a tertiary academic institution. All consecutive patients undergoing right colectomy or ileocecal resection for either primary, histology-proven stage I-III adenocarcinoma or Crohn's disease with an established preoperative diagnosis between July 2011 and November 2017 were included.

The study was conducted in accordance with the STROBE criteria (https://strobe-statement.org).

Demographic information included age, gender, American Society of Anesthesiologists (ASA) and World Health Organization (WHO) mobility performance scores (WHO 0: fully active, able to carry on all pre-disease performance without restriction-WHO 5: dead), body mass index (BMI), social habits including active smoking and alcohol abuse (as defined by DSM-5) at the time of surgery, immunosuppressive medications (i.e. chemotherapy or steroids within 12 weeks of surgery), previous history of abdominal surgery and postoperative nausea or vomiting (PONV). Surgical information included surgical approach (either open or minimally invasive, including pre-emptive or reactive conversion to laparotomy), elective or emergency (within 72 hours of unplanned admission) indication, length of the operation (from anesthesia induction until skin closure) and length of the incision (< 10cm vs. > 10cm). For CD patient a bowel-close resection was performed. None of the cancer patient underwent a D3-lymphadenectomy, however complete mesocolic excision preserving the mesocolic plane and central ligation of the ileocolic vessels at their origin were performed routinely. All anastomoses were performed to a standardized side-to-side anisoperistaltic stapling technique or an isoperistaltic side-to-sid hand-sewn technique.

The institutional ERAS protocol has been previously described[7]. Compliance to individual ERAS items was calculated[8].

Outcomes

Functional outcomes included postoperative pain levels, assessed by visual analogue scales (VAS 0: no pain- 10: highest pain intensity) and opioid use at POD 1-3 for adequate pain control, time from surgery to return to flatus and stool, postoperative oral intake of fluids (L/24h), postoperative weight change (POD 1-3 compared to preoperative weight) and postoperative mobilization (hours at POD 1-3).

Postoperative complications included infectious (surgical site infection and medical infectious including urinary tract infection and pneumonia), respiratory and cardiovascular complications (arrhythmias, deep venous thrombosis, pulmonary embolism), urinary retention (need for in and out catheterization), anastomotic leakage (clinically or radiologically confirmed), postoperative length of stay (surgery to discharge), readmission (to either index or independent facility) and postoperative ileus or small bowel obstruction (SBO). Postoperative ileus was defined as postoperative re-insertion of a nasogastric tube (NGT) after removal at the end of anesthesia. SBO was defined as the need of re-operation. For the purpose of this study, both entities were combined.

Specific assessments for oncological and Crohn's patients

For oncological patients, tumor resection margins and total, peritumoral and central lymph nodes were analyzed.

For the Crohn's patients, preoperative medical therapy including corticosteroids, immunomodulators (Azathioprine - AZA, Methotrexate - MTX) and biologic molecules (Adalimumab - ADA, Certolizumab - CTZ, Infliximab - IFX, Vedolizumab – VED and Ustekinumab – UST), which were stopped at minimal half-life time of drug except for emergency surgical indications, were analyzed. Surgical indication (medically refractory or complicated disease (stenosis, fistula, perforation), need of an oncological resection (high-tie of the ileo-colic axis) and total number of resected lymph nodes were also interpreted.

Statistical analysis

Statistical analyses were performed with the Statistical Software for the Social Sciences (SPSS 22). Descriptive statistics were reported as frequency and percentages and continuous variables were reported as mean (standard deviation). Chi-square test was used for categorical, student's t-test for continuous variables. Variables with a p-value <0.05 indicate statistical significance.

RESULTS

Demographics and surgical details

A total of 195 patients (153 (78%) with cancer and 42 (22%) with CD) were included. Oncological patients were older, sicker (ASA score), and had higher BMI scores, as outlined in **Table 1**. There were no differences in social habits, WHO performance scores, and previous surgery or PONV history between both groups. No significant difference was seen in the rates of minimally invasive approach or conversion, which were all done for a pre-emptive reason.

Compliance with the enhanced recovery protocol

Overall compliance with the ERAS protocol was similar in the two groups. Significant differences were observed in intraoperative EDA use and postoperative opioid use within 48 hours (**Table 2**).

Functional outcome

The CD group experienced significantly more pain at POD 0, POD 1, POD 2 and POD 3, as shown by both increased VAS scores and increased use of opioid medication through POD 3 (**Table 3**). Return of flatus and stool was similar in both groups. Oncological patients gained significantly more weight (POD 2 and 3).

Surgical outcome

Infectious, cardiovascular, respiratory, abdominal, urinary and anastomotic complication rates were similar in both groups (**Table 4**). No difference was seen for length of stay and readmission rate.

Further specifics of CD and cancer patients regarding preoperative immunosuppressive treatments and pathological details are summarized in **Tables 5 and 6**. The adenocarcinoma group had a larger lymph node yield than the CD group (n = 26±13 vs. n = 2.4 ±5 respectively, $p<0.001$).

DISCUSSION

This present study evaluated functional recovery and short-term outcomes after right colectomy in patients with CD and patients undergoing a formal oncological colectomy. Despite more central resection and thus increased lymph node yield in cancer patients and similar compliance to perioperative care items, recovery of bowel function did not differ between the two groups. While CD patients experienced significantly more postoperative pain, no differences were observed in postoperative complications, length of stay and readmissions. Based on these data, more extensive resection in CD patients to prevent disease recurrence may be warranted and will most likely not negatively impact functional recovery.

Surgery is not a curative treatment for CD. Endoscopic recurrence occurs in 30%[9, 10, 11, 12] at 1 year and 85% at 3 years[13] after surgery, while clinical recurrence at one year occurs in 8-20%[10, 11, 13]. Furthermore, surgical recurrence occurs in 30% of patients at 10 years[14, 15]. High visceral fat area and high mesenteric fat index are associated with postoperative recurrence at 6 months[16]. In 2018, Coffey et al[17] evaluated the rate of surgical recurrence between conventional, mesentery-sparing ileocolic resections for CD and those including a wide mesenteric resection and demonstrated that retention of the mesentery was an independent predictor of surgical recurrence. In their study, the rate of surgical recurrence was 40% with the conventional ileocolic resection against 2.9% with wide excision of the mesentery. Therefore, mesenteric resection was suggested as an efficient technique to decrease postoperative recurrence. Widespread resection of the mesentery is linked to a higher resection of lymph nodes and thus reduces potential immunologic reactions. The authors also explained the beneficial effect of mesenteric resection by assuming that it reduces the local recruitment of fibrocytes. The percentage of fibrocytes correlated with the mesenteric disease severity, which in turn correlated to the CD activity index (CDAI) and the mucosal disease activity index. Furthermore, mesenteric resection was associated with reduced intestinal resection and margin positivity rate.

However, the role of the mesentery in CD is still a matter of debate, as some authors suggested an immunological

protection of fat wrapping[18, 19]. According to their studies, radical mesenteric resection could therefore lead to poorer clinical outcomes. Furthermore, resection of the mesentery is associated with a non-negligible risk of bleeding, which can cause major peri- and postoperative complications[20]. In the present study, mesenteric resection did not lead to increased overall and specific postoperative complication rates. Hence, our results may support a more extended surgical approach in CD. However, whether the mesentery has an immunological protection or not in ileocecal CD needs yet to be determined by further studies.

Mascarenhas et al[21] analyzed short-term outcomes after ileocolic resection and right hemicolectomies for CD patients compared with a non-Crohn's comparative group and showed no differences in postoperative needs of surgical re-intervention and postoperative ileus. They concluded that the underlying pathology does not influence functional recovery and surgical outcomes, similar as in our present study, which focused in particular on functional outcomes.

While functional recovery did compare well between the two groups in the present study, CD patients, who were significantly younger than the comparative cancer group, experienced significantly more postoperative pain. Preoperative chronic pain and young age have been repeatedly identified as risk factors for increased postoperative pain[22, 23, 24, 25]. While we did not assess preoperative pain intensity in the setting of this study, both subjective (VAS scores) and objective (opioid consumption) measures were used to assess postoperative pain. Arguably, chronic abdominal pain is a major concern in CD patients[3]. Reasons for higher postoperative pain scores are multifold and may also depend on pain assessment, according to Gagliese[24] et al. who showed that visual analogue scales were not sensitive enough to detect age differences compared to other instruments. However, we did also find a significant difference in opioid requirements.

Many directives exist to promote functional recovery after colorectal surgery. Among them, opioid-sparing pain management with systematic use of anti-inflammatory drugs or spinal/epidural analgesia have been suggested[26, 27, 28]. However, our study did not show differences in functional recovery despite increased use of opioid medication in CD patients.

Our results showed further increased weight gain in oncological patients, potentially due to less water retention in younger patients as a result of decreased intra-operative IV fluid administration and increased post-operative mobilization in the younger CD cohort. Indeed, excessive intraoperative fluid (> 2L) is known to be a risk factor for delayed postoperative mobilization[29]. Better general capacity to eliminate excess fluids in younger patients[30] could also be an explanation. Interestingly, ERAS compliance overall did not differ between the two groups, further supporting feasibility of ERAS care in all age groups[31].

This study has several limitations related to the retrospective study design. The sample size is modest and is based on a single center experience. Thus, our results need independent confirmation by adequately powered prospective studies comparing extended and non-extended resection, ideally solely in CD patients in a randomized fashion. Opioid consumption was not associated with poorer functional outcome. However, we have to be cautious with this interpretation, as the dosage was not specified. Long-term results were not yet available in the setting of this study but are needed to assess the true impact of extended resection on CD recurrence.

In conclusion, this study did not reveal differences in functional and surgical outcome in CD and cancer patients undergoing mesentery-sparing or oncological right colectomy, respectively. Therefore, more extended resection for CD may be considered in order to prevent disease recurrence.

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Table 1: Demographics and surgical details.

	All patients (n = 195)	**Crohn's disease** (n = 42)	**Adeno-carcinoma** (n = 153)	***P*-value**
Age (years; mean±SD)	64±20	37±15	71±14	**<0.001**
> 70 years (%)	97 (50)	1 (2)	96 (63)	**<0.001**
Gender (male; %)	100 (51)	24 (57)	76 (50)	0.486
ASA group (III-IV; %)	65 (33)	3 (7)	62 (41)	**<0.001**
WHO performance score (≥2, %)	45 (23)	7 (17)	38 (25)	0.306
BMI (kg/m^2; mean±SD)	25±6	23±5	26±6	**0.001**
> 25 kg/m^2 (%)	85 (44)	12 (29)	73 (48)	**0.035**
Smoker (%)	40 (21)	13 (31)	27 (18)	0.083
Alcohol (%)	15/155 (10)	14/120 (12)	1/35 (3)	0.193
Immunosuppressant (%)	41 (21)	33 (79)	8 (5)	**<0.001**
Previous abdominal surgery (%)	54 (28)	8 (19)	46 (30)	0.177
Previous PONV (%)	14/189 (7)	4 (10)	10/147 (7)	0.517
Minimally invasive approach (%)	155 (79)	38 (90)	117 (76)	0.053
Pre-emptive conversion(%)	7/155 (5)	2/38 (5)	5/117 (5)	0.683
Emergency indication (%)	49 (25)	7 (17)	42 (27)	0.167
Duration of operation (min; mean ±SD)	150±70	140±60	150±70	0.194
>180 min	55 (28)	10 (24)	45 (29)	0.564
Hand-sewn anastomosis (%)	23 (12)	4 (10)	19 (12)	0.789
Incision > 10cm (%)	75/189 (40)	10/41 (24)	65 (44)	**0.030**

Baseline demographic parameters of patients with Crohn's disease (n = 42) and patients with adenocarcinoma (n = 153) undergoing ileocecal resection or right colectomy. BMI – Body Mass Index, ASA – American Society of Anaesthesiology, WHO – world health organization performance score, PONV – postoperative nausea and vomiting, SD – Standard deviation. Bold P-values indicate statistical significance ($p < 0.05$).

All conversions from laparoscopy to laparotomy were done pre-emptively.

Table 2: ERAS compliance.

	All patients (n = 195)	**Crohn's disease** (n = 42)	**Adeno-carcinoma** (n = 153)	***P*-value**
Preadmission information	165 (85)	38 (90)	127 (83)	0.335
Carbohydrate drinks	162 (84)	36 (86)	126 (83)	0.816
No oral bowel preparation	194 (99)	42 (100)	152 (99)	1.000
No premedication	190 (97)	41 (98)	149 (97)	1.000
Antibiotic prophylaxis	195 (100)	42 (100)	153 (100)	1.000
Thrombo-prophylaxis	188 (96)	42 (100)	146 (95)	0.350
PONV prophylaxis	177 (91)	42 (100)	135 (88)	1.000
Intraoperative EDA	54 (28)	6 (14)	48 (31)	**0.032**
Active warming	193 (99)	42 (100)	151 (99)	1.000
Intraoperative fluids < 2L	142 (73)	34 (81)	108 (71)	0.240
Fluid administration guidance	82/192 (43)	13 (31)	69/150 (46)	0.112
No prophylactic NGT	181 (93)	41 (98)	140 (92)	0.309
No abdominal drains	185 (95)	40 (95)	145 (95)	1.000
Strong opioids within 48 hours	16/54 (30)	6/7 (85)	10/47 (21)	**0.002**
Systematic laxatives	182 (93)	40 (95)	142 (93)	0.441
IV fluids lock at 48 hours	152 (78)	34 (81)	118 (77)	0.678
Energy (ONS) at POD 0 >300 kcal	46/172 (27)	13/36 (36)	33/136 (24)	0.203
Total oral fluids at POD 0 > 800 mL	84/165 (51)	18/33 (55)	66/132 (50)	0.699
Mobilization at all at POD 0	83 (43)	23 (55)	60 (40)	0.101
Removal Foley within 48 hours	136/181 (75)	32/38 (84)	104/143 (73)	0.205
Mobilization > 6 hours at POD 1	64/160 (40)	11/29 (38)	53/131 (40)	0.837
Termination of EDA at POD 2	36/54 (67)	4/6 (67)	32/48 (67)	1.000

Compliance to specific pre-, intra- and postoperative ERAS parameters of patients with Crohn's disease (n=42) and patients with adenocarcinoma (n=153) undergoing ileocecal resection or right colectomy. PONV – postoperative nausea and vomiting, EDA- epidural anaesthesia, NGT – nasogastric tube, IV – intravenous, ONS – oral nutritional supplements, POD – postoperative day. Bold P-values indicate statistical significance ($p < 0.05$).

Table 3: Functional outcome.

	All patients (n = 195)	**Crohn's disease** (n = 42)	**Adeno-carcinoma** (n = 153)	***P*-value**
Pain (VAS, mean±SD)				
POD 0		4.4±2.5	2.8±2.6	**<0.001**
POD 1		5.4±2.4	3.4±2.4	**<0.001**
POD 2		3.7±1.9	2.8±2.5	**0.007**
POD 3		3.5±2.1	1.9±2.2	**<0.001**
Opiod use (% of patients)				
POD 0		73%	44%	**0.013**
POD 1		81%	36%	**<0.001**
POD 2		65%	28%	**0.001**
POD 3		57%	22%	**0.004**
Bowel function (days, mean±SD)				
Return to flatus		2.3±1.2	2.4±2.8	0.642
Return to stool		4.1±6.0	3.0±1.8	0.292
Oral fluids (L, mean±SD)				
POD 1		1.5±0.8	1.4±0.7	0.527
POD 2		1.5±0.7	1.4±0.8	0.486
POD 3		1.3±0.8	1.3±0.8	0.799
Weight change (kg, mean±SD)				
POD 1		0.6±2.2	1.0±2.2	0.436
POD 2		0.3±2.0	1.4±3.0	**0.014**
POD 3		-0.1±2.1	1.5±3.2	**0.002**
Mobilisation (hours, mean±SD)				
POD 1		4.3±2.5	4.7±2.4	0.337
POD 2		5.5±2.2	5.5±2.5	0.861
POD 3		6.1±2.2	6.2±2.2	0.957

Functional outcome parameters of patients with Crohn's disease (n=42) and patients with adenocarcinoma (n=153) undergoing ileocecal resection or right colectomy. VAS – visual analogue scale, POD – postoperative day. Bold P-values indicate statistical significance ($p < 0.05$).

Table 4: Surgical outcome.

Type of complication/LoS	All patients (n = 195)	Crohn's disease (n = 42)	Adeno-carcinoma (n = 153)	*P*-value
Any complication (%)	87 (45)	20 (48)	67 (44)	0.727
Severe complication Clavien >=IIIa (%)	16 (8)	2 (5)	14 (9)	0.530
Infectious complications (%)	31 (16)	6 (14)	25 (16)	1.000
Postoperative ileus/SBO	34(17)	8 (19)	26 (17)	0.756
Respiratory complication (%)	16 (8)	1 (2)	15 (10)	0.201
Cardiovascular complication (%)	6(3)	0	6(4)	0.334
UTI (%)	6 (3)	0	6 (4)	0.344
Urinary retention (%)	13 (7)	4 (10)	9 (6)	0.483
Anastomotic leak (%)	4 (2)	1 (2)	3 (2)	0.512
LoS (days; median, IQR)	5 (3,8)	5 (3,7)	6 (3,8)	0.087
Readmissions (%)	16/190 (8)	3/40 (8)	13/150 (8)	1.000

SBO – small bowel obstruction, UTI – urinary tract infection, LOS – length of stay

Table 5: Specifics Crohn's patients before surgery

Crohn's therapy	N (%)
Corticosteroids	12 (29)
>20mg	4 (10)
Immunomodulator	14 (33)
AZA	7 (17)
MTX	1 (2)
Biologic therapy	
ADA (Humira)	10 (24)
CTZ (Cimizia)	2 (5)
IFX (Remicade)	5 (12)
VED (Entyvio)	6 (14)
UST (Stelara)	1 (2)
Surgical indications	
Medically refractory	8 (19)
Stenosing disease	36 (86)
Fistulizing disease	7 (17)
Perforating disease	2 (5)
Oncologic resection	0
Total lymph nodes (mean±SD)	2.4±5

Preoperative treatments, surgical indications and pathologic specifics of Crohn's patients (n=42).

AZA – azathioprine, MTX – methotrexate, ADA – adalimumab, CTZ – certolizumab, IFX – infliximab, VED – vedolizumab, UST-ustekinumab.

Table 6: Specifics adenocarcinoma patients

Lymph nodes (n, mean±SD)	
Total	26±13
Positive	2±4
Peritumoral	14±9
Positive peritumoral	3±4
Central	12±9
Positive central	1±2
Tumor margins (cm, mean±SD)	
Distal (colonic)	10.2±5.6
Proximal (ileal)	9.8±6.1
Vascular pedicle	7.5±4
R0 resection	152 (99)

Pathologic details of patients with adenocarcinoma (n=153).