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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors for tuberculosis after gastrectomy in gastric cancer

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Abstract

AIM: To examine incidence of tuberculosis (TB) in gastrectomy patients and investigate the risk factors for developing TB after gastrectomy in patients with gastric cancer.

METHODS: A retrospective cohort study of gastrectomy patients with gastric cancer was performed at a university-affiliated hospital in Seoul, South Korea between January 2007 and December 2009. We reviewed patient medical records and collected data associated with the risk of TB, surgery, and gastric cancer. Standardized incidence ratios (SIRs) of TB were calculated to compare the incidence of TB in gastrectomy patients with that in the general Korean population, and risk factors for TB after gastrectomies were analyzed.

RESULTS: Among the 1776 gastrectomy patients, 0.9% (16/1776) developed post-gastrectomy TB, with an incidence of 223.7 cases per 100000 patients per year. The overall incidence of TB in gastrectomy patients, adjusted by sex and age, was significantly higher than

that in the general population (SIR = 2.22, 95%CI: 1.27-3.60). Previous TB infection [odds ratio (OR) = 7.1, $P < 0.001$], lower body mass index (BMI) (kg/m^2; OR = 1.21, $P = 0.043$) and gastrectomy extent (total gastrectomy *vs* subtotal gastrectomy) (OR = 3.48, $P = 0.017$) were significant risk factors for TB after gastrectomy in a multivariate analysis.

CONCLUSION: TB incidence after gastrectomy is higher than that in the general population. Previous TB infection, lower BMI, and total gastrectomy are risk factors for TB after gastrectomy in patients with gastric cancer.

Key words: Tuberculosis; Gastrectomy; Body mass index; Risk factor; Gastric cancer

Core tip: The incidence of tuberculosis (TB) in patients who underwent gastrectomy was found to be more than two-times higher than that in the general population. Also, we found that a previous TB infection [odds ratio (OR) = 7.1, $P < 0.001$], gastrectomy extent (total gastrectomy *vs* subtotal gastrectomy) (OR = 3.48, $P = 0.017$) and lower body mass index (kg/m^2; OR = 1.21, $P = 0.043$) were significant risk factors for TB after gastrectomy in gastric cancer.

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INTRODUCTION

Tuberculosis (TB) is a widespread infectious disease, with worldwide incidence. According to the data of the World Health Organization, one-third of the world's population is estimated to be latently infected with TB and an estimated 8.6 million people developed TB in 2012[1,2]. South Korea is an intermediate TB burden country; the annual incidence was 89.4 cases per 100000 person-years in 2008. Given this reality, preventing active TB and increasing awareness of the risk factors for the development of TB are important issues. Risk factors for development of active TB include HIV infection, TB scars on chest radiographs, diabetes, malnutrition, chronic renal failure, silicosis, and transplantation[3,4]. Impaired immunity is presumed to be a risk factor for reactivation.

Gastrectomy is also considered to be a risk factor for development of TB, likely related to malnutrition and decreased immunity[5,6]. Although studies have reported that an increased risk of TB is associated with gastrectomy[7-11], the influence of gastrectomy on the risk of TB has not been clearly demonstrated and the risk factors for TB in gastrectomy patients with gastric cancer remain unknown. In particular, the highest incidence of gastric cancer is in South Korea, where gastrectomy is frequently performed.

Thus, we determined the incidence of TB among gastric cancer patients who had undergone gastrectomies and investigated risk factors for the development of active TB in gastrectomized patients in South Korea, an intermediate TB burden country.

MATERIALS AND METHODS

Study design and subjects

This retrospective longitudinal cohort study was performed among patients who underwent gastrectomies for gastric cancer at Severance Hospital, a 2000-bed university tertiary referral hospital in Seoul, South Korea, between January 1, 2007 and December 31, 2009. During the period, 2933 patients underwent gastrectomies for stomach cancer. We excluded those patients who received chemotherapy after gastrectomy ($n = 1836$), who had a history of previous gastrectomy ($n = 10$), who were treated for TB within 6 mo before surgery or developed TB within 2 mo after surgery ($n = 8$), and who visited the hospital only once after surgery ($n = 42$). After excluding these patients, the study population consisted of 1776 patients.

We reviewed the medical records and imaging studies and collected data that included baseline characteristics, previous history of TB, chest X-ray (CXR) findings, laboratory data, cancer stage, pathology, surgery extent, duration of follow-up, and mortality. These data were compared between patients with and without post-gastrectomy TB.

Definitions

Diagnosis of active TB: TB diagnosis was confirmed if *Mycobacterium tuberculosis* (*M. tuberculosis*) was isolated in the culture of any clinical specimen or if *M. tuberculosis* DNA was identified by polymerase chain reaction from any clinical specimen. Histopathological diagnoses were also accepted. Patients who had a high clinical likelihood of active TB and a negative mycobacterial culture finding but who also had good clinical and radiographic responses to anti-TB treatment were also included as active TB patients.

Previous TB infection: Previous TB infection was defined as a history of TB treatment or radiological evidence of previously healed TB. Chest films were reviewed by board-certified pulmonologists. Abnormal chest radiographic findings consistent with previously healed TB were defined as fibro-nodular lesions and multiple non-calcified nodules in the upper zones of the lung[3,12,13].

Table 1 Baseline characteristics of gastrectomy patients

Characteristic	Total (*n* = 1776)	No active TB (*n* = 1760)	Active TB (*n* = 16)	*P* value
Age (yr)	58 (20-89)	58 (20-89)	54 (40-83)	0.395
< 40	169 (9.5)	168 (9.5)	1 (6.3)	
41-60	843 (47.5)	834 (47.4)	9 (56.3)	
61-80	743 (41.8)	738 (41.9)	5 (31.3)	
> 80	21 (1.2)	20 (1.1)	1 (6.3)	
Sex, male	1156 (65.1)	1142 (64.9)	14 (87.5)	0.059
Smoking	887 (49.9)	873 (49.6)	14 (87.5)	0.010
Alcohol	591 (33.4)	579 (33.0)	12 (75.0)	0.001
BMI[1] (kg/m^2)	23.4 (21.5-25.2)	23.4 (21.5-25.2)	22.4 (18.5-23.9)	0.015
< 18.5	71 (4.0)	67 (3.8)	4 (25.0)	< 0.001
18.5-24.99	1219 (68.8)	1208 (68.8)	11 (68.8)	
⩾ 25	482 (27.2)	481 (27.4)	1 (0.2)	
Postoperative BMI[2] (kg/m^2)	21.3 (19.5-23.1)	21.3 (19.5-23.1)	18.8 (18.2-20.6)	0.001
Comorbidity				
Diabetes mellitus	173 (9.7)	171 (9.7)	2 (12.5)	0.664
Other malignancy	36 (2.0)	36 (2.0)	0 (0.0)	1.000
Previous TB infection	200 (11.3)	191 (10.9)	9 (56.3)	< 0.001
Laboratory data				
Hemoglobin (g/dL)	13.8 (12.6-14.8)	13.8 (12.6-14.8)	13.6 (12.4-14.6)	0.340
Albumin (g/dL)	4.6 (4.4-4.8)	4.6 (4.4-4.8)	4.6 (4.3-4.9)	0.195
Cholesterol (mg/dL)	182 (160-206)	182 (160-206)	177 (152-190)	0.120
ASA physical status				0.222
Class Ⅰ	1241 (69.9)	1226 (69.7)	15 (93.8)	
Class Ⅱ	495 (27.9)	494 (28.1)	1 (6.3)	
Class Ⅲ	40 (2.2)	40 (2.2)	0	
Surgery extent, total gastrectomy	359 (20.2)	351 (19.9)	8 (50.0)	0.007
Cancer stage				0.616
Ⅰ A	1255 (70.6)	1245 (70.7)	10 (62.5)	
Ⅰ B	253 (14.2)	252 (14.3)	1 (6.3)	
Ⅱ	156 (8.8)	153 (8.7)	3 (18.8)	
Ⅲ	94 (5.3)	92 (5.2)	2 (12.5)	
Ⅳ	5 (0.3)	5 (0.3)	0 (0)	
Cancer cell type				0.762
Adenocarcinoma	1239 (69.7)	1227 (69.7)	12 (75.0)	
Signet-ring cell	454 (25.6)	451 (25.6)	3 (18.7)	
Others	72 (4.0)	71 (4.0)	1 (6.2)	
Death	42 (2.4)	53 (3.0)	1 (6.3)	0.391

Data are presented as *n* (%) or median (interquartile range) unless otherwise indicated. [1]Measured BMI before gastrectomy; [2]Measured BMI about 1 yr after gastrectomy; not measured in 233 (13%) patients. TB: Tuberculosis; BMI: Body mass index; CXR: Chest X-ray; ASA: American Society of Anesthesiologists.

Statistical analysis

Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the *t*-test or Mann-Whitney *U*-test. To evaluate independent risk factors for post-gastrectomy TB, multivariate analysis using logistic regression was conducted using potentially associated explanatory variables detected in a univariate analysis ($P < 0.1$). Multi-collinearity of these variables was checked, and the goodness-of-fit of the model was verified using the Hosmer-Lemeshow test.

Standardized incidence ratios (SIRs) of TB were calculated to compare the incidence of TB in gastrectomy patients with that in the general Korean population[14]. Data covering the incidence of TB in the general population were provided by the Korean Tuberculosis Surveillance Center, and an estimate of the total population was obtained from the Korean National Statistical Office. The observed number of gastrectomy patients with TB was divided by the expected number of gastrectomy patients. The expected number of gastrectomy patients with TB was extrapolated from the TB incidence in the general population in 2008 (the midpoint of 2007-2009). The expected number of TB patients was calculated by multiplying the TB incidence in the general population in 2008 by the number of gastrectomy patients. The 95% confidence intervals (CIs) for the SIRs were estimated by assuming that the observed cases had a Poisson distribution using Byar's normal approximation method. The SPSS software (ver. 19; SPSS Inc., Chicago, IL, United States) was used for all statistical analyses.

RESULTS

Characteristics of gastrectomy patients

The characteristics of the 1776 patients with and without active TB are shown in Table 1. Males accounted for two-thirds of the study populations and

Table 2 Clinical and demographic characteristics of 16 tuberculosis patients after gastrectomy

Case	Sex/age	History of TB	Previous healed TB on CXR	Smoking history	BMI (kg/m^2)	Gastrectomy extent	Cancer stage	From surgery to TB onset (mo)	Site of TB infection	TB diagnosis method	TB treatment outcome
1	M/83	+	-	±	25.3	Total	Ⅰ A	62	Lung	Culture	Death[1]
2	M/59	-	+	+	18.2	Total	Ⅰ A	34	Lung	Culture	Cure
3	M/42	+	-	+	21.8	Total	Ⅰ A	52	Lung	Culture	Cure
4	F/40	-	-	-	17.6	Subtotal	Ⅰ A	13	Lung	Pathology (TBLB)	ND[2]
5	M/54	-	-	±	21.1	Subtotal	Ⅰ A	7	Neck LN	Pathology (LN)	ND[2]
6	M/79	-	+	±	18.3	Subtotal	Ⅰ A	46	Lung	Culture	Cure
7	M/52	-	-	±	17.2	Subtotal	ⅢB	3	Neck LN	Pathology (LN)	Cure
8	M/45	+	+	+	23.6	Total	Ⅰ B	16	Lung	Culture	Cure
9	F/71	-	-	-	24.9	Subtotal	ⅢB	42	Lung	Culture	Cure
10	M/54	+	+	±	19.0	Subtotal	Ⅱ	4	Lung	Pathology (VATS)	Cure[3]
11	M/41	-	-	±	23.4	Subtotal	Ⅰ A	13	Intestine	Pathology (colon)	Cure
12	M/54	-	+	±	23.5	Total	Ⅰ A	18	Lung, pleura	Culture	Cure
13	M/47	-	-	+	23.0	Total	Ⅰ B	39	Lung	Clinical	Cure
14	M/62	+	-	+	24.3	Subtotal	Ⅰ A	10	Lung	Clinical	Cure
15	M/67	-	-	±	20.0	Total	Ⅰ A	9	Lung	Culture	Cure
16	M/67	+	+	±	23.9	Total	Ⅰ B	39	Lung	Clinical	Cure

[1]Death due to lung cancer progression during TB treatment; [2]Patients were referred to other hospitals during TB treatment; [3]Lung lesion by TB was resected and TB medication was used for only 2 wk due to side effects, but the patient was considered to be cured clinically. TB: Tuberculosis; BMI: Body mass index; CXR: Chest X-ray; LN: Lymph node; TBLB: Transbronchial lung biopsy; VATS: Video-assisted thoracoscopic surgery ± former smoker.

Table 3 Sex-age standardized incidence ratios of tuberculosis in gastrectomy patients

Subgroup	Gastrectomy patients, *n*	Sum of observation (patient-years)	Observed TB, *n*	Expected TB, *n*	Standardized incidence ratio	95%CI
Sex						
Male	1156	4628.0	14	4.69	2.99	1.63-5.01[1]
Female	620	2524.5	2	1.81	1.11	0.12-4.01
Age						
20-29	13	57.7	0	0.05	-	-
30-39	112	465.6	0	0.30	-	-
40-49	343	1465.1	5	0.90	5.54	1.79-12.93[1]
50-59	490	2072.3	5	1.60	3.16	1.02-7.38[1]
60-69	557	2234.5	3	2.60	1.18	0.24-3.43
⩾ 70	261	857.3	3	1.90	1.62	0.33-4.74
Total	1776	7152.5	16	7.20	2.22	1.27-3.60[1]

[1]Significantly higher than expected at the 5% level. New TB case notification rates in 2008 were used for estimation of expected TB cases. TB: Tuberculosis.

the median age was 58 (range: 20-89) years. Among the 1776 total patients, 16 were diagnosed with active TB; the remaining 1760 patients were compared with the active TB patients. Smoking history, alcohol history, lower body mass index (BMI), previous TB infection, and gastrectomy extent (total gastrectomy *vs* subtotal gastrectomy) were related to active TB ($P < 0.05$). The mean duration of follow-up was 1469 (range: 42-2279) d. Of the patients, 1687 (95%) were followed for more than 1 year and 1609 (92.1%) of the survivors were followed for more than 2 years.

Characteristics of the TB patients

Of the 1776 patients, 16 (0.9%) developed TB after gastrectomy. Table 2 describes the characteristics of these 16 patients. The median time from gastrectomy to development of TB was 25.3 (range: 4-62) mo, and 5 developed TB within 1 year after gastrectomy. Of the 16 patients with TB, 13 were diagnosed with pulmonary TB and 3 with extrapulmonary TB. Among the 14 patients with available follow-up data, 13 were considered to be "cured" by first line treatment or resection. One patient died during the anti-TB treatment due to lung cancer progression.

Incidence of TB after gastrectomy

The incidence of TB after gastrectomy was 223.7 per 100000 patients per year. Table 3 shows the incidence

Table 4 Multivariate analysis for risk factors of active tuberculosis after gastrectomy

Variable	Odds ratio	95%CI	*P* value
Sex, male	1.29	0.18-9.40	0.801
Low BMI	1.21	1.01-1.46	0.043
Smoking	1.93	0.79-4.75	0.149
Alcohol	1.22	0.55-2.75	0.622
Previous TB infection	7.10	2.47-20.36	< 0.001
Surgery extent, total gastrectomy	3.48	1.25-9.66	0.017

TB: Tuberculosis; BMI: Body mass index; CXR: Chest X-ray.

ratios adjusted by sex and age. The overall incidence of TB in gastrectomy patients, adjusted by sex and age, was significantly higher than that in the general population (SIR = 2.22, 95%CI: 1.27-3.60). The incidence of TB in gastrectomy patients was higher in males and those aged 40-60 years.

Risk factors for TB after gastrectomy

A multivariate logistic regression analysis to assess development of active TB after gastrectomy was performed (Table 4). Previous TB infection (OR = 7.1, 95%CI: 2.47-20.36, $P < 0.001$), lower BMI (kg/m^2; OR = 1.21, 95%CI: 1.01-1.46, $P = 0.043$) and surgical extent (total gastrectomy *vs* subtotal gastrectomy) (OR = 3.48, 95%CI: 1.25-9.66, $P = 0.017$) were significant risk factors for TB after gastrectomy.

DISCUSSION

This retrospective cohort study performed in Korea between 2007 and 2009 showed that gastrectomy increased the risk of developing TB in an intermediate TB burden area. The frequency of TB in gastrectomy patients with gastric cancer was 0.9% and the incidence was 223.7/100000 patients/year. We also documented that prior TB infection, lower BMI, and surgical extent (total gastrectomy) were significant risk factors for developing TB after gastrectomy.

Up to now, no larger-scale prospective study regarding gastrectomies and the risk of TB has been reported. Several studies have argued that gastrectomy increases the risk of TB, although most were reported several decades ago[7-11,15]. One recent study reported that patients had a 2.5-fold higher incidence of TB after gastrectomy than that in the general population[7]. Our study also showed that patients had a higher incidence of TB after gastrectomy than the general population (SIR = 2.22, 95%CI: 1.27-3.60). These results indicate that gastrectomy remains an independent risk factor for developing TB.

Gastrectomy may influence TB reactivation in patients with a latent *M. tuberculosis* infection (LTBI) because it can cause poor nutritional status and an associated reduction in immunity. Patients who have undergone gastrectomy can suffer from malnutrition secondary to poor food intake and intestinal malabsorption. Malnutrition is known to increase susceptibility to TB by impairing the immune response[16-18]. In this study, low BMI was independently associated with the development of TB in the multivariate analysis. Those results can be interpreted as being consistent with the explanation given above as well as in previous reports[8,11,19]. Additionally, we found that patients who underwent total gastrectomy were more likely to develop a reactivation of TB than those who underwent subtotal gastrectomy. This can be explained by the fact that subtotal gastrectomy entails higher calorie intake and better nutritional status[20-23]. To our knowledge, this is the first study that has analyzed gastrectomy extent and identified it as a risk factor for TB after gastrectomy.

Previous TB infection, such as an old TB lesion on CXR, is a well-known risk factor for developing TB[3,4]. Our results also show that prior TB infection was a significant risk factor for developing TB after gastrectomy. This finding is compatible with previous studies showing that many patients who develop pulmonary TB after gastrectomy have an old TB lesion on CXR or a TB history[7,11]. Such patients should be monitored closely for reactivation of TB.

Gastric cancer is one of the most commonly occurring cancers, and gastrectomy is frequently performed in South Korea with advanced surgery showing a 5-year survival rate > 60%[24]; thus, monitoring the development of active TB is of great clinical significance in gastrectomy patients, particularly those with risk factors. We investigated a greater variety of parameters compared with previous studies, not only those associated with the risk of TB but also those related to surgery and gastric cancer. Among the study population, no patient had human immunodeficiency viral infection or silicosis and none was treated with TNF-α inhibitors. Two patients were receiving chronic high-dose steroids, but they did not have TB. Thus, our data would seem to not have been subject to bias by these factors. Nevertheless, some risk factors for TB development were not available for analysis. We did not know the patients' performance status, such as the European Cooperative Oncology Group score. However, we investigated the preoperative American Society of Anesthesiologists (ASA) score. Additionally, detailed glucose control status data, including hemoglobin A1c level, were not available. In particular, most of the patients had not undergone a tuberculin skin test (TST) or interferon-gamma release assay (IGRA), which are relevant to the risk of developing TB and are useful in LTBI diagnosis. TST or IGRA should also be performed to verify the latent TB status and to assess the risk of reactivation after gastrectomy. Another limitation of our study is that it was retrospective in design and conducted at a single medical center. Thus, our

results may not reflect those at other institutions or in other areas. Additionally, the follow-up period differed among subjects, and patients lost to follow-up could have developed TB.

In conclusion, the risk of TB was higher in patients who underwent gastrectomies for gastric cancer compared with that in the general population in Korea. Careful monitoring and timely diagnosis of TB are needed for patients who undergo gastrectomies, especially those with risk factors, such as prior TB infection, low BMI, and total gastrectomy. Further well-designed, large-scale studies, including use of TST and IGRA, are needed to identify the predictors of TB.

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COMMENTS

Background

Korea is an intermediate tuberculosis (TB) burden country, in which gastric cancer has one of the highest incidences of all cancers. Gastrectomy is frequently performed for patients with gastric cancer in East Asian countries, including South Korea. Gastrectomy has been considered to be a risk factor for the development of TB, which is likely related to malnutrition and decreased immunity.

Research frontiers

There is a lack of good data regarding gastrectomy and the risk of TB in patients with gastric cancer. Thus, the authors conducted a retrospective cohort study of patients who underwent gastrectomy for gastric cancer. The authors investigated a wide variety of variables associated with the risk of developing TB and those related to surgery and gastric cancer.

Innovations and breakthroughs

The incidence of TB in gastrectomy patients was more than two-times higher than that in subjects in the general population. Previous TB infection [odds ratio (OR) = 7.1, $P < 0.001$], gastrectomy extent (total gastrectomy *vs* subtotal gastrectomy) (OR = 3.48, $P = 0.017$), and lower body mass index (BMI) (kg/m^2; OR = 1.21, $P = 0.043$) were significant risk factors for TB after gastrectomy for gastric cancer.

Applications

Careful monitoring and timely diagnosis of TB are needed for patients who undergo gastrectomy, particularly those with risk factors, such as prior TB infection, low BMI, and a history of total gastrectomy. Treatment for a latent TB infection can be considered in gastrectomy patients; however, further research is needed.

Peer-review

This is a good descriptive study in which the TB incidence in gastrectomy patients was more than twice as high as that in the general population. Gastrectomy extent, lower BMI, and previous TB infection were significant risk factors for developing TB after gastrectomy.

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