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ORIGINAL ARTICLE

Malignancy is a risk factor for postoperative infectious complications after elective colorectal resection

Thibault Crombe [1,2] · Jérôme Bot [1,2] · Mathieu Messager [1,2] · Vianney Roger [3] · Christophe Mariette [1,2,4] · Guillaume Piessen [1,2,4]

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Abstract
Purpose Patient and technical factors influencing the postoperative infectious complications (ICs) after elective colorectal resections are satisfactorily described. However, the underlying disease-related factors have not been extensively evaluated. This study aimed to measure the effect of malignancy on postoperative surgical site and extra surgical site infections after elective colorectal resection.
Methods This study is a bicentric retrospective matched pair study of prospectively gathered data. Between 2004 and 2013, 1104 consecutive patients underwent colorectal resection in two centers. Patients undergoing elective resection with supraperitoneal anastomosis for benign diseases (excluding inflammatory bowel disease) (group B, $n = 305$) were matched to randomly selected patients with malignancy (group M, $n = 305$). The matching variables were age, gender, American Society of Anesthesiologists (ASA) score, malnutrition, type of resection, and surgical approach. We compared the 30-day IC rates between patients with benign diseases (group B) and malignancy (group M). Multivariate logistic regression analysis was performed to identify the risk factors for ICs.
Results Group M had a higher overall rate of IC (25.6 vs 16.1 %, $P = 0.004$) as well as a higher risk of extra surgical site infections ($P = 0.007$) and anastomotic leakage ($P = 0.039$). The independent risk factors for ICs were malignancy (odds ratio (OR) = 2.02; $P = 0.002$), age ≥70 years (OR = 1.73, $P = 0.018$), tobacco history (OR = 1.87; $P = 0.030$), and obesity (OR = 1.68; $P = 0.039$).
Conclusion Malignancy, age, tobacco history, and obesity increase the risk of ICs after colorectal resection. Improvement of the modifiable risk factors, increased compliance with an enhanced recovery after surgery (ERAS) program in the overall population, and optimization of immune function in patients with malignancy should be considered.

Keywords Colorectal resection · Cancer · Morbidity · Infectious complications · Nutrition · Laparoscopy

Introduction

Colorectal surgery has both a known morbidity (10 to 40 %) and mortality (0.2 to 2 %) rates, which is largely as a result of the postoperative infectious complications (ICs). ICs include surgical site infections (SSIs), which are the most common nosocomial infections in surgical patients [1], and extra SSI (E/SSI), which are commonly pulmonary and urinary tract infections [2]. Because ICs result in longer hospital stays, a delayed resumption of normal activity [3], and a decreased long-term survival in patients undergoing curative surgery for colorectal cancer [4], reducing ICs after colorectal surgery is a major public health issue.

Numerous studies have focused on identifying predictive factors for morbidity and mortality in colorectal surgery.

Thibault Crombe and Jérôme Bot contributed equally to this work.

✉ Guillaume Piessen
guillaume.piessen@chru-lille.fr

1 Department of Digestive and Oncological Surgery, University Hospital Claude Huriez, Centre Hospitalier Régional Universitaire, Place de Verdun, 59037 Lille cedex, France

2 University of Lille Nord de France, Lille, France

3 Mathilde Clinic, Rouen, France

4 Inserm UMR-S 1172, Jean Pierre Aubert Research Center, Team 5 "Mucins, epithelial differentiation and carcinogenesis, Lille, France

Several patients' related factors (advanced age, male gender, high American Society of Anesthesiologists (ASA) score, and malnutrition) and numerous intraoperative factors (surgical site contamination, duration of intervention, and blood loss) have been demonstrated to be predictive in colorectal surgery [5], while the laparoscopic approach has been suggested to reduce SSI.

The study of host- and disease-related factors is a promising area of research for predicting and preventing IC [6]. Because colectomies for cancer are rarely individualized and are usually analyzed with other diseases [6], the influence of neoplastic disease on the rates of postoperative IC has been poorly evaluated in clinical studies [6, 7]. However, neoplastic disease is known to cause immunosuppression through dysregulating lymphocyte function, which may predispose patients to IC development [6, 8]. We recently demonstrated, through a case matched study, that for patients undergoing resection for a colorectal cancer, advanced tumor stage, malnutrition, obesity, and resection by laparotomy increase the risk of infectious complications after colorectal resection [9]. However, it remains unknown whether malignancy alone favors the development of these complications. The primary aim of this case–controlled study was to investigate whether malignancy correlates with the occurrence of IC after colorectal resection.

Materials and methods

Patients

Between June 2004 and December 2013, 1104 consecutive patients underwent open or laparoscopic resection for colorectal cancer (CRC) or benign disease, either electively ($n=980$) or as an emergency ($n=124$), in our department of digestive surgery in Lille University Hospital, France, and in a private hospital, Clinique Mathilde, Rouen, France. All of these patients were included in a prospective evaluation exploring both the mortality and morbidity after colorectal surgery. Resections were performed for CRC ($n=742$) or benign disease ($n=362$), including diverticular disease, benign colorectal polyps, deep pelvic endometriosis, inflammatory bowel disease, colonic volvulus, stenosis secondary to chronic ischemia, and rare causes (redo-anastomosis for previous fistula or stenosis, colonic resection during postoperative hernia repair, and sigmoid resection during a rectopexy for prolapse).

The inclusion criteria for the present matched pair study were elective segmental resection with supra peritoneal anastomosis for CRC ($n=616$) or benign disease ($n=305$). Patients undergoing resection as an emergency ($n=124$), resection for inflammatory bowel disease ($n=23$), or rectal resection with infraperitoneal colorectal anastomosis or coloanal anastomosis were excluded ($n=46$); also, rare causes ($n=8$) were excluded (4 resections for redo-anastomosis and 4 colorectal resection in association with a mesh repair that may have biased analysis of postoperative IC). No patient underwent preoperative radiation.

A matched pair analysis using the frequency matching technique was constructed to test the hypothesis that malignancy favored postoperative IC. The study group (group B, $n=305$) consisted of all patients fulfilling the inclusion criteria who underwent colorectal resection for a benign disease. According to the frequency matching technique, these patients were broadly matched 1:1 to randomly selected patients who underwent resection for a CRC and met the inclusion criteria during the same study period (group M, $n=305$). Patients were matched according to major variables that have been reported to be linked with postoperative IC, including the age, sex, American Society of Anesthesiologists (ASA) grade, malnutrition (defined as weight loss of more than 10 % over a 6-month period), surgical approach (laparoscopy vs laparotomy), and type of resection [2, 10, 11]. Investigators were blinded to the operative outcome during the selection process.

Preoperative treatment and surgical approach

In the M group, patients' cases were individually discussed during multidisciplinary meetings and treatment was decided according to the French national guidelines [12]. All patients received intravenous prophylactic antibiotics, and the type, timing, and duration of the antibiotic treatment were also decided according to French national guidelines [13]. Seven surgeons performed the colorectal resections. Preoperative bowel preparation was not administered. Povidone–iodine scrub was used for skin preparation in all patients. Colectomy was oncologic in group M. The operative technique and anastomotic technique were all performed at the discretion of the operating surgeon. Left colectomy included left hemicolectomy, superior segmental colectomy (resection of the descending colon and distal transverse colon with anastomosis between the remaining transverse and sigmoid colon), and sigmoid colectomy. Rectal resection included resection of the colorectal junction with a supraperitoneal colorectal anastomosis. Sepsis (infected tumor and/or abscess discovered during surgery) and intraoperative fecal soiling were systematically recorded. The use of closed suction drains and creation of a protective defunctioning stoma were based on the individual surgeons' usual practices. Wound protection was standard during laparotomies, including during specimen extraction in laparoscopic procedures. Early mobilization, early resumption of diet, and nutritional supplements were systematically implemented. Otherwise, perioperative care was based on the individual surgeons' usual practices. The 7th UICC/TNM classification was used for histopathological staining.

Variables studied

Data were collected from a prospectively maintained database. Obesity was defined by a body mass index ≥30 kg/m^2 [14] and anemia was defined by a hemoglobin level <10 g dl^{-1} [15]. The blood loss and operative time were dichotomized using the 75th percentile as a threshold [16].

Group B patients were matched to group M patients according to the age, sex, ASA score, malnutrition, surgical approach, and type of resection; hence, preoperative parameters were comparable between the groups.

The primary endpoint was the IC rate within 30 days of surgery. ICs were defined according to the Centers for Disease Control and Prevention classifications by Horan et al. [17, 18] and consisted of the SSI and E/SSI.

The natures of SSIs were categorized as being incisional or organ space. Incisional SSIs were either superficial (involving only the skin and subcutaneous tissue) or deep (involving deep soft tissues, e.g., fascial and muscle layers). Organ space SSI concerned any part of the body, excluding the skin incision, fascia, or muscle layers, which was opened or manipulated during the operative procedure. Two groups of organ space SSI were identified: first, intra-abdominal abscesses in the absence of radiological or clinical evidence of an anastomotic leak and, second, intra-abdominal abscesses with radiological or clinical evidence of an anastomotic leak. E/SSI included symptomatic urinary, respiratory tract, hematological, or gastro-intestinal infections.

The secondary endpoints included (i) the 30-day overall morbidity, defined as any postoperative complication with a Dindo–Clavien score ≥1 [19]; (ii) 30-day major morbidity, including events requiring reinterventions (grade III in the Dindo–Clavien classification) and life-threatening complications (grade IV in the Dindo–Clavien classification) [19]; and (iii) in-hospital postoperative mortality.

Statistical analysis

Statistical analysis was performed using SPSS® version 15.0 software (SPSS, Chicago, IL). Data are shown as the prevalence or median (range). Continuous data were compared using the *t* test and ordinal data by the chi-square test or Fisher's exact test, as appropriate. To determine predictors of IC, variables with $P<0.10$ in univariable analysis were entered into a multivariable analysis using binary logistic regression analysis. All statistical tests were two-sided, and the threshold of significance was set at $P<0.05$. The study complied with the French National Health guidelines on research involving human subjects.

Results

Composition of the study groups

In group B, the reasons for colorectal resection were the following: 188 with diverticular disease (61.7 %), 74 with benign colorectal polyps (including familial polyposis) (24.3 %), 27 with deep endometriosis and digestive involvement (8.9 %), 11 with colonic volvulus (3.6 %), and 5 with stenosis secondary to chronic ischemia (1.6 %).

In group M, the tumor location was the right colon in 79 cases (25.9 %), transverse colon in 11 cases (3.6 %), left colon in 207 cases (67.9 %), and supraperitoneal rectum in 8 cases (2.6 %). *Histopathological analysis* showed that 76 patients had pTNM stage I disease, 102 patients stage II (82 stage IIA and 20 stages IIB and IIC), 83 patients stage III (10 stage IIIA, 45 stage IIB, and 28 stage IIIC), and 44 patients stage IV disease.

Preoperative variables

The median patient age was 60.1 years (range 16.9–95.1) and the male-to-female ratio was 1.24:1. The patients' ASA grade was I or II in 86.6 % of the cases (Table 1). Malnutrition affected 10.8 % of the patients and 20.2 % of patients were obese at the time of presentation. Most of patients underwent a left colectomy (65.4 %). A laparoscopic approach was attempted in 42 % of the patients. Matching variables were well balanced, as expected. The two groups were comparable in terms of the body mass index, alcohol and tobacco history, and neurologic comorbidity. However, diabetes mellitus and anemia were more frequent in group M ($P=0.006$ and $P<0.001$, respectively).

Intraoperative variables

In group B, infected or abscessed lesions and preoperative fecal soiling were more frequent ($P<0.001$ and $P=0.001$, respectively) (Table 2). In addition, the duration of the operation was longer in group B ($P=0.027$). Other intraoperative variables (conversion, anastomotic characteristics, drain placement, and blood loss) did not differ significantly nor did the frequency with which an associated procedure was performed.

Primary endpoint

Details of the ICs are reported in Table 3. The IC rate at 30 days was 20.8 % and was significantly higher in group M than in group B (25.6 vs 16.1 %; $P=0.004$). Anastomotic leaks accounted for 28.3 % of ICs and were significantly higher in group M than in group B (7.9 vs 3.9 %, $P=0.039$). SSIs, incisional SSIs, and organ space SSIs did not

Table 1 Preoperative variables

		Total $n=610$ (%)	M group $n=305$ (%)	B group $n=305$ (%)	*P*
Age[a]	<70 years	434 (71.1)	207 (67.9)	227 (74.4)	0.074
	≥70 years	176 (28.9)	98 (32.1)	78 (25.6)	
Gender[a]	Male	338 (55.4)	162 (53.1)	176 (57.7)	0.254
	Female	272 (44.6)	143 (46.9)	129 (42.3)	
BMI	<30 kg m^{-2}	487 (79.8)	247 (81.0)	240 (78.7)	0.48
	≥30 kg m^{-2}	123 (20.2)	58 (19.0)	65 (21.3)	
ASA grade[a]	<3	528 (86.6)	259 (84.9)	269 (88.2)	0.235
	≥3	82 (13.4)	46 (15.1)	36 (11.8)	
Malnutrition[a]	No	544 (89.2)	267 (87.5)	277 (90.8)	0.192
	Yes	66 (10.8)	38 (12.5)	28 (9.2)	
Diabetes mellitus	No	529 (86.7)	253 (83.0)	276 (90.5)	0.006
	Yes	81 (13.3)	52 (17.0)	29 (9.5)	
Current smoker	No	500 (82)	255 (83.6)	245 (80.3)	0.292
	Yes	110 (18)	50 (16.4)	60 (19.7)	
Alcohol history	No	571 (93.6)	282 (92.5)	289 (94.8)	0.247
	Yes	39 (6.4)	23 (7.5)	16 (5.2)	
Neurologic comorbidity	No	595 (97.5)	296 (97.0)	299 (98.0)	0.433
	Yes	15 (2.5)	9 (3.0)	6 (2.0)	
Anemia	No	572 (94.2)	274 (89.8)	298 (98.7)	<0.001
	Yes	35 (5.8)	31 (10.2)	4 (1.3)	
Type of resection[a]	Right colectomy	151 (24.8)	84 (27.5)	67 (22)	0.224
	Left colectomy	399 (65.3)	194 (63.7)	205 (67.2)	
	Total colectomy	37 (6.1)	19 (6.2)	18 (5.9)	
	Rectal resection[b]	23 (3.8)	8 (2.6)	15 (4.9)	
Surgical approach[b]	Laparotomy	354 (58.0)	185 (60.7)	169 (55.4)	0.189
	Laparoscopy	256 (42.0)	120 (39.3)	136 (44.6)	

M malignancy, *B* benign disease, *BMI* body mass index, *ASA* American Society of Anesthesiologists

[a] Matched variables

[b] With supraperitoneal anastomosis

significantly differ between the two groups ($P>0.258$). The extra SSI rate was higher in group M than in group B (9.8 vs 4.3 %; $P=0.007$).

Based on univariable analysis, in addition to group M ($P=0.004$), six other variables were statistically related to IC as follows: age greater than 70 years ($P=0.039$), obesity ($P=0.037$), tobacco use history ($P=0.018$), alcohol use history ($P=0.047$), surgical approach (i.e., laparotomy; $P\leq0.001$), and protective stomia ($P=0.014$) (Table 4). However, gender ($P=0.184$), ASA score ($P=0.251$), malnutrition ($P=0.172$), diabetes mellitus ($P=0.131$), neurologic comorbidity ($P=0.572$), anemia ($P=0.252$), conversion rate ($P=0.194$), type of resection ($P=0.500$), infected lesion ($P=0.483$), fecal soiling ($P=0.101$), type of anastomosis ($P=0.199$), intra-abdominal drain placement ($P=0.115$), blood loss ($P=0.650$), transfusion ($P=0.376$), and operative duration ($P=0.129$) had no significant impact on the IC occurrence.

In the multivariable analysis, predictive factors of ICs were malignancy ($P=0.002$), age greater than 70 years ($P=0.018$), tobacco history ($P=0.030$), and obesity ($P=0.039$) (Table 5).

Secondary endpoints

The 30-day overall morbidity rate was 36.9 % (Table 3). Neither the 30-day overall morbidity nor the 30-day major morbidity (Clavien–Dindo grade III/IV complications) significantly differed between the groups ($P=0.154$ and $P=0.385$, respectively).

The in-hospital postoperative mortality rate was 1.5 % ($P=0.252$). Peritonitis secondary to anastomotic leak was the primary cause of postoperative mortality in both groups M ($n=4$) and B ($n=2$). Other causes of postoperative mortality were mesenteric infarction ($n=1$ in each group) and liver failure in a cirrhotic patient ($n=1$) in group M.

Table 2 Intraoperative variables

		Total $n = 610$ (%)	M group $n = 305$ (%)	B group $n = 305$ (%)	*P*
Conversion	No	240 (93.8)	111 (92.5)	129 (94.9)	0.438
($n = 256$)	Yes	16 (6.3)	9 (7.5)	7 (5.1)	
Infected/abscessed	No	579 (94.9)	299 (98.0)	280 (91.8)	<0.001
lesion	Yes	31 (5.1)	6 (2.0)	25 (8.2)	
Fecal soiling	No	583 (95.6)	300 (98.4)	283 (92.8)	0.001
	Yes	27 (4.4)	5 (1.6)	22 (7.2)	
Type of anastomosis	Mechanical	530 (86.9)	258 (84.6)	272 (89.2)	0.093
	Handsewn	80 (13.1)	47 (15.4)	33 (10.8)	
Protective stoma	No	485 (79.5)	249 (81.6)	236 (77.4)	0.192
	Yes	125 (20.5)	56 (18.4)	69 (22.6)	
Intra-abdominal	No	345 (56.6)	174 (57.0)	171 (56.1)	0.806
drain	Yes	265 (43.4)	131 (43.0)	134 (43.9)	
Blood loss ≥500 mL	No	572 (95.2)	286 (95.3)	286 (95.0)	0.856
	Yes	29 (4.8)	14 (4.7)	15 (5.0)	
Transfusion	No	593 (97.2)	293 (96.1)	300 (98.4)	0.085
	Yes	17 (2.8)	12 (3.9)	5 (1.6)	
Operative time	No	512 (83.9)	266 (87.2)	246 (80.7)	0.027
≥240 min	Yes	98 (16.1)	39 (12.8)	59 (19.3)	

Discussion

Both host- and disease-related factors are promising areas of research for predicting and preventing the postoperative morbidity [20]. Elective colectomies for cancer are rarely individualized and are usually either analyzed together or with other diseases or mixed with emergency surgery procedures [6]. We recently demonstrated that for patients undergoing colorectal resection for neoplasia, an advanced tumor stage increased the postoperative ICs [9]. In the present study, we investigated the impact of malignancy alone on the postoperative ICs in a large bicentric case-matched study. We have shown that ICs at 30 days are significantly increased in patients who undergo operations for malignancy compared to benign disease.

Table 3 Postoperative complications

		Total $n = 610$ (%)	M group $n = 305$ (%)	B group $n = 305$ (%)	*P*
In-hospital	No	601 (98.5)	299 (98.0)	302 (99.0)	0.252
mortality	Yes	9 (1.5)	6 (2.0)	3 (1.0)	
30-day	No	385 (63.1)	184 (60.3)	201 (65.9)	0.154
morbidity	Yes	225(36.9)	121 (39.7)	104 (34.1)	
Dindo-classification	Grade I-II	158 (70.2)	82 (67.8)	76 (73.1)	0.385
$n = 225$	Grade III-IV	67 (29.8)	39 (32.2)	28(26.9)	
30-day infectious complication	No	483 (79.2)	227 (74.4)	256 (83.9)	0.004
	Yes	127 (20.8)	78 (25.6)	49 (16.1)	
SSI	No	518 (84.9)	254 (83.3)	264 (86.6)	0.258
	Yes	92 (15.1)	51 (16.7)	41 (13.4)	
Incisional SSI	No	557 (91.3)	276 (90.5)	281 (92.1)	0.472
	Yes	53 (8.7)	29 (9.5)	24 (7.9)	
Organ space SSI	No	565 (92.6)	279 (91.5)	286 (93.8)	0.278
	Yes	45 (7.4)	26 (8.5)	19 (6.2)	
Anastomosis Leak	No	574 (94.1)	281 (92.1)	293 (96.1)	0.039
	Yes	36 (5.9)	24 (7.9)	12 (3.9)	
Extra SSI	No	567 (93.0)	275 (90.2)	292 (95.7)	0.007
	Yes	43 (7.0)	30 (9.8)	13 (4.3)	

A advanced tumor, *L* localized tumor, *SSI* surgical site infection

Table 4 Factors linked to infectious complications in univariate analysis

		Total $n = 610$ (%)	IC $n = 127$ (%)	No IC $n = 483$ (%)	*P*
Nature of lesion	Benign group	305 (50.0)	49 (38.6)	256 (53.0)	0.004
	Malign group	305 (50.0)	78 (61.4)	227 (47.0)	
Age	<70 years	434 (71.1)	81 (63.8)	353 (73.1)	0.039
	≥70 years	176 (28.9)	46 (36.2)	130 (26.9)	
Gender	Male	338 (55.4)	77 (60.6)	261 (54.0)	0.184
	Gender	272 (44.6)	50 (39.4)	222 (46.0)	
BMI	<30 kg m^{-2}	487(79.8)	93(73.2)	394 (81.6)	0.037
	≥30 kg m^{-2}	123 (20.2)	34 (26.8)	89 (18.4)	
ASA score	<3	528 (86.6)	106 (83.5)	422 (87.4)	0.251
	≥3	82 (13.4)	21 (16.5)	61 (12.6)	
Malnutrition	No	544 (89.2)	109 (85.8)	435 (90.1)	0.172
	Yes	66 (10.8)	18 (14.2)	48 (9.9)	
Diabetes mellitus	No	529 (86.7)	105 (82.7)	424 (87.8)	0.131
	Yes	81 (13.3)	22 (17.3)	59 (12.2)	
Current smoker	No	500 (82)	95 (74.8)	405 (83.9)	0.018
	Yes	110 (18)	32 (25.2)	78 (16.1)	
Alcohol history	No	571 (93.6)	114 (89.8)	457 (94.6)	0.047
	Yes	39 (6.4)	13 (10.2)	26 (5.4)	
Neurologic comorbidity	No	595 (97.5)	123 (96.9)	472 (97.7)	0.572
	Yes	15 (2.5)	4 (3.1)	11 (2.3)	
Anemia	≥10 $g.dL^{-1}$	572 (94.2)	117 (92.1)	455 (94.8)	0.252
(hemoglobin level)	<10 $g.dL^{-1}$	35 (5.8)	10 (7.9)	25 (5.2)	
Surgical approach	Laparotomy	354 (58.0)	91 (71.7)	263 (54.5)	<0.001
	Laparoscopy	256 (42.0)	36 (28.3)	220 (45.5)	
Conversion	No	240 (93.8)	32 (88.9)	208 (94.5)	0.194
($n = 256$)	Yes	16 (6.3)	4 (11.1)	12 (5.5)	
Type of resection	Right colectomy	151 (24.8)	38 (29.9)	113 (23.4)	0.500
	Left colectomy	399 (65.3)	78 (61.4)	321 (66.5)	
	Total colectomy	37 (6.1)	7 (5.5)	30 (6.2)	
	Rectal resection	23 (3.8)	4 (3.1)	19 (3.9)	
Infected/abscessed lesion	No	579 (94.9)	119 (93.7)	460 (95.2)	0.483
	Yes	31 (5.1)	8 (6.3)	23 (4.8)	
Fecal soiling	No	583 (95.6)	118 (92.9)	465 (96.3)	0.101
	Yes	27 (4.4)	9 (7.1)	18 (3.7)	
Type of anastomosis	Mechanical	530 (86.9)	106 (83.5)	424 (87.8)	0.199
($n = 610$)	Handsewn	80 (13.1)	21 (16.5)	59 (12.2)	
Protective stoma	No	485 (79.5)	91 (71.1)	394 (81.6)	0.014
	Yes	125 (20.5)	36 (28.3)	89 (18.4)	
Intra-abdominal	No	345 (56.6)	64 (50.4)	281 (58.2)	0.115
drain	Yes	265 (43.4)	63 (49.6)	202 (41.8)	
Blood loss	<500 mL	572 (95.2)	118 (94.4)	454 (95.4)	0.650
	≥500 mL	29 (4.8)	7 (5.6)	22 (4.6)	
Transfusion	No	593(97.2)	122 (96.1)	471 (97.5)	0.376
	Yes	17(2.8)	5 (3.9)	12 (2.5)	
Operative time	<240 min	512 (83.9)	101 (79.5)	411 (85.1)	0.129
	≥240 min	98 (16.1)	26 (20.5)	72 (14.9)	

IC infectious complication, *A* advanced tumor, *L* localized tumor, *BMI* body mass index, *ASA* American Society of Anesthesiologists

Table 5 Factors linked to infectious complications in multivariate analysis

	χ^2	Odd ratio	95 confidence interval		P
Malignancy	9.425	2.024	1.290	3.175	0.002
Age ≥70 years	5.597	1.730	1.099	2.725	0.018
Current smoker	4.696	1.873	1.066	3.300	0.030
Laparotomy	3.443	1.535	0.976	2.415	0.064
Intra-abdominal drain	1.741	1.354	0.863	2.124	0.187
Obesity	4.280	1.678	1.028	2.740	0.039
Operative time	1.694	1.510	0.811	2.809	0.193
Fecal soiling	0.025	1.076	0.429	2.703	0.875
Protective stoma	0.797	1.299	0.731	2.288	0.372
Diabetes mellitus	0.020	1.045	0.560	1.949	0.889
Alcohol history	0.451	1.300	0.603	2.801	0.502

BMI body mass index, *ASA* American Society of Anesthesiologists

Taking into account confounding factors, either by the matching technique for preoperative variables or by adjustment through the multivariable analysis for perioperative and postoperative variables, malignancy was identified as an independent predictive factor for ICs (odds ratio (OR) = 2.024, P = 0.002). Three other factors, age ≥70 years, obesity, and tobacco use, have already been described as predictive of increased ICs [20–23] and were confirmed as such in the current study.

The morbidity and IC rates that we report are comparable with previous studies [4, 9]. Despite a higher frequency of abscessed lesion and fecal soiling in group B, SSI, incisional SSI, and organ space SSI remained similar between the groups, suggesting a deleterious effect of malignancy on SSI and its different subcategories. The higher risk of ICs in group M was mainly due to a collective implication of extra SSI and anastomotic leakage. Extent of resection in CRC includes the whole mesocolon for lymphadenectomy reasons, which may impair blood supply of the anastomotic region and consequently explain this higher rate of anastomotic leakage. A recent meta-analysis did not find statistically significant differences between the high and low ligation of the inferior mesenteric artery in the anastomotic leak rate (OR = 1.02, 95 % CI 0.76–1.37) [24]. Anastomotic leak can, indeed, be caused by multiple factors (including host- and disease-related factors), but a significant role of the ligation location has not been identified yet.

To the best of our knowledge, this is the first dedicated comparative controlled study demonstrating the effect of malignancy on the occurrence of postoperative ICs. The impact of malignancy on the IC rates is significant because other factors that are well known to be related to IC that were tested, including the nutritional status and surgical approach (laparoscopy), and significant in univariate analysis were no longer significant in the multivariate analysis. In the specific population of patients undergoing colorectal resection for CRC, we previously demonstrated that predictive factors of IC, in addition to advanced tumor stage, included malnutrition, obesity, and resection by laparotomy [9]. Immunosuppression appears to be the common factor that is shared by all of the independent predictors of postoperative ICs that we identified. Alteration in the balance of lymphocyte subpopulations and reduction in the cytokine production in CRC, especially in advanced stages [25, 26], provides evidence for tumor-induced suppression of immune function. Open compared to laparoscopic resection has been associated with a longer disruption of the immunological homeostasis after CRC resection, mainly in the early stages [27]. Malnutrition and obesity are also known to reduce the cellular and humoral immune responses [28, 29]. Finally, it is well known that smokers have impaired immune function, leading to an increased risk in the postoperative ICs [30].

These results raise the question of what corrective actions in the patient's history or perioperative care may be taken to minimize the postoperative ICs in colorectal resections, regardless of the indication, and more specifically for CRC.

Regarding obesity, it is self-evident that corrective dietary measures may be an option in benign cases, but they cannot be achieved in patients who present with a CRC. Paradoxically, these patients often present in a malnourished state despite their obesity, including sarcopenia, which has recently been showed to predict the postoperative complications after colorectal surgery, including ICs [31]. Recent studies suggest that using BMI to define obesity is suboptimal and that the waist circumference and waist/hip ratio are better predictive risk factors for morbidity and mortality after colorectal surgery [32]. A strict evaluation and correction of the nutritional status of obese patients may significantly improve the postoperative results.

Several recent studies have found that current smokers are at a significantly increased risk of postoperative morbidity, including ICs and mortality, after colorectal surgery [23, 33]. This finding persisted across malignant and benign diagnoses [23], and there was a reduction in the long-term overall survival in smokers who underwent an operation for a CRC [33]. A concerted effort should be made to promoting smoking cessation in all patients who are scheduled for elective colorectal surgery with smoking cessation of 4 or more weeks [23, 34]. However, delaying surgery for colorectal cancer for 4 weeks, with the concurrent risk of tumor growth, needs to be at least critically weighed against the potential benefits of smoking cessation.

Immunonutrition consists of a supplementation in the immuno nutrients, mainly arginine, omega-3 fatty acids, and nucleotides. A systematic short course of preoperative immunonutrition, regardless of the nutritional status, combined with a postoperative course in malnourished patients, has been shown to decrease both the postoperative infectious morbidity (incisional surgical site, extra surgical site, and organ space SSIs) and length of hospital stay through improving the immunometabolic host response, which has a potential positive impact on the long-term prognosis through modifying tumor lymphocyte infiltration [35, 36]. Recently, oral antibiotic bowel preparation has been shown to significantly reduce the SSI, length of stay, and number of readmissions in elective colorectal surgery [37]. Additionally, preoperative probiotics have been shown to decrease ICs with possible mechanisms attributed to the maintenance of the intestinal flora and restriction of bacterial translocation from the intestine. This may be representative of the enhancement of systemic/localized immunity and concurrent attenuation of the systemic stress response [38, 39].

Enhanced recovery after surgery (ERAS) is a perioperative and postoperative care concept that was initiated in the early 1990s with the aim of initially reducing the length of hospital stays following elective abdominal surgery. However, it is now well known that ERAS decreases postoperative complication rates after colorectal surgery compared with conventional postoperative care [40], and there is a potential attenuation of the immune cascade [41]. The LAFA trial reported the superiority of laparoscopic surgery over open surgery for colon cancer when both are combined with an ERAS program [42]. A recent study additionally supported the use of laparoscopic resection within an ERAS program as an independent factor associated with an improved outcome [43].

This study is limited by its retrospective nature, which may introduce bias. However, the bicentric nature of our investigation, which used prospective culling of variables with very limited missing data, strengthens our study. Moreover, the sample size and the combination of a matched pair design to a multivariate analysis provide sufficient statistical robustness. Of note, diabetes mellitus and anemia, two potential factors that may have impact the risk of IC, were more frequent in group M [44, 45]. Both had no significant impact on IC in univariate analysis meaning that the variables do not interfere with the conclusion that malignancy is a predictive factor of IC. On a statistical point of view, introducing too much variables in a matched study may lead to a deleterious impact on the robustness of the results while decreasing strongly the number of patients enrolled. We used ASA score to define existing comorbid conditions in the population, more than detail of each comorbidity to ensure a robust matching. Taking into account independently each comorbid factor may have had some confusions due to (i) no standardized definition of the severity of each complication and (ii) no data about the fact that such comorbid condition are stabilized or not.

We excluded rectal resections with infraperitoneal anastomosis, resections for inflammatory disease, resection for redo-anastomosis, and resections in association with use of non-absorbable mesh because of specificities, including radiation use, immunosuppressive therapies, and surgery that may otherwise introduce bias.

Conclusion

We have shown that malignancy is an independent risk factor for ICs after colorectal resection with other risk factors, including advanced age (≥70 years), obesity, and current smoking status. Optimization of the modifiable risk factors through strict evaluation and correction of the nutritional status and smoking cessation should be favored in an effort to reduce the ICs after CRC resection. Moreover, optimization of immune function in CRC patients and increased compliance with an ERAS program, including the use of laparoscopic surgery, should be considered.

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Compliance with ethical standards

Sources of funding None.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration as well as its later amendments or comparable ethical standards. Because this is a retrospective study, formal informed consent was not required.

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