# Postoperative infections are associated with adverse outcome after resection with curative intent for colorectal cancer

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**Abstract.** This study focused on the impact of post-operative infection on patient outcome after resection with curative intent for colorectal cancer. Postoperative surgical and medical complications have been implicated as a negative predictor of long-term outcome in various malignancies. We studied a population of 1083 patients who underwent resection with curative intent for colorectal cancer. These patients were divided into 2 groups based on the occurrence (65 patients, 6%) or absence (1018 patients, 94%) of postoperative complications due to infection. We investigated the demographic and clinicopathological features of each patient with and without postoperative infectious complications, as well as the impact of postoperative infection on long-term survival. Results showed that patients with postoperative infectious complications had diabetes mellitus more frequently and also had urgent surgery compared to those without infectious complications. In addition, patients with postoperative infectious complications had a significantly more unfavorable outcome compared with those without postoperative infection in cancer-specific, but not overall survival. Multivariate analysis demonstrated that age, rectal cancer and tumor stage correlated with overall survival, but not postoperative infectious complications. However, postoperative infections, as well as gender, were associated with the length of time until the patient succumbed from the recurrence of colorectal cancer after resection for curative intent. Thus, postoperative infectious complications are predictors of adverse clinical outcome in patients with colorectal cancer. However, further immunological study is necessary to confirm the biological significance of these findings.

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## Introduction

Considerable advances have been made in the areas of prevention, diagnosis and therapy. However, postoperative infections following major surgery for gastro-intestinal cancer are the most frequent complications that are noted. Complications due to postoperative infection result in an increased cost of treatment, longer hospital stay and ultimately, premature mortality (1,2).

Many researchers have reported that postoperative surgical and medical complications may contribute to a high rate of recurrence and unfavorable long-term survival in various malignancies such as cervical, colorectal and esophageal cancer (3-5). Increasing evidence has shown that postoperative complications due to infection, especially those caused by anastomotic leakage after colorectal surgery, were significantly associated with a negative long-term outcome (3,6-8). In contrast, beneficial effects of postoperative emphysema and intrapleural infection have been reported after pneumonectomy for lung cancer. Thus, whether or not infection and/or febrile complication after surgery is associated with the long-term survival of patients after curative resection for various types of cancer is still controversial (8-11).

This study focused on the impact of postoperative infection on long-term survival following resection with curative intent for colorectal cancer.

## Materials and methods

*Patients.* Between January 2002 and December 2007, 1669 consecutive patients underwent colorectal surgery at the National Defense Medical College Hospital (Tokorozawa, Saitama, Japan). Among the 1669 patients, 1083 patients (632 men, 451 women; mean age 64.5±11.0 years, range 18-96 years) who underwent colorectal surgery with resection with curative intent were enrolled in this study. The population of 1083 patients was then divided into 2 groups based on the occurrence (65 patients, 6%) or absence (1018 patients, 94%) of complications due to postoperative infection. If no gross residual disease was evident at the time of the operation and the margins of resection were tumor-free on histological examination, the surgery was considered to be curative. Resected specimens were examined histopathologically and were staged according to the International Union Against Cancer (UICC)

TNM classification of malignant tumors (12). Adjuvant therapy by oral anti-cancer agents such as 5-fluorouracil (UFT) was recommended for patients with disease stage III or IV, or those with a high potential of recurrence based on the pathological findings. Adjuvant therapy was then performed in 31 (47.7%) patients with postoperative infectious complications and 466 (45.8%) patients without infectious complication. These patients were retrospectively evaluated for their pre- and post-operative status, pathological findings and surgical procedure, according to our computer database or medical and nursing charts.

*Definition of infectious complications.* Complications due to postoperative infection were defined by a combination of clinical findings and the results of both laboratory and other tests recorded in medical records. Clinical evidence was derived from direct observation of the infection site or from reviewing patient charts. Laboratory evidence included culture results, antigen or antibody detection tests, or analysis by microscopic visualization. Supportive data were derived from other diagnostic studies, such as X-ray, ultrasonography (US) and computed tomography (CT). In our study, complications from postoperative infection included anastomotic leakage (identified by radiography or clinical suspicion), urinary tract infection (pyrexia with microbiological evidence), bacteremia (pyrexia with microbiological evidence), intraperitoneal abscess (pyrexia with fluid collection diagnosed by US or CT, or identified radiographically), pneumonia (pyrexia with infiltrate on chest X-ray), pseudomembrane colitis (identified by colonoscopy and microbiological evidence) and central venous catheter-related infections (pyrexia with microbiological evidence). This study included a wound infection involving deep soft tissues, e.g., facial and muscle layers, but excluded infection involving only skin and subcutaneous tissue of the skin because of its minimal effect on the systemic immune response.

*Follow-up.* Survival time was measured from the date of resection to the date the patient succumbed due to any cause. Patients who survived were censored in our survival analysis. The patients were observed at our hospital or the outpatient clinic at 3- to 4-month intervals during the first 2 years of the study, and then every 6 or 12 months for 3 years. After 5 years, an annual follow-up was conducted through telephone conversations with the patients, their family or practitioner.

Table I. Frequency of complications due to postoperative infection.

| Infectious complications | No. | % |
| --- | --- | --- |
| Anastomotic leakage | 29 | 2.7 |
| Wound infection | 25 | 2.3 |
| Urinary tract infection | 5 | 0.5 |
| Bacteremia | 3 | 0.3 |
| Intraperitoneal abscess | 2 | 0.2 |
| Pneumonia | 2 | 0.2 |
| Pseudomembrane colitis | 1 | 0.1 |
| Central venous catheter-related infections | 1 | 0.1 |
| Total | 68 | |

*Definition of recurrence patterns.* Recurrences were identified by CT, positron emission tomography (PET), US or colonoscopy. They were classified as locoregional, liver, lung, brain, bone, distant lymph node and peritoneal recurrence. Recurrence at cervical, celiac or paraaortic lymph nodes was classified as distant lymph node recurrence. When simultaneous recurrences were detected, the site of massive and/or life-threatening recurrence was regarded as a main pattern of recurrence.

*Statistical analysis.* Statistical calculations were performed using StatView version 5.0 (SAS Institute, Inc., Cary, NC, USA). Data are expressed as mean ± SD. Statistical analyses were performed using either the Mann-Whitney U or Chi-square tests with Fisher's exact test, as appropriate. Survival rates were obtained using Kaplan-Meier, and the significance of the difference in the survival rate was determined by a log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards model. $P<0.05$ was considered statistically significant.

## Results

Frequencies of complications due to postoperative infection are shown in Table I. Anastomotic leakage was the most frequent infectious complication after colorectal cancer, followed by wound infection. No difference was noted in the age, gender and incidence of hypertension between patients with
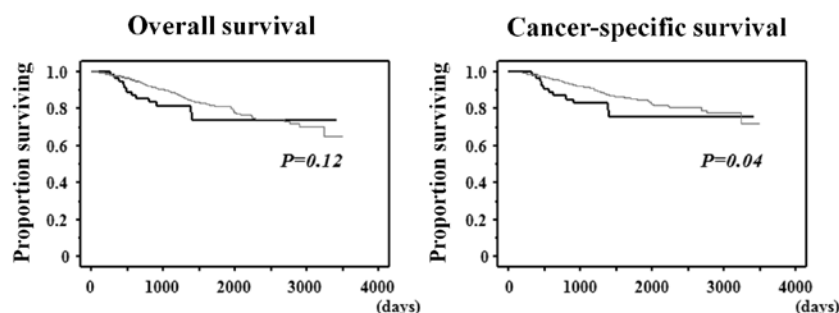


Figure 1. Overall and cancer-specific survival after surgery with curative intent for colorectal cancer. Bold and fine lines indicate survival curves for patients with and without postoperative infectious complications, respectively. P-values of the log-rank test are shown in each graph.

Table II. Demographic and clinicopathological data of patients with or without postoperative complications due to infection.

| | Complications | No complications | P-value |
|---|---|---|---|
| Number | 65 | 1018 | |
| Age | 65.6±9.0 | 64.5±11.1 | 0.44 |
| Gender (M:F) | 44:21 | 588:430 | 0.11 |
| Co-morbidity | | | |
|   Hypertension | | | |
|     Yes | 10 (15.4) | 159 (15.6) | 0.99 |
|     No | 50 (84.6) | 859 (84.4) | |
|   Diabetes mellitus | | | |
|     Yes | 13 (20.0) | 86 (8.5) | 0.01 |
|     No | 52 (80.0) | 932 (91.5) | |
| Emergency surgery | | | |
|   Yes | 2 (3.1) | 4 (0.4) | 0.04 |
|   No | 63 (96.9) | 1014 (99.6) | |
| Location | | | |
|   Colon | 30 (46.2) | 532 (52.3) | 0.31 |
|   Rectum | 35 (53.8) | 474 (57.7) | |
| Laparoscopic surgery | | | |
|   Yes | 3 (4.6) | 30 (2.9) | 0.44 |
|   No | 62 (95.4) | 988 (97.1) | |
| Inflammatory bowel disease | | | |
|   Yes | 0 (0.0) | 2 (0.2) | 0.99 |
|   No | 65 (100) | 1016 (99.8) | |
| Stoma construction | | | |
|   Yes | 16 (24.6) | 159 (15.6) | 0.07 |
|   No | 49 (75.4) | 859 (84.4) | |
| Curability | | | |
|   A | 6 (9.2) | 51 (5.0) | 0.15 |
|   B | 59 (90.8) | 967 (95.0) | |
| Stage | | | |
|   0 | 1 (1.5) | 33 (3.2) | 0.50 |
|   I | 14 (21.5) | 222 (21.8) | |
|   II | 23 (35.4) | 336 (33.0) | |
|   III | 22 (33.8) | 388 (38.1) | |
|   IV | 5 (7.7) | 39 (3.8) | |
| Outcome | | | |
|   Alive | 49 (75.4) | 826 (81.1) | 0.28 |
|   Succumbed to tumor relapse | 12 (18.5) | 122 (12.0) | |
|   Succumbed to another cause | 1 (1.5) | 40 (3.9) | |
|   Unknown | 3 (4.6) | 30 (2.9) | |

Percentage of patients with resection with curative intent is shown in parentheses.

and without postoperative infectious complications (Table II). Patients with infectious complications had a significantly higher frequency of diabetes mellitus and urgent surgery. We also found no statistical difference in the tumor location, incidence of laparoscopic surgery, inflammatory bowel disease, stoma construction, curability and tumor stage between the two groups. Fourteen (21.5%) and 159 (15.6%) patients, with and without infectious complications, respectively, had a relapse of cancer. Twelve (18.5%) and 122 patients (12%), with and without infectious complications, respectively, succumbed to recurrence of the primary tumor. One (1.5%) and 40 patients, respectively, succumbed to other causes such as secondary malignancy, cerebral and heart infarction, arrhythmia and accidents. Although there is no difference in survival between patients with and without infectious complications, we found statistical difference in cancer-specific survival between the two groups (Fig. 1). Specifically, in stage III of colorectal cancer, patients with infectious complications had a poorer

Table III. Univariate and multivariate analysis of factors that affect survival in patients with colorectal cancer.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | P-value | Hazard ratio | 95% CI | P-value |
| Age, 1-year increment | 1.03 | 1.02-1.05 | <0.0001 | 1.05 | 1.03-1.06 | <0.0001 |
| Gender (male) | 1.04 | 0.76-1.42 | 0.8000 | - | - | - |
| Urgent operation (Yes) | 2.84 | 0.70-11.5 | 0.1400 | - | - | - |
| Laparoscopic operation (Yes) | 0.40 | 0.10-1.62 | 0.2000 | - | - | - |
| Tumor location (rectum) | 1.42 | 1.04-1.92 | 0.0300 | 1.51 | 1.04-2.00 | 0.0100 |
| Infectious complications (Yes) | 1.58 | 0.88-2.85 | 0.1300 | - | - | - |
| Curability (A) | 0.21 | 0.14-0.32 | 0.0010 | 0.50 | 0.31-1.29 | 0.0600 |
| Stage (compared with Stage I) | | | | | | |
|   II | 2.92 | 1.41-6.06 | 0.0040 | 2.65 | 1.27-5.52 | 0.0100 |
|   III | 8.08 | 4.09-16.0 | <0.0001 | 7.78 | 3.92-15.4 | <0.0001 |
|   IV | 20.20 | 9.19-44.4 | <0.0001 | 12.5 | 4.41-35.4 | <0.0001 |

CI, confidence interval.
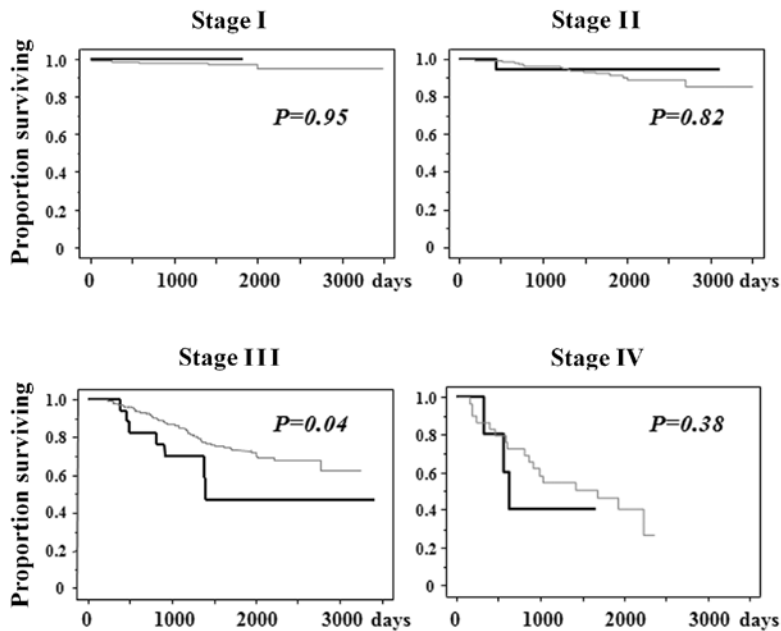


Figure 2. Overall survival after surgery with curative intent for colorectal cancer according to tumor stage. Bold and fine lines indicate the survival curve of patients with and without postoperative infectious complications, respectively. P-values of the log-rank test are shown in each graph.
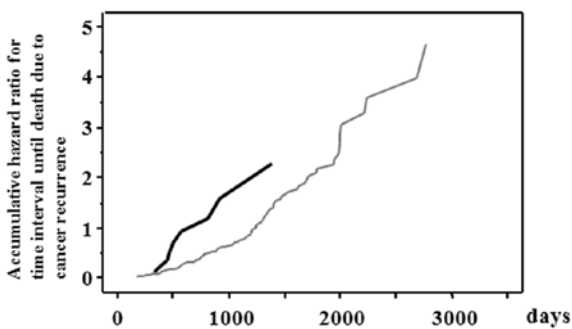


Figure 3. Accumulative hazard ratio for time interval until death due to cancer recurrence. Bold and fine lines indicate the survival curve of patients with and without postoperative infectious complications, respectively.

cancer-specific survival than those without infectious complications (Fig. 2). This was not the case, however, with patients in stages I, II and IV of colorectal cancer.

In univariate analysis, age, tumor location, curability and tumor stage, but not postoperative infectious complications, were significantly associated with the overall survival rate (Table III). Multivariate analysis demonstrated that age, tumor location and tumor stage were significantly associated with overall survival.

Of the 134 patients who succumbed due to a recurrence of colorectal cancer, 52 (38.8%), 95 (70.9%) and 128 patients (95.5%) had a recurrence of cancer before 12, 24 and 60 months, respectively. In order to identify which factors are

Table IV. Univariate and multivariate analysis for time interval until patients succumbed due to recurrence from colorectal cancer.

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | P-value | Hazard ratio | 95% CI | P-value |
| Age, 1-year increment | 1.03 | 1.01-1.05 | 0.001 | 1.01 | 0.99-1.03 | 0.14 |
| Gender (male) | 0.57 | 0.39-0.84 | 0.005 | 0.60 | 0.41-0.88 | 0.01 |
| Emergency operation (Yes) | 2.00 | 0.28-14.5 | 0.490 | - | - | - |
| Laparoscopic operation (Yes) | 0.39 | 0.05-2.80 | 0.350 | - | - | - |
| Tumor location (rectum) | 1.27 | 0.87-1.84 | 0.220 | - | - | - |
| Infectious complications (Yes) | 2.10 | 1.09-4.07 | 0.030 | 2.16 | 1.11-4.24 | 0.03 |
| Curability (A) | 0.78 | 0.48-1.25 | 0.290 | - | - | - |
| Stage (compared with stage I) | | | | | | |
| II | 1.01 | 0.34-2.94 | 0.990 | - | - | - |
| III | 1.14 | 0.42-3.13 | 0.800 | - | - | - |
| IV | 1.55 | 0.53-4.54 | 0.430 | - | - | - |

CI, confidence interval.

Table V. The influence of infectious complications for the time interval until patients succumbed due to cancer recurrence.

| Infections | No. | Hazard ratio | 95% CI | P-value |
|---|---|---|---|---|
| Anastomotic leakage | 29 | 3.48 | 1.49-8.14 | 0.004 |
| Wound infection | 25 | 1.54 | 0.49-4.85 | 0.470 |
| Urinary tract infection | 5 | 0.93 | 0.23-3.77 | 0.920 |

CI, confidence interval.

Table VI. Main recurrence pattern of colorectal cancer.

| Site of reccurence | Complications | | | No complications | | | P-value |
|---|---|---|---|---|---|---|---|
| | Total (%) | Colon | Rectum | Total (%) | Colon | Rectum | |
| Locoregional | 8 (57.1) | 2 | 6 | 46 (28.9) | 16 | 30 | |
| Liver | 5 (35.7) | 1 | 4 | 58 (36.5) | 28 | 30 | |
| Lung | 0 (0.0) | 0 | 0 | 42 (26.4) | 17 | 25 | 0.04 |
| Distant lymph nodes | 0 (0.0) | 0 | 0 | 11 (6.9) | 2 | 9 | |
| Brain | 0 (0.0) | 0 | 0 | 1 (0.6) | 0 | 1 | |
| Bone | 1 (7.1) | 1 | 0 | 1 (0.6) | 0 | 1 | |
| Total | 14 (100.0) | 4 | 10 | 159 (100.0) | 63 | 96 | |

responsible for the time interval until patients succumbed to the disease due to cancer recurrence, univariate and multivariate analyses were performed (Table IV). Univariate analysis revealed that age, gender and infectious complications were associated with a shorter time interval of survival due to cancer recurrence, but this was not the case for tumor location, curability and tumor stage. Multivariate analysis revealed that infectious complications, as well as gender, were related with

a shorter time interval of survival due to cancer recurrence. In patients with infectious complications, the mean time interval until death due to cancer recurrence was 708.8±114.4 days, while that of patients without infectious complications was 1046.0±54.9 days. The accumulative hazard ratio for time interval until death due to cancer recurrence was significantly higher in patients with infectious complications, than that in patients without infectious complications (Fig. 3). The

univariate analysis performed with regard to the influence of infectious complications for the time interval for poor survival due to cancer recurrence showed that only an anastomotic leakage affects the time interval in patients with infectious complications (Table V). Patients with infectious complications had a more frequent locoregional relapse as compared to those without infectious complications as a main pattern of recurrence (Table VI).

## Discussion

We demonstrated that complications due to postoperative infection are important prognostic factors after resection with curative intent for colorectal cancer, especially in patients with stage III disease. In addition, infectious complications were associated with time interval until patients succumbed due to the recurrence of colorectal cancer after resection for curative intent.

Although many previous reports demonstrated that postoperative infectious complications contribute to a high rate of recurrence and an unfavorable long-term survival in various malignancies (5,7,8,13), the precise mechanism(s) relating long-term survival and postoperative infection remains unclear.

We also demonstrated that patients with infectious complications had more frequent locoregional relapse as compared to those without infectious complications. Substantial evidence exists indicating the presence of viable cancer cells in the bowel lumen of patients with colorectal cancer at the time of operation (14-16), which can be detected on suture or staple lines of anastomosis (17). Anastomotic leakage, the most frequent infectious complication found in this study, may lead to extraluminal implantation, which has the effect of upstaging the disease and increasing the incidence of locoregional relapse (13). Fujita *et al* demonstrated that the incidence of local recurrence in patients with anastomotic leakage was significantly higher than that in patients without leakage in colorectal cancer (18), which is consistent with our findings.

Another possible mechanism relating diminished survival and postoperative infection is a deregulated host immune response during infection that may contribute to tumorigenesis. It is known that inflammation caused by bacterial infection could develop systemic inflammatory response syndrome and lead to a shift towards a Th2-type lymphocyte pattern (19,20), which is especially enhanced after surgical trauma (21-23). Th-2 cytokines, such as IL-10, were shown to down-regulate tumor-specific immune responses by directly suppressing IFN$\gamma$ and IL-12 production. This caused a reduction in MHC expression on the surface of tumor cells and inhibited tumor antigen presentation by antigen-presenting cells (24-26). Taken together, these findings suggest that development of a postoperative Th-2 response during infectious complications following major surgical trauma likely contributes to the proliferation of occult or dormant cancer cells, resulting in decreased survival (27).

In conclusion, our study indicates that complications due to postoperative infection are a favorable predictor of adverse clinical outcome in patients with colorectal cancer. Further immunological study, however, is essential to substantiate our current data and to provide an assessment of their overall bio-logical effects. Nonetheless, more effort is required to prevent such postoperative infections to improve long-term as well as short-term survival in colorectal cancer patients.

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