Original Article

Effects of Surgical Site Infection on Long-term Oncological Outcomes in Patients with Colorectal Cancer Undergoing Minimally Invasive Surgery

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Key Words
Surgical site infection (SSI);
Minimally invasive surgery (MIS);
Colorectal cancer (CRC)

Background. Surgical site infection (SSI) can influence oncological outcomes for various cancers. However, their association with minimally invasive surgery (MIS) in patients with colorectal cancer (CRC) remains poorly understood. This study explored the association between SSI and long-term outcomes in patients with CRC undergoing MIS.

Methods. A retrospective analysis was conducted on patients with Stage I to III CRC who underwent R0 resection through MIS at a single institution between September 1, 2007, and December 31, 2018. A total of 2,543 patients were included. Propensity score matching and Kaplan-Meier analysis were used to evaluate the effects of SSI on the long-term patient outcomes.

Results. Deep infection following MIS for CRC was significantly associated with adverse long-term outcomes, including a higher recurrence rate ($p = 0.003$), shorter overall survival (OS) ($p = 0.017$), and shorter disease-free survival (DFS) ($p = 0.001$). By contrast, superficial infection did not significantly influence recurrence rates ($p = 0.205$) or OS ($p = 0.097$) but was associated with poorer DFS ($p = 0.013$).

Conclusion. Postoperative deep infection following MIS for patients with CRC is associated with an increased recurrence rate and worse OS and DFS. These findings underscore the urgency of preventing and managing deep infections to improve long-term outcomes in patients with CRC undergoing MIS. Further research is required to elucidate the mechanisms behind these outcomes and improve treatment options for this group of patients.

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Colorectal cancer (CRC) is a critical public health concern in Taiwan; it is the second most frequently diagnosed cancer and the third leading cause of cancer-related deaths. Surgical resection is the primary treatment for patients with Stage I to III CRC. Identifying and addressing risks associated with these surgical procedures is crucial.

Surgical site infection (SSI) is one risk associated with surgical resection. SSI may cause complications such as delayed wound healing, lead to prolonged hospital stays, and lead to increased health-care costs. SSI has been linked to adverse long-term oncological out-

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comes in several types of cancer.[1-5] However, the influence of SSI on the long-term oncological outcomes of patients undergoing CRC surgery remains unclear.[6-13]

SSI can be categorized into two types on the basis of severity: deep and superficial. Deep infection, such as anastomotic leaks or intra-abdominal infection, require extended hospital stays, advanced antibiotics, and meticulous care and potentially necessitate additional surgical procedures. By contrast, less severe, superficial infection, such as wound infection or dehiscence, does not cause these long-term effects.

Minimally invasive surgery (MIS), such as laparoscopic and robot-assisted surgery, is the preferred approach for CRC resection because of its numerous benefits, including reduced postoperative pain, shorter hospital stays, and faster recovery times.[14]. MIS has also been demonstrated to reduce the risk of SSI compared with open surgery.[15-17] Despite these advantages, the association between SSI and long-term oncological outcomes in patients with CRC undergoing MIS remains poorly understood.

This study analyzed the association between SSI and long-term oncological outcomes in patients undergoing MIS for CRC. We analyzed data from a single hospital over a period of two decades to investigate whether SSI was linked with adverse long-term outcomes, including recurrence rate; disease-free survival (DFS); and overall survival (OS). Furthermore, we assessed whether MIS moderated this association. The findings of this study provide crucial insights into the optimal surgical approach that can be employed to achieve favorable long-term oncological outcomes for patients with CRC.

Materials and Methods

The clinicopathological features of the tumors of patients with CRC were acquired from the Colorectal Section Tumor Registry Database of Chang Gung Memorial Hospital in Linkou, Taiwan. Data collection was conducted by four nursing specialists, who obtained information by interviewing patients and evaluating clinicopathological reports. The clinicopathological reports were completed by physicians by using a standardized form during patient admission. The database includes information on various factors, such as clinical features, primary conditions leading to admission, underlying medical conditions, preoperative blood tests, intraoperative variables, postoperative morbidities and mortality, and tumor-related clinicopathological variables. The Institutional Review Board of Chang Gung Memorial Hospital approved this study (IRB No: 202400653B0).

Patient selection and classification of SSI

We initially enrolled 3,223 patients who underwent MIS at Chang Gung Memorial Hospital between September 1, 2007, and December 31, 2018, and retrieved data from the database. Subsequently, 417 patients who had undergone palliative surgery, had recurrent disease, or had Stage IV cancer were excluded. Patients undergoing neoadjuvant chemotherapy or lacking essential data were also excluded. Finally, 2,543 patients were included in our analysis (Fig. 1).

The patients were segmented into groups on the basis of whether they had postoperative SSI, which was classified as superficial or deep infection. Superficial infection, that is, wound infection or dehiscence occurring within 30 days after the operation, typically involves the skin and subcutaneous tissue and is less severe than deep infection. By contrast, deep infection, including anastomotic leakage or intra-abdominal infection (such as an abscess or peritonitis) within the 30-day postoperative period, is more serious, often challenging to manage, and associated with increased morbidity and mortality rates.

Propensity score matching

Propensity score matching (PSM) was conducted to match the two groups at a 1:1 ratio to address potential selection biases arising from variations in sample sizes and covariates. A match tolerance of 0.0001 was applied. Nine variables — sex, age, body mass index, preoperative albumin level, tumor location, tumor-node-metastasis stage, preoperative carcinoembryonic antigen (CEA) level, operation date, and adjuvant treatment — were used for PSM. The PSM ensured

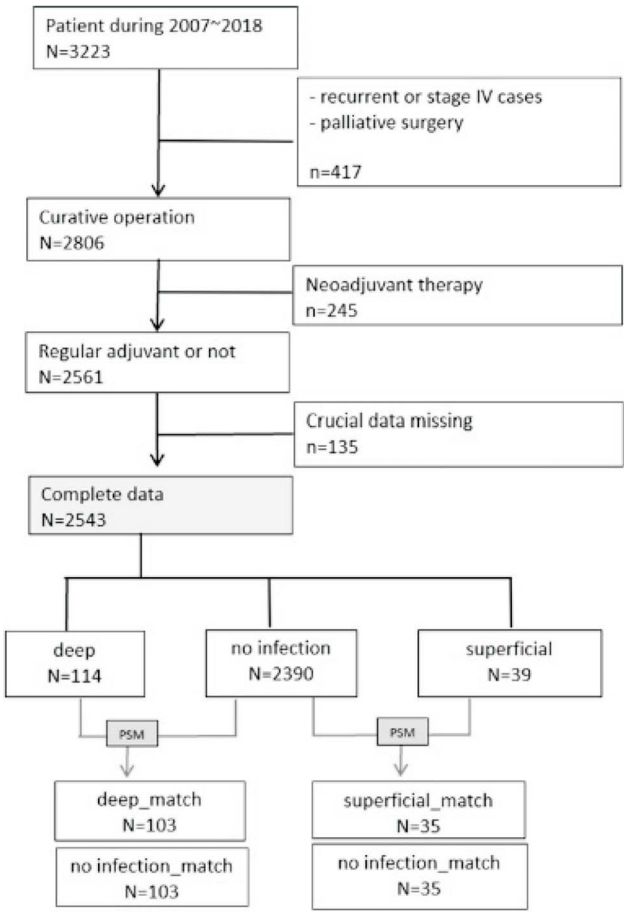

Fig. 1. Flow chart for enrollment of post-operation infection group and no post-operation infection group. deep, deep infection; superifical infection; PSM, propensity score matching.

that the superficial SSI and control groups and the deep SSI and control groups were balanced across these variables and were comparable in the analysis.

Study outcomes

The primary outcomes of the study were recurrence rate, OS, and DFS. OS was defined as the duration from surgery to death from any cause, whereas DFS was defined as the time from surgery to disease recurrence or death from any cause, whichever occurred first. Comparative subanalyses were conducted using PSM to compare patients who experienced superficial SSI with those who did not and to compare patients with deep SSI with those without SSI. These subanalyses provided a detailed understanding of the influence of SSI on long-term oncological outcomes.

Statistical analysis

Statistical analyses were conducted using SPSS, version 25.0 (International Business Machines, Armonk, NY, USA). Categorical variables are presented as frequencies and proportions and were compared using the chi-square test. Continuous variables are presented as means with standard deviations and were analyzed using Student's t test. A multivariate logistic regression analysis was conducted to adjust for potential confounders. Survival analyses were conducted using Kaplan-Meier curves for DFS and OS. All statistical tests were two-tailed, and significance was set at $p < 0.05$.

Results

Fig. 1 depicts the baseline characteristics of the 3,223 patients with CRC who underwent MIS between 2007 and 2018. After 399 patients with Tis carcinoma, Stage IV cancer, or recurrence were excluded, in addition to 18 patients who received local excision or palliative resection, 245 patients who underwent neoadjuvant therapy, and 135 patients with missing data, 2,543 patients were included in the analysis. Of these, 114 had deep SSI, whereas 39 had superficial SSI. PSM was conducted to match patients with deep SSI and with no SSI at a 1:1 ratio and to match patients with superficial SSI and with no SSI at a 1:1 ratio. Consequently, the deep SSI and no SSI matched groups contained 103 patients each, whereas the superficial SSI and no SSI matched groups contained 35 patients each.

The characteristics of the patients before PSM are detailed in Table 1. Before PSM, significant differences were observed between the deep infection group and the noninfected group in terms of sex, tumor location, and CEA levels. Moreover, before PSM, the recurrence rate was markedly higher in the deep infection group than in the noninfected group ($p = 0.015$). In addition, before PSM, significant differences were observed between the superficial infection group and

Table 1. Patient characteristics before propensity score matching

Variable	Non_SSI	SSI_deep		SSI_superficial	
	n = 2390	n = 114	*p*	n = 39	*p*
Sex, n (%)			0.000		0.945
Male	1335 (55.9)	90 (78.9)		22 (56.4)	
Female	1055 (44.1)	24 (21.1)		17 (43.6)	
Age, n (%)			0.433		0.227
< 55	555 (23.2)	34 (29.8)		9 (23.1)	
55-64	704 (29.5)	31 (27.2)		12 (30.8)	
65-74	596 (24.9)	27 (23.7)		5 (12.8)	
≥ 75	535 (22.4)	22 (19.3)		13 (33.3)	
BMI, n(%)			0.878		0.942
< 25	1390 (58.2)	65 (57.0)		22 (56.4)	
≥ 25	996 (41.6)	49 (43.0)		17 (43.6)	
Missing	4 (0.2)	0 (0.0)		0 (0.0)	
Lab of Alb (g/dL), n (%)			0.690		0.013
≤ 3.5	152 (6.4)	8 (7.0)		8 (20.5)	
> 3.5	2224 (93.1)	106 (93.0)		31 (79.5)	
Missing	14 (0.6)	0 (0.0)		0 (0.0)	
Tumor location, n (%)			0.000		0.340
Right-side	665 (27.8)	19 (16.7)		15 (38.5)	
Left-side	1021 (42.7)	17 (14.9)		14 (35.9)	
Rectum	704 (29.5)	78 (68.4)		10 (25.6)	
Tumor stage, n (%)			0.400		0.655
I	718 (30.0)	41 (36.0)		10 (25.6)	
II	740 (31.0)	33 (28.9)		11 (28.2)	
III	932 (39.0)	40 (35.1)		18 (46.2)	
Lab of CEA (ng/ml), n (%)			0.010		0.007
≤ 5	1906 (79.7)	88 (77.2)		24 (61.5)	
> 5	473 (19.8)	23 (20.2)		14 (35.9)	
Missing	11 (0.5)	3 (2.6)		1 (2.6)	
Operation date, n (%)			0.742		0.003
2007-2012	556 (23.3)	25 (21.9)		17 (43.6)	
2013-2018	1834 (76.7)	89 (78.1)		22 (56.4)	
Adjuvant treatment, n(%)			0.071		0.671
Yes	1022 (42.8)	39 (34.2)		21 (53.8)	
No	1368 (57.2)	75 (65.8)		18 (46.2)	
Recurrent			0.015		0.227
Yes	381 (15.9)	28 (24.6)		9 (23.1)	
No	2009 (84.1)	86 (75.4)		30 (76.9)	

the noninfected group in terms of albumin levels, CEA levels, and operation date. However, the recurrence rate was comparable between the superficial infection and noninfected groups ($p = 0.229$). Kaplan-Meier analysis revealed that before PSM the OS (Fig. 2) and DFS (Fig. 3) were shorter in both infection groups than in the noninfected group.

The characteristics of the patients after PSM for the nine study variables are presented in Table 2, and the data indicate balance between the groups for these variables.[18] In the deep infection group, 24.3% of the patients experienced recurrence, which is significantly more than in the control group (8.7%, $p = 0.003$). By contrast, in the superficial infection group, after PSM, no significant difference was observed in the recurrence rate compared with that in the control group (22.9% vs. 11.4%, $p = 0.205$). After PSM, Kaplan-Meier analysis revealed that OS was significantly

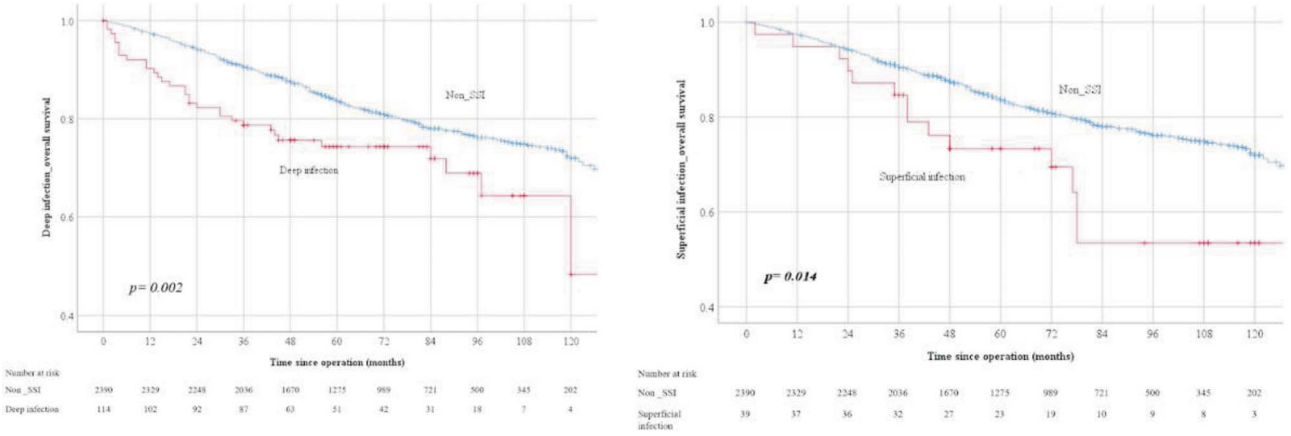

Fig. 2. Relation between overall survival and surgical site infection before match.

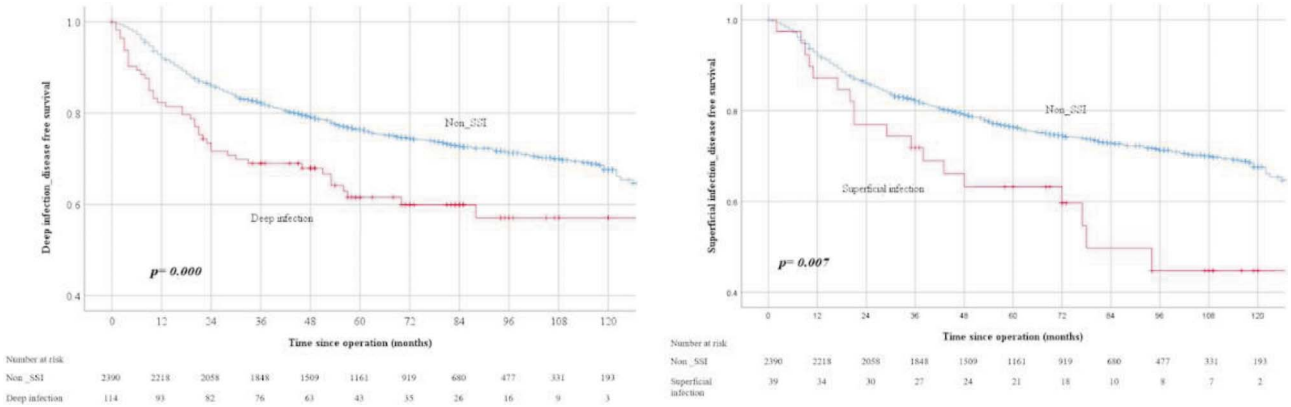

Fig. 3. Relation between disease free survival and surgical site infection before match.

shorter in the deep SSI group than in the noninfection group (p = 0.017), whereas no significant difference was observed in the superficial SSI group (p = 0.097) (Fig. 4). Moreover, DFS was significantly shorter in both the deep (p = 0.001) and superficial (p = 0.013) infection groups than in the noninfection groups (Fig. 5).

Discussion

This study investigated the influence of SSI on the long-term outcomes of patients with CRC who underwent MIS. PSM was employed to match patients with and without SSI, with the matching resulting in balanced groups for analysis. After PSM, the patients with deep SSI were discovered to have significantly worse recurrence rates and OS compared with those of the noninfected group, whereas these outcomes did not significantly differ in the superficial SSI groups. However, DFS was significantly shorter in both infection groups compared with in the noninfected group. These findings indicate that SSI, particularly deep infection, may adversely affect the long-term outcomes of patients with CRC undergoing MIS.

Before PSM, the deep infection rate following MIS was 4.48% (114 out of 2,543 patients), with a notably higher rate of 9.97% (78 out of 782 patients) being observed in rectal cancer cases. These rates are consistent with data reported in another database.[6,19,20] When rectal cancer cases were excluded, the recurrence rate in patients with deep infection before PSM was 19.4% (7 out of 36 cases), which is lower than the recurrence rate in patients with rectal cancer with deep infection before PSM (26.9%, 21 out of 78 cases). Furthermore, a disparity was noted in the recurrence rates between the patients with rectal and colon cancer in the control group before PSM (20.6% vs. 14.1%).

Table 2. Patient characteristics after propensity score matching

Variable	After match			After match		
	SSI_deep (n = 103)	Non_SSI (n = 103)	*p*	SSI_superficial (n = 35)	Non_SSI (n = 35)	*p*
Sex, n (%)			0.866			1.000
Male	80 (77.7)	81 (78.6)		20 (57.1)	20 (57.1)	
Female	23 (22.3)	22 (21.4)		15 (42.9)	15 (42.9)	
Age, n (%)			0.882			0.067
< 55	32 (31.1)	32 (31.1)		9 (25.7)	10 (28.6)	
55-64	30 (29.1)	31 (30.1)		12 (34.3)	5 (14.3)	
65-74	21 (20.4)	24 (23.3)		4 (11.4)	12 (34.3)	
≥ 75	20 (19.4)	16 (15.5)		10 (28.6)	8 (22.9)	
BMI, n(%)			0.575			0.629
< 25	59 (57.3)	55 (53.4)		21 (60.0)	19 (54.3)	
≥ 25	44 (42.7)	48 (46.6)		14 (40.0)	16 (45.7)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Lab of Alb (g/dL), n (%)			0.307			0.428
≤ 3.5	6 (5.8)	3 (2.9)		5 (14.3)	2 (5.7)	
> 3.5	97 (94.2)	100 (97.1)		30 (85.7)	33 (94.3)	
Missing	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Tumor location, n (%)			0.969			0.881
Right-side	16 (15.5)	17 (16.5)		13 (37.1)	11 (31.4)	
Left-side	16 (15.5)	15 (14.6)		12 (34.3)	13 (37.1)	
Rectum	71 (68.9)	71 (68.9)		10 (28.6)	11 (31.4)	
Tumor stage, n (%)			0.985			0.464
I	33 (32.0)	32 (31.1)		9 (25.7)	12 (34.3)	
II	33 (32.0)	34 (33.0)		10 (28.6)	12 (34.3)	
III	37 (35.9)	37 (35.9)		16 (45.7)	11 (31.4)	
Lab of CEA (ng/ml), n(%)			0.591			0.892
≤ 5	84 (81.6)	86 (83.5)		23 (65.7)	25 (71.4)	
> 5	18 (17.5)	17 (16.5)		11 (31.4)	9 (25.7)	
Missing	1 (1.0)	0 (0.0)		1 (2.9)	1 (2.9)	
Operation date, n (%)			0.420			0.229
2007-2012	23 (22.3)	28 (27.2)		13 (37.1)	18 (51.4)	
2013-2018	80 (77.7)	75 (72.8)		22 (62.9)	17 (48.6)	
Adjuvant treatment, n (%)			1.000			0.334
Yes	37 (35.9)	37 (35.9)		17 (48.6)	13 (27.1)	
No	66 (64.1)	66 (64.1)		18 (51.4)	22 (62.9)	
Recurrent			0.003			0.205
Yes	25 (24.3)	9 (8.7)		8 (22.9)	4 (11.4)	
No	78 (75.7)	94 (91.3)		27 (77.1)	31 (88.6)	

This discrepancy indicates that tumor location may influence the recurrence rate and long-term outcomes. PSM was employed to address these imbalances. Even after matching, the results revealed that the deep infection group exhibited a higher recurrence rate and shorter DFS and OS than the noninfection group did, highlighting the adverse effects of deep infection on patient outcomes following MIS for CRC.

The superficial infection group exhibited no significant increase in the recurrence rate compared with the control group. However, before PSM, we observed a higher prevalence of low albumin levels (below 3.5 g/dL) in this group (20.5% of patients). This finding is consistent with those of Peng et al., who identified preoperative nutritional status as a predictor of survival outcomes in patients with Stage III colon cancer

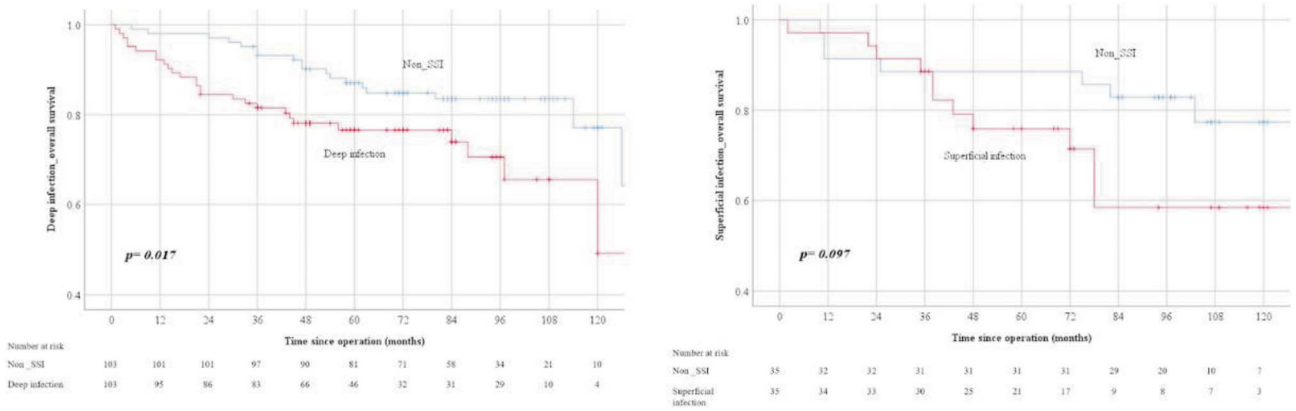

Fig. 4. Relation between overall survival and surgical site infection after match.

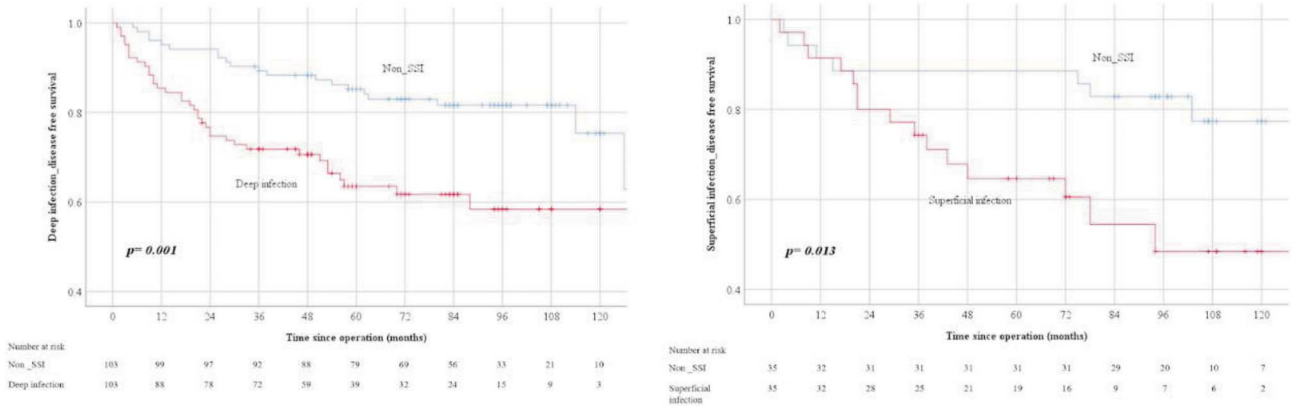

Fig. 5. Relation between disease free survival and surgical site infection after match.

who are undergoing curative tumor resection.[21] Although the number of cases in the superficial infections group in the present study was somewhat small due to the rarity of superficial infection in MIS for CRC, our analysis based on PSM results indicated that the results that were obtained are fairly reliable. Thus, the severity of inflammation must be carefully considered when the long-term outcomes of CRC are being investigated. Additionally, although the superficial infection group had shorter DFS, no differences were observed in OS or the recurrence rate between this group and the noninfected group. This finding is consistent with those of previous studies that have indicated that DFS did not vary between patients who developed serious infection and those with superficial infection.[19,22]

In patients with CRC undergoing curative surgery, determining the influence of inflammation severity and postoperative SSI on long-term outcomes is challenging. Odermatt et al., Cienfuegos et al., and Duraes et al. have identified associations between higher Clavien-Dindo (CD) IV scores, indicating more severe inflammation, and shorter OS and DFS.[9-11] By contrast, Oh et al. reported comparable oncological outcomes in patients with major (CD grade III or IV) and minor (grade I or II) complications after surgery, which underscores the complex association between inflammation severity and outcomes.[13]

Matsuda et al. studied the influence of postoperative infections on long-term outcomes.[23] They revealed that patients with superficial SSI alone did not experience significant differences in cancer-specific survival compared with those without postoperative SSI. However, postoperative infection other than superficial SSI was associated with a negative prognosis. Although they included open surgery alongside laparoscopic surgery, the findings of Matsuda et al. were consistent with those of the present study, indicating

that the type and severity of postoperative SSI are critical influencers of long-term outcomes for patients with CRC after curative surgery. Further research is required to elucidate this association and develop strategies to mitigate the adverse effects of postoperative SSI on the outcomes of patients with CRC.

The mechanisms through which postoperative inflammation influences long-term outcomes in patients with CRC are complex. Although the exact mechanisms remain poorly understood, several potential pathways have been proposed. First, inflammation is critical to tumor growth and progression. Cytokines, including tumor necrosis factor α, tumor growth factor β, interleukin 6, and hepatocyte growth factor, promote tumor cell proliferation, angiogenesis, and metastasis.[24-26] These cytokines create proinflammatory microenvironments that enable tumor advancement and infiltration. Second, postoperative intra-abdominal infections promote angiogenesis, which is essential for tumor growth and metastasis. Angiogenesis may enable residual tumor cell proliferation and dissemination, increasing the chance of recurrence.[27] Furthermore, nuclear factor (NF)κβ is associated with cancer cell migration and metastasis. NFκβ facilitates expression of CXCR4, a chemokine receptor crucial for organ-specific metastasis in various solid tumors.[28] Activation of NFκβ during postoperative inflammation can enhance tumor cell metastatic potential, leading to a poorer prognosis in patients with CRC. Although the exact mechanisms behind the link between inflammation after surgery and long-term outcomes in patients with CRC are not fully understood, inflammation is crucial in promoting tumor growth and metastasis. Further investigations are required to elucidate the mechanisms of these pathways and identify treatment targets to improve outcomes for patients with CRC.

Another factor potentially influencing the outcomes of patients with CRC who develop SSI is delayed or dose-reduced adjuvant chemotherapy,[29] the incidence of which was slightly high in the deep infection group in our database. However, detailed documentation of chemotherapy dose reductions was limited in the database. Sprenger et al. revealed that the risks of distant metastases and local recurrence were higher after anastomotic leakage (deep infection), especially in patients who did not receive neoadjuvant or adjuvant chemoradiotherapy, with this higher risk even noted in patients with Stage I cancers.[30] In the current study, even after we excluded cases with neoadjuvant therapy and balanced the rate of adjuvant therapy through PSM, deep infection had an influence on the recurrence rate. This finding indicates that factors beyond adjuvant chemotherapy may contribute to the association between deep infection and higher recurrence rates. This association warrants further investigation.

For further discussing the possible cause leading to higher recurrence rate in SSI group. We extract pathology and histological grade after propensity score matching (Appendix Table 1). No matters deep infection or superficial infection group, there is no obvious difference comparing to controlled group. We also analyzed the days from surgery to chemotherapy after propensity score matching (Appendix Table 2), not all of the stage III patients received adjuvant chemotherapy due to old age and underlying disease or refuse due to personal reason. There was no significant difference in superficial infection group comparing to controlled group. In deep infection group, the days from surgery to chemotherapy was longer than controlled group. But the patients still could receive the adjuvant chemotherapy in 47 days after surgery on average in deep infection groups.

This study has several limitations. First, it was a retrospective study and may have been subject to data collection and analysis biases. Second, an extended study timeframe — September 1, 2007, to December 31, 2018 — was employed to increase the sample size. However, the use of this timeframe also introduces variability in the data because of potential changes over time in treatment protocols, surgical techniques, and advancements in perioperative care, which can influence the outcomes and prognoses of patients. Although we attempted to mitigate bias through PSM, residual confounding from unmeasured variables may have affected the results. Third, patients with protective stomas may not exhibit typical symptoms of anastomotic leakage, and therefore, the incidence of deep infection may have been underestimated. This limitation could have affected the accuracy of the estimations regarding recurrence rates and the overall as-

sessment of the influence of deep infection on long-term outcomes. Furthermore, because the study used data from a single institution, the findings may not apply to all populations. Variations in patient demographics, treatment modalities, and environments may affect the generalizability of the results to different health-care settings.

In conclusion, this study elucidates the influence of postoperative infection, specifically superficial and deep infection, on the long-term outcomes of patients with CRC undergoing curative MIS. Our findings indicate that deep infection, such as anastomotic leakage or intra-abdominal infection, is associated with a higher recurrence rate and shorter OS and DFS. By contrast, superficial infection does not significantly affect the recurrence rate or OS but may affect DFS. Future research should validate our findings through prospective studies with larger and more diverse populations. Determining the effects of postoperative infection on outcomes for patients with CRC is crucial to enhancing patient care and outcomes in this population.

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Appendix

Appendix Table 1. Pathology and histological grade after propensity score matching

Variable	After match			After match		
	SSI_deep (n = 103)	Non_SSI (n = 103)	*p*	SSI_superficial (n = 35)	Non_SSI (n = 35)	*p*
Adenocarcinoma, n			0.446			0.131
Total	96	99		32	34	
Well differentiation	17	11		4	2	
Moderate differentiation	74	86		24	30	
Poor differentiation	5	2		4	2	
Signet ring cell adenocarcinoma, n	1	2		0	0	
Mucinous adenocarcinoma, n	5	2		3	0	
Others	1*	0		0	1#	

* The pathology is adenosquamous carcinoma. # The pathology is neuroendocrine tumor.

Appendix Table 2. The days of surgery to chemotherapy after propensity score matching

Variable	Stage III, after match			Stage III, after match		
	SSI_deep (n = 34)	Non_SSI (n = 34)	*p*	SSI_superficial (n = 14)	Non_SSI (n = 11)	*p*
Surgery to chemotherapy, days (average, SD)	47.03 (22.39)	32.59 (9.93)	0.001	35.29 (6.22)	39.45 (14.59)	0.392

原　著

微創手術感染在大腸直腸癌病人的長期預後影響

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在接受微創手術 (MIS) 治療結直腸癌 (CRC) 的病人中，深部感染會造成較差的長期預後，包括更高的復發率 (p = 0.003)、較短的總生存期 (OS) (p = 0.017) 和無病生存期 (DFS) (p = 0.001)。相反地，表淺感染並未顯著影響復發率 (p = 0.205) 或 OS (p = 0.097)，但與較差的 DFS 有關 (p = 0.013)。

對於接受微創手術治療結直腸癌的患者而言，術後深部感染與增加的復發率及較差的 OS 和 DFS 相關。這些發現突顯了預防和治療深部感染的迫切性，以改善病人的長期預後。未來需要進一步研究這些預後與機制的關係,以改善治療方式。

關鍵詞　微創手術、結直腸癌、手術感染。