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Pulmonary Dysfunction Function and Poor Nutritional Status are Risk Factors for Remote Infections Following Surgery for Colorectal Cancer

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Objective: We evaluated the preoperative patient status including nutrition, immunity, and inflammation as a predictive factor of remote infection (RI) in colorectal cancer surgery.

Subjects and Methods: A total of 351 patients who underwent colorectal cancer resection were retrospectively analyzed. Factors correlated with RI incidence were identified by logistic analysis and stepwise selection.

Results: RI occurred in 27 patients, with an incidence of 7.7%. In univariate logistic analysis, a significantly high incidence of RI was associated with excessive blood loss (>423 mL), long duration of surgery (>279 minutes), ileus, pulmonary dysfunction, performance status (PS)≥1, American Society of Anesthesiologists (ASA) classification>2, prognostic nutritional index (PNI)≤40, and controlling nutritional status (CONUT)≥2 , modified Glasgow Prognostic Score (mGPS) (Score 2). In multivariate analysis, pulmonary dysfunction (odds ratio=2.83; 95% CI: 1.14−6.97; p=0.02) and PNI≤40 (odds ratio=3.87; 95% CI: 1.45−10.31; p=0.006) were independent risk factors of RI incidence.

Conclusion: RI is caused by poor nutrition, immune system dysfunction and pulmonary dysfunction.
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Key words: remote infection (RI), colorectal cancer surgery, pulmonary dysfunction, prognostic nutritional index (PNI), modified Glasgow Prognostic Score (mGPS)

Introduction

Recently, the importance of cachexia assessment with the modified Glasgow Prognostic Score (mGPS) has been reported[1]. Cachexia is a condition attributed to host-tumor interactions, and is a systemic inflammatory reaction to Interleukin-6 (IL-6) produced by systemic and cancer immunocompetent cells. In patients with colorectal cancer, cachexia occurs from an early clinical stage. Under invasive operative conditions, an abnormally enhanced inflammatory reaction is triggered, leading to the development of infectious complications during the early postoperative period[2].

The occurrence of infectious complications leads not only to the prolongation of postoperative hospitalization, but also a poor prognosis[3]. Infectious complications are classified into surgical site infections (SSIs) and remote infections (RIs), which differ in pathogenesis[4]. We previously reported that cachexia is an independent risk factor for SSI using mGPS as an index[5]. However, among infectious complications, whether or not cachexia affects only SSI remains inconclusive[4].

In colorectal cancer surgery, the incidence of both SSI and RI is high[3]. Accordingly, clarifying risk factors for RI is important[4]. To this end, we examined whether risk factors associated with SSI are also risk factors for RI.

Subjects and Methods

Subjects

A total of 351 patients who underwent colorectal surgery between January 2005 and December 2008 were en-

rolled for analysis. Subjects were those who underwent colorectal cancer resection with anastomosis. Those who underwent colorectal cancer resection without anastomosis were excluded. The study population did not include patients who underwent surgery for benign disease.

Informed Consent

We followed the retrospective observational research information disclosure procedure (opt-out) of Tokyo Women's Medical University for obtaining informed consent from research subjects. This study was approved by the Ethics Committee of Tokyo Women's Medical University (No.4567).

Methods

We analyzed clinicopathological factors associated with RI, as categorized in a previous report[5]. We also calculated prognostic nutritional index (PNI)[6], neutrophil lymphocyte ratio (NLR)[7], and controlling nutritional status (CONUT)[8], and mGPS, as previously reported. Blood loss, duration of surgery, and NLR were categorized by the 75th percentile.

Location was classified into the rectum and colon. We defined as follows; The Colon is divided into the cecum, ascending colon, transverse colon, descending colon, and sigmoid colon. The rectum is divided into the rectosigmoid, upper rectum, and lower rectum. The appendix and the anal canal are handled separately from the large intestine.

Assessment of RI and Complications

We focused on the following RIs: pulmonary infection, urinary tract infection, retrograde drain infection, enterocolitis, and catheter infection. Postoperative infection was diagnosed when pneumonia was accompanied by fever and a clear x-ray finding. Urinary tract infection was diagnosed when the subject had a fever and a positive result by urinalysis or urine culture. Intestinal inflammation was diagnosed when the patient presented with fever, diarrhea, nausea, and a positive result by fecal culture. Retrograde drain infection was diagnosed by signs of infection at the drain insertion site and in a drain culture. Catheter infection was diagnosed when the subject developed a fever within 48 hours after central venous catheter withdrawal.

The authors confirmed and summarized patients' medical records. Grade II or higher complications according to the Clavien-Dindo classification[9] were included in the calculation of incidence rates.

Statistical Analysis

Statistical analyses were performed using SAS ver. 9.2 (SAS Institute, Inc., Cary, NC, USA). Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables were used for between-group comparisons. Univariate and multivariate logistic regression analyses were performed to identify factors associated with RI incidence. Variables for inclusion in the multivariate analysis were selected by the stepwise procedure with all variables (stepwise forward selection with entry and stay criteria both set to p=0.25). P<0.05 was considered statistically significant.

Results

Baseline Characteristics by Presence of RI

RI was observed in 27 patients, with an incidence of 7.7%. Ten patients (2.8%) had pneumonia, nine patients (2.6%) had urinary tract infection, six patients (1.7%) had enteritis, three patients (8.5%) had retrograde drain infection, and one patient (0.3%) had a catheter infection. Some patients had more than one of these complications. Baseline characteristics by presence of RI are shown in **Table 1**.

Predictive Factors for RI in Colorectal Cancer Surgery (Table 2)

Univariate logistic regression analyses: In univariate logistic analysis, a significantly high incidence of RIs was associated with excessive blood loss (>423 mL), long duration of surgery (>279 minutes), ileus, pulmonary dysfunction, PS (≥1), ASA (>2), PNI≤40, and CONUT≥2, mGPS (Score 2).

Furthermore, when a stepwise multivariate logistic regression analysis was conducted RI incidence as the dependent variable and all other factors as independent variables, sex (male), excessive blood loss (>423 mL), long duration of surgery (>279 minutes), ileus, pulmonary dysfunction, ASA (>2), BMI<18.5, BMI≥25, and PNI ≤40, were associated with an increased RI incidence.

In multivariate logistic regression analysis, pulmonary dysfunction (odds ratio 2.83 95% CI 1.14−6.97 p=0.02), PNI≤40 (odds ratio 3.87 95% CI 1.45−10.31 p=0.006) were independent risk factors for RI.

Discussion

Given the high operative mortality rate after surgery for colorectal cancer among patients who develop infectious complications, clarifying their risk factors is an important issue[3,4].

RIs observed in this study included respiratory infection, urinary tract infection, enteritis, retrograde drain infection, and catheter infection. Respiratory failure is often caused by ventilator management[10]. Urinary tract infec-

Table 1 Baseline characteristics by presence of remote infections (RIs)

Variables		RI (n=27)			non-RI (n=324)			p-value
Sex	male:female	19	:	8	187	:	137	0.23
Age (years)	≥75:<75	8	:	19	78	:	246	0.50
Depth of tumor invasion	≥T3:≤T2	23	:	4	256	:	68	0.62
Approach	laparotomy:laparoscopy	25	:	2	260	:	64	0.13
Location	rectum:colon	12	:	15	91	:	233	0.08
Resection of other organs	yes:no	5	:	22	56	:	268	0.80
Colostomy	yes:no	3	:	24	24	:	300	0.45
Timing of operation	emergency:elective	3	:	24	13	:	311	0.12
Blood loss (mL)	large (>423):small	13	:	14	72	:	252	0.005
Operating time (min)	long (>279):short	12	:	15	75	:	249	0.02
Histology	others:tub1, 2	6	:	21	60	:	264	0.61
Ileus	yes:no	6	:	21	29	:	295	0.04
Diabetes mellitus	yes:no	8	:	19	67	:	257	0.33
Pulmonary dysfunction	yes:no	12	:	15	69	:	255	0.01
Performance status	≥1:0	9	:	18	41	:	283	0.007
American Society of Anesthesiologists classification	3:1・2	5	:	22	23	:	301	0.05
Body mass index (kg/m²)	<18.5:≥18.5	4	:	23	22	:	302	0.13
	≥25:<25	8	:	19	74	:	250	0.48
Prognostic nutritional index	≤40:>40	11	:	16	47	:	277	0.001
Neutrophil lymphocyte ratio	>4:≤4	9	:	18	85	:	239	0.50
Controlling nutritional status	≥2:0・1	17	:	10	134	:	190	0.04
modified Glasgow prognostic score (Score)	2:0・1	8	:	19	30	:	294	0.004
Smoking habit	yes:no	8	:	19	119	:	205	0.54

Location was classified into rectum and colon. We defined as follows; The Colon is divided into cecum, ascending colon, transverse colon, descending colon, and sigmoid colon. The rectum is divided into recto-sigmoid, upper rectum, and lower rectum. The appendix and the anal canal are handled separately from the large intestine.

Baseline characteristics were divided by the presence of RI. Fisher's exact test for categorical variables was used for between-group comparisons.

Blood loss, duration of surgery, and NLR were divided into 75th percentile groups based on a cumulative frequency distribution. Pulmonary dysfunction was defined as less than 80% of % vital capacity (%VC) or less than 70% of forced expiratory volume in one second % (FEV1.0%).

PNI was calculated using the following formula, as proposed by Onodera at al.: serum albumin levels (g/dL)×10+total lymphocyte count (per mm3)×0.005. NLR was calculated by dividing the number of neutrophils by the number of lymphocytes. The CONUT Score takes the serum albumin value, total lymphocyte count, and total cholesterol value, and integrates them to evaluate nutritional status using the "CONUT score" (0–12 points) in 4 levels. Specifically, patients with CONUT scores of 0–1 have a normal nutritional status, those with CONUT scores of 2–4 are at mild risk, those with CONUT scores of 5–8 are at moderate risk, and those with CONUT scores of 9–12 are at severe risk of malnutrition.

mGPS was scored as follows: score 2, CRP>1.0 mg/dL and Alb<3.5 g/dL; score 1, CRP>1.0 mg/dL; and score 0, CRP ≤1.0 mg/dL and Alb ≥3.5 g/dL.

tions occur frequently after colorectal cancer surgery[10] and are likely to occur in patients whose urinary catheters have been placed for a long period of time due to voiding dysfunction[10]. In enteritis cases, pseudomembranous enterocolitis and methicillin-resistant Staphylococcus aureus (MRSA) enteritis caused by antibacterial agents are typically observed[10]. Retrograde drain infections occur due to the long-term placement of drains[11]. Finally, catheter infections occur due to ventilator management and long-term placement of endotracheal tubes and catheters[10].

As described above, although the underlying mechanisms and risk factors differ depending on the type of infection[10], most RIs can be attributed to perioperative management. However, some reports have noted that host-associated factors (physical function[12], nutritional status[13–15], and immune status[13–16]) affect the incidence of RI. The results of our study are consistent with previous reports, showing that pulmonary dysfunction and PNI≤ 40 influence the incidence of RI.

In the first place, the reference value for pulmonary dysfunction, as assessed by spirometry, associated with a risk for developing postoperative complications has not been established. Preoperative pulmonary function is in-

Table 2 Predictive factors for remote infections (RIs) in colorectal cancer surgery

Variables		n	(%)	Univariate logistic regression			Multivariate logistic regression		
				crude OR	95% CI	p-value	adjusted OR	95% CI	p-value
Sex	male	206	58.7	1.73	0.76–4.32	0.20	2.31	0.89–6.76	0.10
Age (years)	≥75	86	24.5	1.59	0.44–4.45	0.42			
Depth of tumor invasion	≥T3	279	79.5	1.53	0.56–5.34	0.45			
Approach	laparotomy	285	81.2	2.05	0.91–4.54	0.08			
Location	rectum	103	29.3	3.08	0.88–19.43	0.13			
Resection of other organs	yes	61	17.4	1.09	0.35–2.79	0.87			
Colostomy	yes	27	7.7	1.56	0.35–4.90	0.49			
Timing of operation	emergency	16	4.6	2.99	0.65–10.08	0.10			
Blood loss (mL)	large (>423)	85	24.2	3.25	1.45–7.26	0.004	2.10	0.76–5.76	0.15
Operating time (min)	long (>279)	87	24.8	2.66	1.17–5.91	0.02	2.53	0.89–7.24	0.08
Histology	others	66	18.8	1.26	0.45–3.08	0.64			
Ileus	yes	35	10.0	2.91	1.00–7.41	0.03	3.08	0.91–9.58	0.06
Diabetes mellitus	yes	75	21.4	1.62	0.64–3.73	0.28			
Pulmonary dysfunction	%VC<80 or FEV1.0%<70	81	23.1	2.96	1.30–6.60	0.008	2.83	1.14–6.97	0.02
Performance status	≥1	50	14.2	3.45	1.40–8.03	0.005			
American Society of Anesthesiologists classification	3	28	8.0	2.98	0.93–8.07	0.04	2.24	0.59–7.29	0.20
Body mass index (kg/m²)	<18.5	26	7.4	2.39	0.66–6.90	0.14	3.32	0.78–11.96	0.08
	≥25	82	23.3	1.42	0.57–3.28	0.43	2.36	0.83–6.55	0.10
Prognostic nutritional index	≤40	58	16.5	4.05	1.73–9.21	0.0009	3.87	1.45–10.31	0.006
Neutrophil lymphocyte ratio>4/≤4	>4	94	26.8	1.40	0.58–3.18	0.43			
Controlling nutritional status	≥2	151	43.0	2.41	1.09–5.62	0.03			
modified Glasgow prognostic score (Score)	2	38	10.8	4.13	1.59–9.97	0.002			
Smoking habit	yes	127	36.2	0.73	0.29–1.65	0.46			

Univariate and multivariate logistic regression analyses were performed to identify factors associated with RI incidence. Variables for inclusion in the multivariate analysis were selected by the stepwise procedure with all variables (stepwise forward selection with entry and stay criteria both set to p=0.25). P<0.05 was considered statistically significant.

Univariate logistic regression analyses: In univariate analysis, a significantly high incidence of RIs was associated with excessive blood loss (>423 mL), long duration of surgery (>279 minutes), ileus, pulmonary dysfunction, PS (≧1) , ASA (>2) , PNI≤40 and CONUT≥2, mGPS (Score 2).

Furthermore, when a stepwise multivariate logistic regression analysis was conducted RI incidence as the dependent variable and all other factors as independent variables, Sex (male), excessive blood loss (>423 mL), long duration of surgery (>279 minutes), ileus, pulmonary dysfunction, ASA (>2), BMI<18.5, BMI≥25 and PNI≤40 were selected as being associated RI incidence.

In multivariate logistic regression analyses were performed in these variable, pulmonary dysfunction (Odds ratio2.83 95%CI 1.14–6.97 p=0.02) , PNI≤40 (Odds ratio3.87 95%CI 1.45–10.31 p=0.006) were independent risk factor RI incidence.

cluded in the risk score of the Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system for the assessment of surgical risk proposed by Haga et al.[17], with reference values of %VC<60% and/or $FEV_{1.0}$%<50%. Although these values are stricter than those used in the present study, pulmonary function was reported to be a risk factor for postoperative complications.

Kido et al[18] reported a reference value for requiring artificial ventilation management of %VC≤50%. This value is also associated with a high incidence of pulmonary complications. Kita et al.[19] defined %VC<80% and FEV 1.0%<70% as pulmonary dysfunction, and other studies have followed these criteria. Accordingly, the present study also used %VC<80% or FEC1.0%<70% to define pulmonary dysfunction.

%VC is the ratio of actual vital capacity to predicted vital capacity[20], and a %VC<80% is associated with restraint disorder[20]. %VC reflects an individual's potential abilities such as exercise capacity[20], and values lower than 80% indicate the presence of restrictive impairment[19]. Decreases in %VC postoperatively in patients who have preoperative restrictive impairment suggest that the patient may have developed a severe pulmonary complication[18], particularly if atelectasis occurs due to suppressed deep breathing from pain[19]. Tajima et al.[21] reported %VC may be a predictor of postoperative complications, especially pneumonia in colorectal cancer surgery.

FEV1.0% is an indicator of peripheral airway obstruction. Obstructive impairment is diagnosed when FEV1.0% is <70% and is associated with decreased sputum expectoration[22]. In patients with a low preoperative FEV1.0%, alveolar-to-arterial PO2 difference (A-aDO2), lung capacity, and effective ventilation deteriorate markedly after surgery[22].

In brief, pulmonary dysfunction causes not only pulmonary complications but also an oxygen supply disorder, and circulatory disorders might make it difficult to supply sufficient energy for tissue repair. As a result, patients with pulmonary dysfunction might develop RI at a high rate.

Second, PNI[6] is an indicator for the feasibility of digestive tract resection and/or anastomosis, and is obtained by quantifying the patient's preoperative nutrition and immune condition based on albumin (Alb) and peripheral lymphocyte counts. Alb is inversely correlated with immunosuppressive acidic protein (IAP), granulocytic granulocyte, granulocyte-lymphocyte ratio (G/L), and is an indicator of nutritional status[23]. TLC is an indicator of loss of cellular immune defense, as a decrease in lympho-

cyte count due to malnutrition causes a decrease in T-lymphocytes.

PNI≤40 represents malnutrition and reduced neutrophil function and cell-mediated immunity[16], which have a negative effect on recovery from surgical invasion. Since invasive procedures such as surgical operations can impair the host immunity of patients with cancer, the incidence of infection is considered to be high if PNI is already low before surgery[13]. In fact, a PNI≤40, the Onodera criteria, is associated with a high incidence of postoperative complications and frequently used in the preoperative assessment in the context of surgery for colorectal cancer.

At low PNI, muscle strength of the diaphragm (muscle fiber size of the diaphragm), which is the main respiratory muscle, decreases and is accompanied by a decrease in coughing power, potentially leading to pneumonia and atelectasis[23]. When the load on the respiratory muscles increases, pneumonia and atelectasis may become more severe and are highly likely to lead to respiratory failure, underscoring the importance of evaluating lung function together with PNI[24,25].

Although both PNI and mGPS are Alb-based indicators, they reflect different states; PNI is recognized as an indicator of nutritional immune status[6,26], whereas mGPS is an indicator of inflammation-based nutritional status.

In the present study, we focused on examining whether mGPS, an SSI risk factor, would also affect the incidence of RI. Our results show that, although mGPS score 2 was a risk factor of RIs in univariate analysis, when adjusted for other factors, the association was no longer significant. These findings suggest that, although SSI and RI are both postoperative infectious complications, their mechanisms of onset might differ.

RI is not directly caused by surgical interventions but rather attributed to deterioration of a patient's general condition, reduction of immune function due to malnutrition, or host disorder, given that there is a possibility of nosocomial infection and opportunistic infection. In other words, RI is suggested to have a greater involvement with physical function, nutritional status and immune status than the presence of systemic metabolic abnormality, such as cancer cachexia caused by IL-6 in circulating blood. The aforementioned reasons may explain why pulmonary dysfunction and low PNI were identified as risk factors for RIs in the present study.

Several reports exist on preoperative therapy aimed at addressing these risk factors. For example, for patients with pulmonary dysfunction, the effectiveness of preop-

erative smoking cessation instructions and respiratory function training using incentive spirometers has been reported[12,18,27].

For low PNI, nutritional therapy is reportedly effective[28,29]. The required duration of nutritional therapy is about two weeks by energy administration of 40 to 50 kcal per kilogram of body weight if the patient has moderate or high malnutrition and if organ proteins and protein synthesis ability are considered decreased[28]. When targeting improvements in muscle protein mass, it takes four weeks or more with high calorie infusion[29]. Therefore, with shortened preoperative hospitalization periods, intervention during hospitalization is typically insufficient, and early initiation of nutritional assessments and nutritional therapy in the outpatient setting are required.

If physical function, nutritional status, and immune status can be improved, it may be possible to decrease the frequency of RI. Thus, prospective studies are warranted in the future. Moreover, since risk factors for the development of postoperative complications in patients with colorectal cancer appear to differ between SSIs and RIs, evaluations must be performed at the first outpatient visit, postoperative course predicted based on risk factors, and appropriate measures taken for each.

One limitation of the present study is that it was a single-arm, single-center retrospective study which involved a relatively small number of patients. Accordingly, in the future, a prospective study will be needed to examine whether RI incidence can be decreased by improving RI risk factors preoperatively.

Conclusion

RI is caused by poor nutrition and reduction of immune status and pulmonary dysfunction. In contrast to SSI, RI may be affected more by physical function, nutritional status, and immune status than by cancer cachexia.

Conflict of Interest: The authors declare no conflicts of interest.

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