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Treatment Outcomes of Patients Treated for Pulmonary Tuberculosis after Undergoing Gastrectomy

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Gastrectomy is a proxy of malnutrition, which may lead to increased risk for developing pulmonary tuberculosis (TB). Malabsorption in gastrectomy patients could lead to low serum levels of rifampicin, which may be related to higher treatment failure. However, there is limited information on treatment outcomes of TB in patients who have undergone gastrectomy. This study aims to determine treatment outcomes and adverse effects in patients treated for TB after undergoing gastrectomy for gastric cancer. During the study period, 112 patients were treated for active TB that developed after gastrectomy for gastric cancer. Among them, we selected 15 patients who were culture positive at initial diagnosis and had evidence of active TB on imaging studies; namely, the remaining 97 patients without initial culture or imaging studies were excluded. We thus performed a case-control study of gastric cancer patients treated for TB after undergoing gastrectomy (n = 15). The control group was defined as age- and sex-matched TB patients who had not received gastrectomy (n = 45). Treatment failure in clinical, microbiological aspects, and adverse events were analyzed. Patients who had undergone gastrectomy exhibited higher 4-month clinical failure rates, compared to non-gastrectomy patient: 4 (26.7%) vs. 1 (2.2%), P = 0.012. Gastrointestinal adverse effects were more frequent in patients with gastrectomy, compared to non-gastrectomy patients: 9 (60%) vs. 5 (11.1%), P < 0.001. In conclusion, patients treated for TB after undergoing gastrectomy are associated with higher rates of gastrointestinal adverse events and treatment failure.

Keywords: gastrectomy; gastric cancer; gastrointestinal adverse events; pulmonary tuberculosis; treatment failure
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Introduction

Pulmonary tuberculosis (Pul TB), a communicable infectious disease, is transmitted through aerosol and presents an important global health problem (Lee et al. 2015). Pulmonary tuberculosis (TB) is caused by *Mycobacterium tuberculosis*, which most commonly infects the lungs and is characterized by necrotizing granulomatous inflammation on pathological examinations (Dheda et al. 2016).

Given that TB is a widespread infectious disease, several previous studies have attempted to determine the risk factors for Pul TB (Dooley and Chaisson 2009; Kim et al. 2014). In particular, factors associated with impaired immunity such as HIV infection, malnutrition, diabetes mellitus, chronic renal failure, and organ transplantation are considered as risk factors for developing Pul TB (Munoz et al. 1995; Choi et al. 2015; Shen et al. 2015; Jung et al. 2016). Approximately 19% of patients who have undergone gastrectomy for gastric cancer suffer from malnutrition (Fukuda et al. 2015). The alteration of the digestive system after gastrectomy could lead to malabsorption and deficiencies of nutritive components, which could result in decreased immunity and consequently a higher risk for TB development (Skodrić-Trifunović 2003). In gastrectomy patients, the potential mechanisms underlying the low serum anti-tuberculosis drug levels include malabsorption and decreased retention due to decreased bile salt reuptake, which could both lead to low serum levels of rifampicin (Reed and Blumer 1983).

In South Korea, the incidence of gastric cancer is high (80.2 cases per 100,000 person-years in 2013), and gastrectomy is frequently performed (Oh et al. 2016). Moreover, South Korea has an intermediate TB burden (Dye et al. 1999), and the incidence in 2014 was 97 cases per 100,000

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person-years (Lee and Kim 2014). To our knowledge, no larger scale retrospective study has identified the treatment response and medication related adverse effects of Pul TB in patients who have undergone gastrectomy for gastric cancer. Thus, the aim of this study is to identify treatment outcomes and adverse events in patients treated for Pul TB after undergoing gastrectomy due to gastric cancer.

Methods

Study design and subjects

We conducted a case-control study at a 2000-bed tertiary referral hospital in South Korea over a 10-year period (January 2005 to December 2014). The aim was to identify treatment failure based on rates of absence of negative conversion of sputum culture and progression at 2 and 4 months imaging studies. The rate of treatment failure was identified by comparing results at 2 and 4 months to initial culture and imaging results.

During this period, 10,564 patients received gastrectomy due to gastric cancer. Of these patients, 112 patients were treated for Pul TB after receiving gastrectomy. To enhance diagnostic accuracy, only 15 patients with positive culture results for *M. tuberculosis* and evidence of active tuberculosis on radiographic studies (chest radiography or computed tomography) at initial diagnosis were included (American Thoracic Society Medical Section of the American Lung Association 1990). This study included all patients who received treatment with the standard regimen at the start of the treatment (initiation therapy with isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months plus maintenance therapy with isoniazid, rifampin, and ethambutol for 4 months; or initiation therapy with isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months plus maintenance therapy with isoniazid and rifampin for 4 months).

We excluded patients without available data regarding the initial culture results or those with a negative culture result at the time of diagnosis (n = 57). Patients without evidence of active Pul TB on imaging studies (chest radiography or computed tomography) at the time of diagnosis or those without initial studies were also excluded (n = 40). Since it is difficult to evaluate the treatment response of extrapulmonary tuberculosis in clinical practice, patients diagnosed with extra-pulmonary tuberculosis (n = 5), drug-resistant tuberculosis (n = 2) were excluded. Patients with other immunosuppressive conditions; receiving immunosuppressive therapy, transplant recipients, underlying rheumatologic diseases, hematologic malignancies, and solid organ malignancies (other than gastric cancer) and those receiving active chemotherapy or radiation therapy after gastrectomy were also excluded (n = 25). Furthermore, patients who defaulted from treatment, and those who were transferred to another center during treatment were excluded (n = 10). There were overlapping samples with multiple exclusion criterias.

After exclusion, 15 Pul TB patients who had undergone gastrectomy and 45 age and sex-matched (1:3 matched) Pul TB controls who had not undergone gastrectomy were reviewed. This study was performed in compliance with relevant institutional guidelines.

Collected data

The following information was collected: demographic data; comorbidities; cancer staging; surgery extent; sputum smear microscopy for acid-fast bacilli (AFB) and sputum culture for *M. tuberculosis*; duration of treatment; pharmaceutical formulation used; changes from the drug regimen initially prescribed; and reported adverse reactions. The results of sputum smear microscopy for AFB and cultures at time of diagnosis, and at 2 and 4 months after treatment were obtained from the electronic hospital records. The findings of chest radiography and computed tomography (CT) at the time of diagnosis, and 2 and 4 months after treatment, were reviewed by a radiologist and recorded as "improving," "unchanged," or "worsening."

Definition

Microbiological failure was considered in patients with ≥ 1 positive AFB smear or culture result after 4 months of anti-tuberculous treatment (Jasmer et al. 2004). Clinical failure was defined as the evidence of progressive tuberculosis on radiography—i.e., "worsening" on chest radiography or chest CT after 4 months of anti-tuberculosis treatment, as confirmed by a radiologist (Bhalla et al. 2015).

Adverse reactions that were more severe than grade 3 were documented by the treating clinician and classified in accordance with the concepts and severity criteria described by the World Health Organization (1989). The adverse reactions included gastrointestinal problems: > 6 episodes of vomiting of all food/fluids within 24 hours or the need for hospitalization or parenteral nutrition; hepatotoxicity: increase in liver transaminase (AST/ALT) levels to > 5 times the upper limit of normal, or an increased bilirubin level; arthralgia: joint pain causing marked impairment of the activities of daily living or mobility; skin rash: vesiculation or moist desquamation or ulceration; ocular toxicity: symptomatic visual impairment and impairment of the activities of daily living; neuropathy: marked decrease in sensation to the level of the knees or wrists, or sensory loss involving the limbs and trunk, or paralysis or seizures; and fever: oral temperature > 39.6°C.

Body mass index (BMI) was measured at the time of Pul TB diagnosis. Prior Pul TB was defined as a history of prior TB treatment or radiological evidence of previously healed TB. Alcohol was defined in individuals who drink more than 40 g alcohol per day or have an alcohol use disorder.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as numbers and percentages. Continuous variables were analyzed using independent sample *t*-tests. We used the Mann-Whitney *U* test to compare the continuous variables in skewed distribution. Categorical variables were compared by the Fisher's exact test, respectively. All categories were calculated as a percentage with 95% confidence intervals (CIs). The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20 software package. P values less than 0.05 were considered statistically significant.

Results

From January 2005 to December 2014, a total of 15 patients who had undergone gastrectomy and 45 age and sex-matched controls who had not undergone gastrectomy were treated for culture positive active Pul TB.

The clinical and demographic data are summarized in Table 1. The median age was 60 (53-71) years in the gastrectomy group and 67 (53-78) years in the control group with no statistical difference. A total of 13 (86.7%) patients in the gastrectomy group and 35 (77.8%) patients in the control group were men (P = 0.712). Except for alcohol

Table 1. The Baseline Characteristics of the Patients.

Characteristics	Control (n = 45)	Gastrectomy (n = 15)	P value
Age (years)	60 (53 - 71)	67 (53 - 78)	0.521[a]
Male, n (%)	35 (77.8)	13 (86.7)	0.712[b]
BMI	21.53 ± 3.88	22.60 ± 2.64	0.328[c]
Smoking	19 (42.2)	8 (53.3)	0.454[b]
Alcohol	3 (6.7)	8 (53.3)	< 0.001[b]
Underlying diseases, yes (%)			
Prior TB	5 (11.1)	7 (46.7)	0.006[b]
CVD	5 (11.1)	0 (0)	0.318[b]
CKD	2 (4.4)	0 (0)	1.000[b]
HTN	6 (13.3)	4 (26.7)	0.250[b]
DM	11 (24.4)	6 (40.0)	0.324[b]
Tuberculosis factors			
PCR	3 (6.7)	4 (26.7)	0.058[b]
IGRA	1 (2.2)	0 (0)	1.000[b]
Pathology	4 (8.9)	4 (26.7)	0.098[b]
Medication			
HERZ	27 (60.0)	7 (46.7)	0.367[b]
HR	13 (28.9)	5 (33.3)	0.754[b]
Others	8 (17.8)	3 (20.0)	1.000[b]

BMI, body mass index; TB, tuberculosis; CVD, cardiovascular disease; CKD, chronic kidney disease; HTN, hypertension; DM, diabetes mellitus; PCR, polymerase chain reaction; IGRA, Quantitative interferon-gamma; HERZ, isoniazid ethambutol rifampin pyrazinamide; HR, isoniazid rifampin; others, tubes or quinolone added.
Data are expressed as the mean ± SD or number (percent).
[a]Mann Whitney *U* test, Median (IQR, interquartile range).
[b]Fisher's exact test.
[c]Student *t*-test.

intake (gastrectomy group: 8 [53.3%]; control group: 3 [6.7%]; P < 0.001), the baseline characteristics including body mass index, smoking, congestive heart failure, chronic kidney disease, hypertension, and diabetes mellitus did not significantly differ between the 2 groups. Patients with a prior history of treated Pul TB was higher in the gastrectomy group (46.7% vs. 11.1%, P = 0.006).

Table 2 shows the clinical and microbiological treatment response. The clinical treatment failure rate at 4 months was significantly higher in the gastrectomy group than in the control group (26.7% vs. 2.2%, respectively; P = 0.012). The clinical treatment failure rate at 2 months was also significantly different between the 2 groups, where the rate was higher in the gastrectomy group (26.7% vs. 4.4%, respectively; P = 0.030). Microbiological treatment failure rate at 2 months (20.0% vs. 15.6%, P = 0.700) and 4 months (13.3% vs. 4.4%, P = 0.258) did not significantly differ between the groups.

The common anti-tuberculosis medication-related adverse effects experienced by the patients are shown in Table 3. The frequency of adverse gastrointestinal effects was significantly higher in the gastrectomy group than in the control group (60% vs. 11.1%, respectively; P < 0.001). The other common side-effects of anti-tuberculosis medication, including hepatotoxicity, arthralgia, skin rash, ocular toxicity, and neuropathy, as well as drug-related fever, did not significantly differ between the 2 groups. Furthermore, there were no differences between the surgery extent, such as total gastrectomy and distal gastrectomy, in the treatment outcome and the adverse events for Pul TB in this study.

Table 2. The Results of Microbiological and Clinical Failure.

	Control (n = 45)	Gastrectomy (n = 15)	P value
Microbiological failure, n (%)			
2 months	7 (15.6)	3 (20.0)	0.700
4 months	2 (4.4)	2 (13.3)	0.258
Clinical failure, n (%)			
2 months	2 (4.4)	4 (26.7)	0.030
4 months	1 (2.2)	4 (26.7)	0.012

Fisher's exact test.

Table 3. The Results of Adverse Effects.

	Control (n = 45)	Gastrectomy (n = 15)	P value
Gastrointestinal	5 (11.1)	9 (60.0)	< 0.001
Hepatotoxicity	8 (17.8)	1 (6.7)	0.427
Arthralgia	2 (4.4)	2 (13.3)	0.258
Skin rash	1 (2.2)	2 (13.3)	0.151
Ocular toxicity	5 (11.1)	4 (26.7)	0.208
Neuropathy	1 (2.2)	1 (6.7)	0.441
Fever	1 (2.2)	0 (0)	1.000

Fisher's exact test.

Discussion

We documented that gastrectomy patients experience higher rates of gastrointestinal adverse effects, and clinical treatment failure rates. In the current study, the 4-month microbiological failure rate was slightly higher (although not significantly) in the gastrectomy group than in the control group, whereas the 2-month microbiological outcomes did not show any difference. In a review and meta-analysis, the sensitivity (57%) of the 2-month smear examination for monitoring treatment failure was low and the specificity (81%) was higher but modest (Horne et al. 2010). For this reason the authors stated that 2-month sputum culture positivity was relatively insensitive for determining treatment failure (Wallis et al. 2009). Since both sputum smear microscopy and mycobacterial culture had a low sensitivity and modest specificity for predicting treatment outcomes, the above mentioned findings may be responsible for the lack of any difference in microbiological failure observed in the present study.

A case-control study in 1977 showed that patients who had undergone gastrectomy had a delayed peak serum concentration of rifampicin, as compared to patients who had not undergone gastrectomy (Hagelund et al. 1977). Welsh (1991) presented a case of a patient who documented a lower than minimal therapeutic range of serum anti-tuberculosis drug levels despite being treated with higher than average doses of rifampicin, isoniazid, and pyrazinamide after gastrectomy. The potential mechanisms underlying the low serum anti-tuberculosis drug levels include malabsorption and decreased retention due to decreased bile salt reuptake, which could both lead to low serum levels of rifampicin (Reed and Blumer 1983). Hence, low absorption of anti-tuberculous medications may be examined in gastrectomy patients, our studies imply that these findings may be related to treatment failure in clinical practice. Further studies regarding serum anti-tuberculosis medication levels and treatment failure rates are needed to support this hypothesis.

Cellular immunity is a key factor in the host defense against TB (Cegielski and McMurray 2004). Factors related to a decrease in cellular immunity, including malabsorption and deficiencies in nutritive components (caused by the alteration of the digestive system), may lead to an increased risk for TB (Skodrić-Trifunović 2003; Cegielski and McMurray 2004). Approximately 19% of patients who have undergone gastrectomy for gastric cancer suffer from malnutrition (Fukuda et al. 2015). Hence, several studies have identified gastrectomy patient to experience higher rates of malnutrition leading to increased risk for developing Pul TB (Dooley and Chaisson 2009; C. Kim et al. 2014). From the results of this study, it is likely that gastrectomy is a proxy measure of malnutrition which may be related to treatment failure. Future studies considering

nutritional status could provide additional evidence for this hypothesis.

During Pul TB treatment, the incidence of major adverse reactions has been reported as 1.48 per 100 person-months (Yee et al. 2003). Kim et al. (2013) showed that older patients with Pul TB presented with dermatologic toxicity, which was most commonly followed by gastrointestinal problems. The alteration of the digestive system in gastrectomy patients may be the possible for the explanation of increased gastrointestinal adverse events as shown in our study. To our knowledge, no study has assessed the anti-tuberculous medication-related gastrointestinal adverse effects in gastrectomy patients. Hence, our finding of an increased risk for gastrointestinal effects related to anti-tuberculosis medications in gastrectomy patients is unique.

The risk for active TB development is known to be higher in individuals who drink more than 40 g alcohol per day or have an alcohol use disorder (Lonnroth et al. 2008). Excessive alcohol intake is also associated with lower rates of negative sputum culture conversion and higher rates of mortality (Volkmann et al. 2015). In the present study, the gastrectomy group had a higher prevalence of alcohol consumption than the control group (53.3% vs. 6.7%; $P < 0.001$).

There several limitations to our study. One is the small sample size. However, this is because we included only proven Pul TB cases for accurate diagnosis; initially culture positive and with confirmed active Pul TB on radiographic imaging. If cases in which culture negative with only clinical suspicion of tuberculosis were included, more cases would have been apt for study but with less diagnostic certainty. Also, considering the small incidence of Pul TB in gastric cancer patients at our hospital, we could not include a larger number of patients. As South Korea has an intermediate TB burden and a high prevalence of stomach cancer, we believe that no other country would be able to conduct a larger scale study regarding tuberculosis and gastrectomy. Second, we excluded other well-known risk factors of decreased cellular immunity. The inclusion of such factors could have provided additional information on the treatment outcome for immune-compromised hosts at high risk for developing tuberculosis. Finally, the study was conducted retrospectively, and other clinical data on nutritional status and therapeutic drug level monitoring, that could influence the treatment response and explain the pharmacokinetics and pharmacodynamics for higher treatment failure, were not analyzed in this study.

In conclusion, patients who have undergone gastrectomy are independently associated with adverse gastrointestinal effects, clinical treatment failure when undergoing Pul TB treatment. These findings emphasize that patients who have received gastrectomy are prone adverse gastrointestinal effects, and hence, clinicians should carefully assess for signs or symptoms on a regular basis in these patients.

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Author Contributions

Jung, I.Y. designed the study and acquired data, analyzed and interpreted the data, drafted the initial manuscript, reviewed, and critically revised and approved the final manuscript as submitted. Choi, J.Y. conceptualized the study and is responsible for the content of the manuscript, including the data and analysis. Kim, M.H., Jeong, W.Y., Ahn, M.Y., Jeon, Y.D., Ahn, H.W., Song, J.E., Oh, D.H., Kim, Y.C., Kim, E.J., Jeong, S.J., Ku, N.S., and Kim, J.M. provided statistical assistance and revised and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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