



Oncological outcome of surgical site infection after colorectal cancer surgery

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Abstract

Background This study evaluated the oncological outcome of surgical site infection (SSI) after colorectal cancer surgery.

Methods A total of 3675 consecutive patients with colorectal cancer who underwent curative resection from January 2009 to December 2011 were analyzed. The prognostic significance of SSI was evaluated. Risk factors for SSI were also identified using multivariate regression analysis.

Results Overall SSI rate was 9.6%, in which 5.5% was superficial or deep SSI and 4.1% was organ/space SSI. Incidence of SSI varied significantly with tumor location ($P < 0.001$): 7.1% in colon cancer and 14.0% in rectal cancer. With a median follow-up period of 49.8 months, the 5-year disease-free survival rates of patients without and with SSI were 87% and 83%, respectively ($P = 0.018$). SSI predicted disease-free survival in univariate analysis. However, SSI was not an independent predictor of survival in multivariate analysis. Body mass index, ASA score, preoperative WBC count, rectal tumor, open surgery, operation time, and transfusion during surgery were independent predictors of SSI.

Conclusion SSI predicted disease-free survival in colorectal cancer patients following curative surgery. Patient' demographics, tumor characteristics, and perioperative conditions were independently associated with an increased likelihood of SSI.

Keywords Colorectal cancer · Surgical site infection · Survival

Introduction

Surgical site infection (SSI) is one of the most common post-operative morbidities, occurring in 5% to up to 40% of patients undergoing colorectal surgery.[1–7] SSI following surgery is an important marker of surgical quality and is associated with longer length of stay, higher rates of reoperation and readmission, and increased mortality.[8, 9] Poor survival was observed in patients with various types of cancer showing SSI after surgery.[10–13] However, the long-term impact of SSI

on disease-free survival after colorectal cancer surgery is limited and unclear.

The aim of this study is to evaluate the long-term oncological outcome of SSI after colorectal cancer surgery. Furthermore, we sought to determine the predictive risk factors for SSI using clinical preoperative factors.

Methods

Consecutive patients who underwent curative surgery for colorectal cancer at our institution between January 2009 and December 2011 were reviewed. All patients had biopsy-proven colorectal adenocarcinoma. Patients with metastatic and recurrent disease, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, local resection, or no follow-up data were excluded from the study cohort. Ultimately, 3575 patients were included in the analysis. This project was reviewed and approved by the appropriate institutional review board.

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All patients underwent curative resection of the tumors, which were staged according to the 7th American Joint Committee on Cancer (AJCC) TNM classification. Postoperative chemotherapy was considered for all patients with stage II and III colorectal cancer. The decision to administer postoperative chemotherapy depended on the general health of the patients as well as their acceptance of therapy. SSI was defined according to the Center for Disease Control and Prevention (CDC) guidelines as a clinically reported infection of any incision site occurring within 30 days after surgery.[14] SSI was diagnosed based on the clinical pattern recognition by the treating surgeon, as follows: abnormal redness, warmth, localized swelling, purulent discharge, unexplained isolated organisms, and opening of the wounds. The categories of superficial, deep, and organ/space SSI were defined by the CDC.

The patients were followed up every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. The follow-up examination was conducted on a semi-annual basis or when recurrence was suspected. The follow-up examination included clinical history, physical examination, serum carcinoembryonic antigen (CEA) level, chest X-ray, chest and abdominopelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI), colonoscopy, and positron emission tomography (PET) scanning if available.

Statistical evaluation was carried out using the statistical package SPSS for Windows (Version 18.0; SPSS Inc., Chicago, IL, USA). Differences between the groups were tested using the Student's *t* test and the Chi-squared test or Fisher's exact test as appropriate. Survival curves were calculated using the Kaplan-Meier method and differences between curves were evaluated using the log-rank test. A Cox proportional hazard model generated by a forward stepwise selection of variables was used for multivariate analysis. Only factors for which a *P* value ≤ 0.05 , as determined in the univariate analysis, were entered into the multivariate analysis. A *P* value ≤ 0.05 was considered statistically significant.

Results

The clinicopathological characteristics of the 3675 colorectal cancer patients are summarized in Table 1. Of the 352 patients (9.6%) with overall SSI, 202 patients (5.5%) were classified as superficial or deep SSI and 150 (4.1%) as organ space SSI. Incidence of SSI varied significantly according to tumor location ($P < 0.001$): 7.1% (5.0% of superficial/deep SSI and 2.1% of organ/space SSI) in colon cancer and 14.0% (6.3% of superficial/deep SSI and 7.7% of organ/space SSI) in rectal cancer. SSI was significantly associated with gender, preoperative serum CEA level and WBC count, operative method, tumor location and diameter, operation time, transfusion

Table 1 Patient characteristics ($n = 3675$)

	No. (%)
Median age, years (range)	60 (16–90)
Gender	
Male	2243 (61.0)
Female	1432 (39.0)
BMI, kg/m ²	
< 25	2364 (64.3)
≥ 25	1090 (29.7)
Unknown	221 (6.0)
ASA score	
1–2	2260 (61.5)
3–4	92 (2.5)
Unknown	1323 (36.0)
Tumor location	
Colon	2381 (64.8)
Rectum	1294 (35.2)
Operation method	
Open	1229 (33.4)
Laparoscopic assisted	2446 (66.6)
Positive lymphovascular invasion	1334/3497 (38.1)
Positive perineural invasion	471/3474 (13.6)
Positive tumor budding	1427/3350 (42.6)
Median No. of lymph nodes harvested (range)	17 (0–138)
Median preoperative CEA, ng/mL (range)	1.9 (0.1–294.5)
Positive circumferential resection margin	104 (2.8)
Adjuvant chemotherapy	1677/2470 (67.9)
Pathologic TNM stage	
0	148 (4.0)
I	929 (25.3)
II	1103 (30.0)
III	1495 (40.7)
SSI	
No	3323 (90.4)
Superficial/deep	202 (5.5)
Organ space	150 (4.1)

BMI body mass index, *ASA* American Society of Anesthesiologists, *CEA* carcinoembryonic antigen, *SSI* surgical site infection

during operation, hospital stay, readmission, and postoperative chemotherapy (Table 2).

Univariate analysis indicated that the factors associated with disease-free survival were preoperative serum CEA level, preoperative WBC count, preoperative CRP level, operative method, tumor location, tumor diameter, operation time, transfusion during operation, hospital stay, readmission, differentiation, pathologic stage, number of lymph nodes retrieved, circumferential resection margin, lymphovascular invasion, perineural invasion, administration of postoperative chemotherapy, and SSI (Table 3).

Table 2 Comparison of patients according to the surgical site infection (SSI)

	No (<i>n</i> = 3323)	Superficial/deep (<i>n</i> = 202)	Organ space (<i>n</i> = 150)	<i>P</i>
Age, years				0.324
< 60	1618 (48.7)	93 (46.0)	81 (54.0)	
≥ 60	1705 (51.3)	109 (54.0)	69 (46.0)	
Gender				< 0.001
Male	2002 (60.2)	126 (62.4)	115 (76.7)	
Female	1321 (39.8)	76 (37.6)	35 (23.3)	
Body mass index, kg/m ²				0.680
< 25	2149 (64.7)	126 (62.4)	89 (59.3)	
≥ 25	964 (29.0)	72 (35.6)	54 (36.0)	
Unknown	210 (6.3)	4 (2.0)	7 (4.7)	
ASA score				0.069
1–2	2029 (61.1)	130 (64.4)	101 (67.3)	
3–4	81 (2.4)	9 (4.5)	2 (1.3)	
Unknown	1213 (36.5)	63 (31.2)	47 (31.3)	
Diabetes mellitus				0.596
No	1310 (39.4)	82 (40.6)	58 (38.7)	
Yes	515 (15.5)	36 (17.8)	29 (19.3)	
Unknown	1498 (45.1)	84 (41.6)	63 (42.0)	
Preoperative CEA, ng/mL				0.003
< 5	2761 (83.1)	151 (74.8)	117 (78.0)	
≥ 5	482 (14.5)	39 (19.3)	27 (18.0)	
Not available	80 (2.4)	12 (5.9)	6 (4.0)	
Preoperative WBC, cells/mL				< 0.001
< 11,000	3231 (97.2)	185 (91.6)	144 (96.0)	
≥ 11,000	92 (2.8)	17 (8.4)	6 (4.0)	
Preoperative CRP, mg/L				0.171
< 1	2917 (87.8)	163 (80.7)	126 (84.0)	
≥ 1	329 (9.9)	33 (16.3)	22 (14.7)	
Not available	77 (2.3)	6 (3.0)	2 (1.3)	
Operative method				< 0.001
Open	1005 (30.2)	154 (76.2)	70 (46.7)	
Laparoscopic	2318 (69.8)	48 (23.8)	80 (53.3)	
Tumor location				< 0.001
Colon	2210 (66.5)	120 (59.4)	51 (34.0)	
Rectum	1113 (33.5)	82 (40.6)	99 (66.0)	
Maximal diameter of tumor, cm				0.008
< 4.5	1953 (58.8)	99 (49.0)	78 (52.0)	
≥ 4.5	1370 (41.2)	103 (51.0)	72 (48.0)	
Operation time, min				0.001
< 135	1208 (36.4)	53 (26.2)	40 (26.7)	
≥ 135	2115 (63.6)	149 (73.8)	110 (73.3)	
Transfusion during surgery				< 0.001
No	3232 (97.3)	184 (91.1)	140 (93.3)	
Yes	91 (2.7)	18 (8.9)	10 (6.7)	
Hospital stay, day				< 0.001
≤ 7	2098 (63.1)	28 (13.9)	7 (4.7)	
> 7	1225 (36.9)	174 (86.1)	143 (95.3)	
Readmission				< 0.001
No	3190 (96.0)	186 (92.1)	110 (73.3)	
Yes	133 (4.0)	16 (7.9)	40 (26.7)	
Differentiation				0.697
Well + moderate	3056 (92.0)	183 (90.6)	142 (94.7)	
Poor + mucinous	267 (8.0)	19 (9.4)	8 (5.3)	
Pathologic TNM stage				0.183
0–II	1987 (59.8)	109 (54.0)	84 (56.0)	
III	1336 (40.2)	93 (46.0)	66 (44.0)	
No. of lymph nodes retrieved				0.961
< 12	611 (18.4)	39 (19.3)	25 (16.7)	
≥ 12	2712 (81.6)	163 (80.7)	125 (83.3)	
Circumferential resection margin, mm				0.398
< 1	89 (2.7)	12 (5.9)	3 (2.0)	
≥ 1	3234 (97.3)	190 (94.1)	147 (98.0)	
Lymphovascular invasion				0.519
Negative	1964 (59.1)	111 (55.0)	88 (58.7)	
Positive	1204 (36.2)	77 (38.1)	53 (35.3)	

Table 2 (continued)

	No (<i>n</i> = 3323)	Superficial/deep (<i>n</i> = 202)	Organ space (<i>n</i> = 150)	<i>P</i>
Unknown	155 (4.7)	14 (6.9)	9 (6.0)	0.456
Perineural invasion				
Negative	2728 (82.1)	159 (78.7)	116 (77.3)	
Positive	418 (12.6)	29 (14.4)	24 (16.0)	0.038
Unknown	177 (5.3)	14 (6.9)	10 (6.7)	
Postoperative chemotherapy				
No	718 (21.6)	42 (20.8)	33 (22.0)	0.038
Yes	1512 (45.5)	108 (53.5)	57 (38.0)	
Unknown	1093 (32.9)	52 (25.7)	60 (40.0)	

ASA American Society of Anesthesiologists, CEA carcinoembryonic antigen, WBC white blood cells, CRP C-reactive protein

Multivariate analysis revealed that preoperative CRP level, tumor location, differentiation, pathologic stage, number of lymph nodes retrieved, lymphovascular invasion, perineural invasion, and administration of postoperative chemotherapy were independent prognostic factors for disease-free survival (Table 3). SSI predicted disease-free survival in univariate analysis ($P = 0.018$). However, the multivariate analysis revealed that SSI was not an independent prognostic factor for survival.

In the median follow-up of 49.8 months (range, 0.1–75.9), the 5-year disease-free survival of this cohort was 85%. The survival curves among the SSI groups differed significantly (Fig. 1). The 5-year disease-free survival rates of patients without and with SSI were 87% and 83%, respectively ($P = 0.018$, Fig. 1). Given the potential importance of clinical prediction for SSI, we performed a multivariate analysis to identify clinical and perioperative predictors independently associated with SSI (Table 4). Body mass index ≥ 25 kg/m² ($P = 0.008$), ASA score 3 ($P = 0.001$), preoperative WBC count of $\geq 11,000$ cells/mcL ($P = 0.022$), rectal tumor ($P < 0.001$), open surgery ($P < 0.001$), operation time ≥ 135 min, and transfusion during surgery ($P = 0.011$) were independent predictors of SSI.

Discussion

The overall incidence of SSI in this study was 9.6%: 7.1% in colon cancer and 14.0% in rectal cancer.

Significant SSI risk factors in the preoperative setting were identified. In addition to rectal location of tumor, preoperative WBC count and CRP level were independently associated with a significant increase in SSI. Most importantly, there was an association between SSI and poor disease-free survival in patients with colorectal cancer surgery. However, this result was not confirmed in the multivariate logistic analysis in our study.

The long-term impact of SSI on several cancers such as head and neck cancer, breast cancer, colon cancer, and gastric

cancer suggested worse outcomes, specifically shorter disease-free and overall survival.[10–13] Nespoli et al.[13] showed that postoperative infection was associated with poor 5-year survival in 192 patients with colon cancer. The postoperative morbidities of colorectal surgery adversely affect patient mortality.[15, 16] Organ/space SSI including anastomotic leakage has associated with poor long-term survival in numerous studies.[17–19] We also reported that anastomotic leakage was associated with poor survival following rectal cancer surgery.[19] Similarly, the development of SSI was associated with poor disease-free survival in our analysis.[19]

The incidence of SSI in colorectal cancer patients in our study was comparable to other recent studies.[1–7] The national incidence of SSI following colorectal surgery is 9% according to the American College of Surgeons National Surgical Quality Improvement Program[1] and is comparable to our results. However, the incidence of SSI varies widely, ranging 5 to 40% throughout the literature, due to several factors.[1–4] First, the variability is based on case mix and patient demographics. Studies did not include organ/space SSI due to inherent differences from incisional SSI. Another important consideration is that a number of studies reporting SSI excluded rectal cancer due to challenges associated with rectal surgery rather than colectomies, and consequently higher rate of SSI after rectal surgery compared with colectomies. In addition, the recent advances for prevention of SSI in cancer surgery may be attributed to a multifaceted effort, including understanding and prevention for patient's risk factors, appropriate timing of prophylactic antibiotic administration, proper skin preparation and draping, and active surveillance. The overall SSI of 9.6% following colorectal cancer surgery in our study is definitely not inferior to the recent results reported anywhere.

Risk factors for SSI are broadly divided into patient factors (age, body mass index, ASA score, smoking status, and diabetes mellitus), tumor factors (location of tumor), and procedural factors (general anesthesia, operative time,

Table 3 Univariate and multivariate analyses of factors for 5-year disease-free survival

Factor	Univariate analysis		Multivariate analysis		
	Survival (%)	<i>P</i>	HR	CI (95%)	<i>P</i>
Age, years		0.132			
< 60	86.8				
≥ 60	86.3				
Gender		0.974			
Male	86.5				
Female	86.6				
Body mass index, kg/m ²		0.097			
< 25	86.2				
≥ 25	87.9				
ASA score		0.110			
1–2	87.8				
3–4	82.6				
Diabetes mellitus		0.092			
No	86.3				
Yes	89.3				
Preoperative CEA, ng/mL		< 0.001			
< 5	87.9		1		
≥ 5	80.0		1.201	0.912–1.582	0.192
Preoperative WBC, cells/mL		0.001			
< 11,000	86.9		1		
≥ 11,000	77.2		1.393	0.825–2.351	0.215
Preoperative CRP, mg/L		< 0.001			
< 1	86.9		1		
≥ 1	77.8		1.436	1.002–2.056	0.049
Operative method		< 0.001			
Open	82.2		1		
Laparoscopic	88.8		0.837	0.649–1.079	0.169
Tumor location		< 0.001			
Colon	89.2		1		
Rectum	81.8		2.180	1.710–2.778	< 0.001
Maximal diameter of tumor, cm		< 0.001			
< 4.5	88.4		1		
≥ 4.5	84.0		1.297	1.013–1.660	0.039
Operation time, min		0.002			
< 135	89.0		1		
≥ 135	85.2		1.196	0.936–1.528	0.152
Transfusion during surgery		0.006			
No	86.8		1		
Yes	80.7		1.063	0.582–1.943	0.842
Hospital stay, day		< 0.001			
≤ 7	89.0		1		
> 7	83.1		1.185	0.925–1.517	0.180
Readmission		0.011			
No	86.9		1		
Yes	80.4		1.091	0.726–1.639	0.675
Differentiation		< 0.001			
Well + moderate	87.1		1		
Poor + mucinous	80.3		1.456	1.025–2.069	0.036
Pathologic TNM stage		< 0.001			
0–II	92.8		1		
III	77.4		2.697	1.958–3.714	< 0.001
No. of lymph nodes retrieved		0.024			
< 12	83.5		1		
≥ 12	87.2		0.723	0.544–0.961	0.026
Circumferential resection margin, mm		< 0.001			
< 1	87.0		1		
≥ 1	70.2		1.214	0.727–2.025	0.459
Lymphovascular invasion		< 0.001			
Negative	91.5		1		
Positive	77.6		1.604	1.218–2.104	0.001
Perineural invasion		< 0.001			
Negative	88.7		1		
Positive	69.4		2.081	1.597–2.712	< 0.001

Table 3 (continued)

Factor	Univariate analysis		Multivariate analysis		
	Survival (%)	<i>P</i>	HR	CI (95%)	<i>P</i>
Postoperative chemotherapy		<0.001			
No	90.8		1		
Yes	83.1		0.696	0.502–0.964	0.029
Surgical site infection		0.018			
No	86.9		1		
Yes	82.9		1.049	0.731–1.504	0.795

ASA American Society of Anesthesiologists, CEA carcinoembryonic antigen, WBC white blood cells, CRP C-reactive protein

open procedures, and perioperative transfusion).[6, 7, 20–25] Multivariate analysis revealed seven independent risk factors for the development of SSI in our study, consistent with previous study. The majority of our risk factors are not modifiable (body mass index, ASA score, preoperative WBC count, location of tumor). Importantly, for early detection and prompt treatment, surgeons should be aware of the role of these risk factors in increased incidence of SSI postoperatively. Consistent with other studies, we found that blood transfusion was an important risk factor for SSI.[26, 27] Transfusion-related immune modulation may result in a higher incidence of hospital-acquired infection.[28, 29] In addition, our analysis identified open surgery and lengthy operations as independent risk factors for SSI. A number of studies have also reported that laparoscopic methods and shorter operative time were associated with a lower SSI rate.[30, 31] Thus, surgeons should

endeavor to limit the duration of operation and opt for minimally invasive surgery if possible.

This study has several potential limitations. Given the retrospective design of the analysis, there was the potential of selection bias. Additionally, several risk factors that have been previously reported to be associated with the development of SSI (smoking status and perioperative hyperglycemia) were not considered in our analysis. Future validation of these data is required to overcome these limitations.

In conclusion, SSI predicted disease-free survival in colorectal cancer patients following curative surgery. Several risk factors, including patient factors and perioperative condition, are independently associated with development of SSI following colorectal cancer surgery. Knowledge of risk factors associated with SSI is essential for postoperative vigilance for early detection and prompt management.

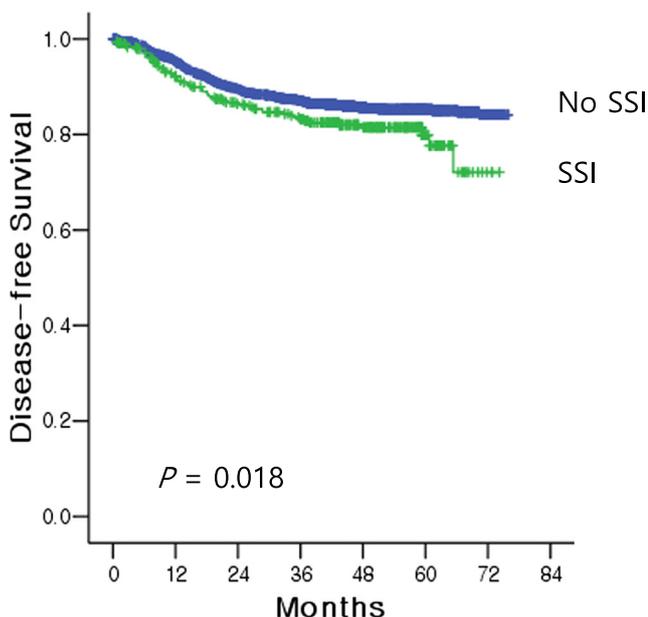


Fig. 1 Disease-free survival curves according to the surgical site infection after colorectal cancer surgery

Table 4 Multivariate analyses of clinical and perioperative predictors of surgical site infection (SSI) after colorectal cancer surgery

	Odds ratio (CI)	<i>P</i>
Age	1.234 (0.964–1.581)	0.095
Gender	1.270 (0.992–1.626)	0.058
Body mass index	1.396 (1.090–1.788)	0.008
ASA score	1.577 (1.211–2.054)	0.001
Preoperative CEA	1.256 (0.919–1.715)	0.152
Diabetes mellitus	1.148 (0.827–1.595)	0.410
Clinical stage	1.071 (0.791–1.449)	0.657
Preoperative WBC	1.834 (1.091–3.084)	0.022
Preoperative CRP	1.022 (0.706–1.477)	0.910
Tumor location	1.788 (1.391–2.297)	<0.001
Tumor size	1.285 (0.982–1.682)	0.068
Operative method	4.104 (3.174–5.306)	<0.001
Operation time	1.632 (1.252–3.091)	<0.001
Transfusion during operation	1.889 (1.154–3.091)	0.011

ASA American Society of Anesthesiologists, CEA carcinoembryonic antigen, WBC white blood cells, CRP C-reactive protein

Compliance with ethical standards

This project was reviewed and approved by the appropriate institutional review board.

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

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