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Original Article

Risk Factors for Candidiasis as an Intra-Abdominal Infection after Gastrectomy in Patients with Gastric Cancer

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ABSTRACT: Intra-abdominal infections (IAIs) develop in 2.4%–26.6% of patients who underwent gastrectomy for gastric cancer and are occasionally serious. However, there are few reports on the causative organisms of IAI following upper gastrointestinal tract surgery and subsequent risk factors for *Candida* infections. This study aimed to identify the microorganisms that cause IAIs after gastrectomy and risk factors for *Candida*-related IAI. The records of patients who underwent gastrectomy for gastric cancer between January 2009 and December 2019 at Shizuoka General Hospital were retrospectively collected. Patients with IAIs of grade II or higher, as measured by the Clavien–Dindo classification, were included in the analysis. The selected patients were divided into the *Candida* and non-*Candida* groups according to the presence or absence of *Candida* as the causative organism. Of 1,379 patients, 56 (4.1%) were diagnosed with IAIs after gastrectomy. Fifty-two patients were included in the study based on culture analyses. A total of 111 strains and 28 bacterial species were isolated during the initial culture test. *Candida* constituted 7.2% of all identified pathogens. Regarding the risk factors for *Candida*-related IAI, a history of antimicrobial use and ≥ 4 postoperative days of IAI development were independent risk factors for *Candida*-related IAI.

INTRODUCTION

Gastric cancer is the third most common cause of cancer-related death worldwide (1). Intra-abdominal infections (IAIs) develop in 2.4%–26.6% of patients who underwent gastrectomy for gastric cancer and are occasionally severe (2–5). IAIs may also be associated with the long-term prognosis of gastric cancer (6). Although there have been several investigations on the causative microorganisms of IAIs (7,8), few bacteriological studies that have been restricted to the upper gastrointestinal tract have been reported.

The Surgical Infection Society guidelines recommend antimicrobial regimens that have activity against typical gram-negative Enterobacteriaceae, gram-positive cocci, and obligate anaerobes for IAIs (9). The guidelines also recommend antifungal agents for empirical therapy of severely ill patients at risk for hospital-associated infections with *Candida* species. The mortality rate in patients with hospital-associated IAIs from *Candida* spp. is 20%–64% (9,10). Moreover, delayed treatment initiation for candidemia has been associated with a worse prognosis (11). Therefore, both appropriate diagnosis and early treatment are crucial in cases of postoperative *Candida* infections.

This study aimed to identify the microorganisms responsible for IAIs after gastrectomy and risk factors for *Candida*-related IAI.

MATERIALS AND METHODS

Study design and patient population: The study design was approved by the institutional review board of Shizuoka General Hospital (SGHIRB#2020090). The requirement for patient consent was waived owing to the retrospective nature of the study. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and the Declaration of Helsinki 1964 and its later amendments. The records of patients who underwent gastrectomy for gastric cancer between January 2009 and December 2019 at Shizuoka General Hospital were retrospectively collected from a prospectively maintained database. TNM staging (the amount and spread of cancer in a patient's body) was based on the Union for International Cancer Control (UICC) 8th edition. All gastrectomy cases were

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included, except for cases of emergency and concurrent surgery for other cancers. Patients with IAIs of grade II or higher, as measured using the Clavien–Dindo classification, and in whom culture tests were performed were included in the analysis. The selected patients were divided into the *Candida* and non-*Candida* groups according to the presence or absence of *Candida* as the causative organism.

Surgical procedure: All surgeries were performed under the supervision of surgeons with sufficient experience in radical gastrectomy. The surgical fields were distinguished using 10% povidone-iodine before surgery. Lymph node dissection and gastric reconstruction were performed according to the Japanese gastric cancer treatment guidelines available at the time (12–14). Lymph node dissection was not performed during palliative surgery. All patients without contraindications received cefazolin as a perioperative prophylactic antimicrobial, with an additional dose for surgeries lasting longer than 3 h (15). Clindamycin or quinolones are used in patients with cephalosporin allergies. Antibiotic therapy was discontinued on postoperative days 0–2.

Clinical and surgical factors: The following data were collected from the medical records: age, sex, comorbidities, American Society of Anesthesiologists physical status classification, body mass index, laboratory data, history of antimicrobial use, surgical procedure (total gastrectomy or other gastrectomies), surgical approach (laparotomy, laparoscopy/robot-assisted), surgical time, blood loss, intraoperative complications, Acute Physiology and Chronic Health Evaluation (APACHE) II, presence of sepsis, blood cultures, and postoperative day of IAI development.

Comorbidities were scored according to the Charlson comorbidity index (16). Medical history of gastric cancer was not included in the index calculations. A history of antimicrobial use was defined as antimicrobial use from three months before surgery to the time of gastrectomy. It did not include prophylactic antimicrobials administered at the time of surgery. Sepsis was diagnosed based on Sepsis-3 criteria (17). The postoperative day of IAI development was calculated as the number of days since gastrectomy.

Definition of IAI and pathogenic microorganisms: The responsible surgeon examined IAI development daily during the hospital stay and at every outpatient visit until 30 days postoperatively. IAI was diagnosed based on several combinations of physical examination, drainage characteristics, blood tests, upper gastrointestinal video fluoroscopy, and computed tomography. IAI was defined as an abscess or diffuse infection within the abdominal cavity or the presence of anastomotic leakage (18). Culture specimens were collected from the drainage fluid or abscess during the reoperation. Aerobic culture was performed on sheep blood agar (Eiken Chemical Co., Ltd., Tokyo, Japan), chocolate agar (Kyokuto Pharmaceutical Industrial Co., Ltd., Tokyo, Japan), and modified Drigalski agar (Eiken Chemical Co., Ltd.). If multiple types of bacteria were grown, KBM Columbia CA Sheep Blood Agar (Kohjin Bio Co., Ltd., Saitama, Japan) was added to obtain the gram-positive bacteria. To culture fungi, Sabouraud agar (Nissui Pharmaceutical Co., Ltd., Tokyo, Japan) or CHROMagar Candida II plate (BD, Franklin Lakes, NJ, USA) was added. Anaerobic culture was performed on Brucella HK agar (Kyokuto Pharmaceutical Industrial Co., Ltd.) or Bacteroides Bile Esculin agar (Kyokuto Pharmaceutical Industrial Co., Ltd.). Aerobic bacteria were incubated in a 5% CO_2 incubator at 35°C for 18 h. Anaerobic bacteria were incubated in an anaerobic chamber, Te-Her Anaerobox (Hirasawa, Tokyo, Japan) or AnaeroPack (Mitsubishi Gas Chemical Company, Inc., Tokyo, Japan), for ≥ 48 h. Fungal and anaerobic bacteria were incubated at 35°C for ≥ 48 h. API20E and Rapid ID32A API (bioMerieux Japan Ltd., Tokyo, Japan) were used to identify the bacteria. Since September 2016, the MALDI Biotyper (Beckman Coulter K.K., Tokyo, Japan) (19) has been used to identify the bacteria. Only microorganisms in the initial culture after IAI development were identified as causative agents.

Statistical analysis: Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). The two groups were compared to identify the risk factors for *Candida* infection. Continuous variables were presented as median and range and tested using Wilcoxon's rank-sum test. Categorical variables were expressed as numbers and frequencies and tested using Fisher's exact test. Statistical significance was set at a P-value < 0.05.

RESULTS

Incidence of IAI and patients' background: During the observation period, 1,379 patients underwent gastrectomy for gastric cancer at our institution. Fifty-six (4.1%) patients were diagnosed with postoperative IAI. Of the 56 patients, four were excluded because a culture test was not performed. The remaining 52 patients were included in the study (Table 1). The median age of the patients was 72.5 years, and 41 patients were male. The median postoperative duration of IAI development was 4 days after gastrectomy. Postoperative IAIs included anastomotic leakage in 38 cases (grade IIIa, 15 cases; IIIb, 7 cases; IVa, 3 cases; IVb, 10 cases; V, 3 cases), pancreatic fistulae in 13 cases (grade II, 2 cases; IIIa, 8 cases; IIIb, 2 cases; IVa, 1 case), and lymphorrhea in one case (grade IIIa).

Pathogens: A total of 111 strains and 28 bacterial species were isolated during the initial culture test. The sample collection methods were as follows: drainage fluid from drains inserted during gastrectomy in 22 cases, drainage fluid from percutaneously inserted drains after gastrectomy in 14 cases, and drainage fluid or abscess at the time of reoperation in 16 cases. The most commonly identified microorganism was *Streptococcus* spp. (Table 2). Gram-positive cocci constituted 38.7%, and Enterobacteriaceae constituted 20.7% of the identified microorganisms. *Candida* spp. constituted 7.2% of all identified pathogens. Multiple organisms were detected in 31 cases: 27 in the non-*Candida* group and four in the *Candida* group. The bacteria coinfected with *Candida* species were *Streptococcus anginosus*, *Enterococcus faecium*, *Klebsiella aerogenes*, *Prevotella melaninogenica*, *Pseudomonas aeruginosa*, *Corynebacterium* spp., *Sphingobacterium multivorum*, and unspecified gram-positive rods. Among the 52

Table 1. The background of the patients

	Postoperative IAI (n = 52)
Age (years), median (range)	72.5 (38–94)
Male sex (%)	41 (79)
ASA (%)	
Class I	13 (25)
Class II	34 (65)
Class III	5 (10)
Charlson Comorbidity Index, median (range)	0 (0–5)
Pathological Stage	
Stage I	25
Stage II	11
Stage III	12
Stage IV	4
Postoperative intra-abdominal infection	
Anastomotic leakage	38
Pancreatic fistula	13
Lymphorrhea	1
Postoperative day of IAI development (days), median (range)	4 (1–19)
Hospital stays (days), median (range)	37.5 (14–121)
In-hospital death (%)	3 (5.8)

IAI, intra-abdominal infection; ASA, American Society of Anesthesiologists.

patients, blood culture specimens were obtained from 23 patients, and three patients showed positive blood cultures. *Streptococcus constellatus* and *Serratia marcescens* were detected in blood cultures from one and two patients, respectively. The same organism was identified in the abdominal specimen of each patient.

Risk factors for candidiasis in IAI: In the univariate analysis, a history of antimicrobial use and postoperative days of IAI development differed significantly between the *Candida* group (n = 44) and non-*Candida* group (n = 8) (< 0.01 each) (Table 3). There was no significant difference in other preoperative, intraoperative, and postoperative factors.

Postoperative outcomes: No significant differences were observed in the length of hospital stay between the two groups (Table 4). There was no statistically significant difference in in-hospital mortality between the two groups; however, the mortality rate tended to be higher in the *Candida* group (*Candida* group, 25%; non-*Candida* group, 2% [P = 0.058]).

DISCUSSION

Determining the bacterial profile of each infection is necessary to select the empirical antimicrobial therapy. In this retrospective study, we identified the causative microorganisms of IAI after gastrostomy, such as *Streptococcus* spp., *Staphylococcus* spp., *Enterococcus* spp., and *Candida* spp., in patients with gastric cancer. We also found that a history of antimicrobial use and ≥ 4 postoperative days of IAI development were independent risk factors for *Candida*-related IAI.

Table 2. Microorganisms identified in the initial culture after the development of intra-abdominal infection

Microorganisms	Case (%)	No. of cases
Streptococcus spp.	18 (16.2)	
Streptococcus anginosus		5
Streptococcus mitis group		5
Streptococcus constellatus		3
α hemolytic streptococcus		1
Streptococcus sanguinis		1
Streptococcus parasanguinis		1
Streptococcus spp. (unspecified)		2
Staphylococcus spp.	10 (9.0)	
Staphylococcus aureus		6
Staphylococcus epidermidis		4
Enterococcus spp.	9 (8.1)	
Enterococcus faecium		4
Enterococcus faecalis		4
Enterococcus raffinosus		1
Candida spp.	8 (7.2)	
Candida albicans		7
Candida sp. (unspecified)		1
Klebsiella spp.	7 (6.3)	
Klebsiella aerogenes		4
Klebsiella pneumoniae		2
Klebsiella oxytoca		1
Escherichia sp.	5 (4.5)	
Escherichia coli		5
Haemophilus spp.	5 (4.5)	
Haemophilus influenzae		3
Haemophilus parainfluenzae		2
Prevotella spp.	5 (4.5)	
Prevotella melaninogenica		2
Prevotella intermedia		2
Prevotella disiens		1
Serratia sp.	5 (4.5)	
Serratia marcescens		5
Neisseria spp.	4 (3.6)	
Neisseria spp. (unspecified)		4
Pseudomonas sp.	4 (3.6)	
Pseudomonas aeruginosa		4
Bacteroides spp.	3 (2.7)	
Bacteroides fragilis		2
Bacteroides sp. (unspecified)		1
Enterobacter spp.	3 (2.7)	
Enterobacter cloacae		2
Enterobacter sp. (unspecified)		1
Peptostreptococcus spp.	3 (2.7)	
Peptostreptococcus spp. (unspecified)		3
Miscellaneous	22 (19.8)	
Capnocytophaga spp. (unspecified)		2
Corynebacterium spp. (unspecified)		2
Rothia mucilaginosa		2
Stenotrophomonas maltophilia		2
Aeromonas sp. (unspecified)		1
Arcanobacterium hemolyticum		1
Bifidobacterium breve		1
Bifidobacterium sp. (unspecified)		1
Citrobacter freundii		1
Eikenella corrodens		1
Fusobacterium sp. (unspecified)		1
Morganella morganii		1
Parvimonas micra		1
Proteus mirabilis		1
Sphingobacterium multivorum		1
Gram Positive rod (unspecified)		2
Gram Negative cocci (unspecified)		1

Table 3. Risk factors for candidiasis as an intra-abdominal infection after gastrectomy

Factor	*Candida* group (n = 8)	non-*Candida* group (n = 44)	Univariate analysis P value
Preoperative factors			
Age (years), median (range)	74.0 (61–82)	71.5 (38–94)	0.79
Male sex (%)	6 (75)	35 (80)	1.00
ASA (%)			0.73
Class I	3 (37)	12 (27)	
Class II	5 (63)	27(61)	
Class III	0 (0)	5 (11)	
Charlson comorbidity index, median (range)	0.5 (0–2)	0 (0–5)	0.47
Body mass index (kg/m^2), median (range)	23.9 (20.9–43)	22.8 (16.4–33.4)	0.35
Albumin(g/dl), median (range)	3.9 (2.6–4.9)	4.0 (2.3–4.6)	0.88
History of antimicrobial use (%)	6 (75)	10 (23)	< 0.01
Intraoperative factors			
Surgical procedure (%)			0.28
Total gastrectomy	6 (75)	23 (52)	
Others	2 (25)	21 (48)	
Surgical approach (%)			0.47
Laparotomy	6 (75)	28 (64)	
Laparoscopy/Robot-assisted	2 (25)	16 (36)	
Operation time (minutes), median (range)	302 (192–353)	271 (120–470)	0.77
Blood loss (ml), median (range)	410 (50–900)	268 (5–2540)	0.63
Intraoperative complication (%)	0 (0)	3 (7)	0.59
Postoperative factors			
APACHE II score (points), median (range)	7 (5–9)	8 (3–27)	0.39
The presence of sepsis (%)	1 (13)	12 (27)	0.66
Postoperative days of IAI development			< 0.01
≥ 4 postoperative days	8	21	
< 4 postoperative days	0	23	

ASA, American Society of Anesthesiologists; APACHE, acute physiology and chronic health evaluation; IAI, intra-abdominal infection.

Table 4. The outcomes of the patients with postoperative intra-abdominal infection

	Candida group (n = 8)	non-*Candida* group (n = 44)	Univariate analysis P value
Hospital stay (days), median (range)	36 (28–80)	39.5 (14–59)	0.55
In-hospital death (%)	2 (25)	1 (2.2)	0.058

A Japanese nationwide survey reported that the causative microorganisms of IAI after gastroenterological surgery were *Escherichia coli* (21.4%), *Enterococcus faecalis* (19.0%), *Staphylococcus aureus* (13.9%), *Bacteroides fragilis* (13.7%), *Pseudomonas aeruginosa* (12.7%), *Enterobacter cloacae* (10.7%), and *Klebsiella pneumoniae* (8.5%) (7). We hypothesized that the pathogens of IAI after gastrectomy were different from those after whole gastroenterological surgery because the intestinal resident microbiota varies from site to site, and the normal gastric microbiota is less abundant than the normal colonic microbiota (20). However, the microbial profile in our study was similar to that of IAI after whole gastroenterological surgery, except for a slightly higher proportion of *Streptococcus* spp. and *Candida* spp.. These findings suggest that, for the treatment of IAI after gastrectomy, typical gram-negative Enterobacteriaceae, gram-positive cocci, and obligate anaerobes should be considered as well as general gastroenterological surgery.

A study from China revealed that the microbial profile of IAI after gastrectomy included *Escherichia coli* (36.8%), *Klebsiella pneumonia* (15.1%), *Enterococcus* (13.7%), and *Candida* (5.5%) (18). We found two differences between this study and our study: the absence of *Bacteroides* spp. and prevalence of Enterobacteriaceae. Their study did not isolate *Bacteroides* spp. and did not provide details of the anaerobic culture method. We assume that their anaerobic culture method differs from our method. The prevalence of Enterobacteriaceae in this study was higher than that in our study, which may be due to the differences in the types of prophylactic antibiotics

used and duration of treatment. The prophylactic antibiotic used in their study was a second-generation cephalosporin administered for 3–5 days after surgery, whereas cefazolin was administered for 0–2 days after surgery. These differences may influence the microbial profile of IAI.

Candida spp. accounted for 6.4% of the causative pathogens of IAI (8). Xiao et al. reported that *Candida* spp. are responsible for 5.5% of IAI after gastrectomy (18). The reported mortality rate of *Candida*-related IAI is 20–64% (9,10). Because any delay in antifungal therapy for candidemia increases the mortality rate (11), appropriate diagnosis of candidiasis is critical. Leon et al. reported that the Candida score was useful in identifying invasive candidiasis from Candida colonization (21). Since the Candida score was calculated from total parenteral nutrition, surgery, multifocal Candida species colonization, and severe sepsis, patients tended to have a high score after abdominal surgery. Moreover, recent abdominal surgery was reported to be a risk factor for *Candida*-related IAI (22). Although patients after abdominal surgery are at a high risk for invasive candidiasis, detailed risk factors among patients after abdominal surgery have not been elucidated. Our study identified additional risk factors for *Candida*-related IAI, such as a history of antimicrobial use and ≥ 4 postoperative days of IAI development. Therefore, antifungal treatment should be considered for patients with IAI with these risk factors.

This study had several limitations. First, this was a single-center retrospective study with a small sample size. Second, culture specimens from previously inserted drains are at risk of contamination. Third, our observational period was 10 years, and surgical techniques, bacterial identification methods, and bacterial drug resistance trends changed significantly during this period. Therefore, the obtained results may not be entirely applicable to the current situation.

In this study, we identified the causative microorganisms of IAI after gastrectomy in patients with gastric cancer. We also found that a history of antimicrobial use and ≥ 4 postoperative days of IAI development were independent risk factors for Candida-related IAI. Therefore, these causative organisms and risk factors of candidiasis should be considered in the empirical treatment of IAI after gastrectomy.

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Conflict of interest None to declare.

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