Increased risk of tuberculosis after gastrectomy and chemotherapy in gastric cancer: a 7-year cohort study

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Abstract

Background Gastrectomy for peptic ulcers and chemotherapy for malignancy are known risk factors for tuberculosis (TB). However, this relationship has rarely been investigated in patients with gastric cancer.

Methods In a retrospective cohort study from 2000 to 2006, data for 2215 patients diagnosed with gastric cancer

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at our hospital were compared with data from the Centers for Disease Control (CDC), Taiwan, to identify confirmed cases of TB.

Results In patients with gastric cancer without a history of gastrectomy and without previous anti-TB treatment, the overall crude incidence of new-onset TB was 788 per 100,000 person-years. Compared with the general population, the overall age-sex standardized incidence (SI) in gastric cancer patients was 134.3 (SI ratio [SIR]: 2.11, $p < 0.05$), and the recurrence rate among patients with previous anti-TB treatment was 18% (4/22) after gastric cancer diagnosis. Gastrectomy was a significant risk factor for active TB incidence [SI 159 (95% confidence interval [CI], 80–237, SIR: 2.5, $p < 0.05$), and chemotherapy alone seemed to be a risk factor, but was without statistical significance (SIR: 12.5, $p > 0.05$). Multivariate analysis showed old age, male gender, previous anti-TB treatment, and gastrectomy as significant risk factors for TB. In stratified analysis, an interaction between old TB patterns on chest films and chemotherapy was observed.

Conclusions Old age, male gender, previous anti-TB treatment, and gastrectomy were significant risk factors for TB. An increased risk of TB incidence after chemotherapy was observed in patients with old TB pattern chest films initially, suggesting an interaction between chest film patterns and chemotherapy.

Keywords Chemotherapy · Gastric cancer · Gastrectomy · Standardized incidence ratio · Tuberculosis

Introduction

Tuberculosis (TB) is a widespread infectious disease, with an incidence of 139 cases per 100,000 person-years.

In Taiwan, the annual incidence was 63.7 cases per 100,000 person-years in 2006. Risk factors related to the incidence of TB include older age, smoking, and male gender [1, 2]. A decrease in immunity has been hypothesized to be a risk factor for symptomatic TB and reactivation, especially in HIV-infected individuals [3], individuals with malignancies [4–10] including lung cancer and hematologic malignancies [11, 12], and individuals with malnutrition [1].

Some investigations have revealed a relationship between chemotherapy in malignancy and TB re-infection or reactivation [13]. However, the results included all malignancies, and other treatment methods such as gastrectomy or palliative treatment were not considered. Gastrectomy in patients with peptic ulcers is a risk for TB [14–16], and although gastrectomy and chemotherapy are standard treatments for gastric cancer, the role of these two treatments in the risk for TB has not been clearly demonstrated.

The aim of this study was to investigate the relationship between the incidence of TB and gastric cancer treatment. Information on this relationship may be able to provide clinical physicians with a better understanding of how to manage patients with gastric cancer with regard to TB.

Patients, materials, and methods

Data source

The patients were collected from the Cancer Center of Taipei Veterans General Hospital database, which contains records of newly diagnosed cancer patients since 1994, with a 96.9% follow-up rate.

Study population

All patients were retrospectively selected using the ICD-9 code 151 for gastric cancer from January 1, 2000 to December 31, 2006. Patients were excluded if they had a history of gastrectomy. Each patient had an individual profile including pathology, diagnosis information, TNM stage, comorbidity, treatment (gastrectomy, chemotherapy, radiation, radiofrequency, palliative treatment or without treatment), and follow-up status. Patients who received palliative surgery without gastrectomy and those who received radiotherapy alone were combined into the palliative treatment group. Each patient was followed until 2010 if still alive.

All patients were checked against the registration system of the Centers for Disease Control (CDC) in Taiwan or by chart review to identify a case of active TB. Details were obtained including notification date, sputum collection

date, re-activation or first time diagnosis of TB, and confirmed status. Patients who had had anti-TB treatment before gastric cancer were also identified.

All information that allowed a specific individual patient to be identified was encrypted. This study was approved and informed consent was waived by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No. 20102004IC).

Incidence of TB

Due to the possibility of negative sputum TB smears with positive TB cultures after 2–3 months, only cases identified with TB two months after starting gastric cancer treatment were recognized as newly diagnosed active TB. Patients with TB notification within the two-month interval of gastric cancer diagnosis or treatment were categorized as concurrent TB with gastric cancer.

The baseline incidence (n/N) of TB each year was calculated as the number of concurrent TB cases (n) divided by the number of gastric cancer cases (N) per year. The crude incidence (CI) of active TB was calculated as the number of new active TB cases per observation person-year under risk, and the crude incidence ratio (CIR) represented a subgroup comparison of incidence to the reference group. The age-sex standardized incidence (SI) was calculated by a direct method [17], setting the general population in Taiwan in 2006 as the reference population, and the standardized incidence ratio (SIR) was calculated by comparing the standardized active TB incidence with the incidence in the general population in 2006.

Chest film review

Chest films were reviewed by two board-certified pulmonologists, who were blinded to the patients' information. The images showed infiltration patterns and date of examination, and were categorized into subgroups as follows: (1) old healed TB (old TB pattern) if bronchovascular distortion, fibrotic bands, small calcified nodules, or bronchiectasis were observed as apical lesions in either upper lobe [18]; (2) metastasis pattern, which included a single nodule/mass or bilateral multiple nodules, with/without mediastinum lymphadenopathy; (3) unilateral pleural effusion, with no other abnormality on the chest film; (4) mixed pattern, which represented both an old TB pattern and suspected metastasis pattern on the chest film; and (5) "others", which represented abnormal chest film images that could not be categorized into the other patterns. If there was no consensus between the two pulmonologists on the type of pattern, the image was discussed further until a consensus was reached.

Statistics

Tests for significance were performed using the χ^2 test and Fisher's exact test (2-sided) for categorical data, and Student's *t*-test for continuous data in univariate analysis. A logistic regression model was used for multivariate analysis. The data were analyzed using SPSS software version 17 (SPSS, Chicago, IL, USA), the incidence was calculated using Stata 10.0 (Stata Corporation, College Station, TX, USA), and the age-standardized incidence was calculated using StatsDirect software 2.7 (StatsDirect, Altrincham, Cheshire, UK).

Results

Study population

From January 1, 2000 to December 31, 2006, 2257 patients were selected. Forty-two of them with a history of subtotal or partial gastrectomy before the diagnosis of gastric cancer, and 6 patients with active TB within 6 months before the diagnosis of gastric cancer and receiving anti-TB treatment were excluded. In total, 2212 patients were enrolled, and they were divided into two groups: with and without previous anti-TB treatment.

Three of the 25 patients with previous anti-TB treatment and ten of the 2187 patients without a previous anti-TB treatment history had concurrent TB, and were excluded from the analysis. In total, 2177 patients without

and 22 patients with previous anti-TB treatment were included in the analysis. The case selection is demonstrated in Fig. 1.

The characteristics of the 2199 patients with and without active TB are shown in Table 1. The majority of the patients were male (male/female ratio = 3.12), and they were older than the females ($p < 0.05$, data not shown). The type of gastric cancer, clinical stage, veteran status, and presence of diabetes or other solid-organ malignancy were not related to the presence of active TB ($p > 0.05$). However, younger age, male gender, previous anti-TB treatment, and chest film findings during gastric cancer diagnosis were related to active TB ($p < 0.05$). The percentage of patients who received surgery alone was higher in patients with active TB (64.6 vs. 45.4%) and the percentages of patients who received chemotherapy alone or palliative treatment were lower in the active TB group (6.3 vs. 15.7%, 12.5 vs. 19.8%, respectively).

Follow-up interval

The mean follow-up interval ranged from zero to ten years. Seven hundred and twenty-six (33.1%) of the patients were followed for more than three years, 717 (32.6%) of the patients died, and 44 (2%) were lost to follow-up within one year. The follow-up interval was related to the cancer cell type (pathology, $p < 0.05$). There was no significant relationship between the interval of loss of follow-up and TNM stage, age, sex, treatment for gastric cancer, previous anti-TB treatment, and identification of active TB.

Fig. 1 Flow chart of case selection of patients with gastric cancer from 2000 to 2006, Taipei Veterans General Hospital. *Incidence (A)*: cumulative incidence of TB at the time of diagnosis of gastric cancer, calculated by the number of concurrent TB cases (n) divided by the number of gastric cancer cases (N). $\text{Incidence (A)} = n/N \times 100,000$. *Incidence (B)*: overall incidence of active TB in patients without previous anti-TB treatment, calculated by the number of identified active TB cases divided by observation person-years under risk

Table 1 Characteristics of the patients with active TB, with or without treatment, more than 2 months after gastric cancer was diagnosed from 2000 to 2006 ($n = 2199$)

Variable	Total <i>N</i> (%)	No active TB <i>n</i> = 2151 (%)	Active TB <i>n</i> = 48 (%)	<i>p</i> ^a
Age at diagnosis (years)				0.022
<40	98 (4.5)	98 (4.6)	0 (0)	
41–60	431 (19.6)	428 (19.9)	3 (6.3)	
61–80	1333 (60.7)	1296 (60.3)	37 (77.1)	
>80	333 (15.2)	329 (15.2)	8 (16.7)	
Mean $\pm$ SE	68.5 $\pm$ 0.29	68.4 $\pm$ 0.29	74.1 $\pm$ 1.1	<0.001
Gender				
Male	1671 (75.9)	1627 (75.6)	44 (91.6)	0.007
Previous TB complete treatment				
Yes	12 (0.5)	18 (0.8)	4 (8)	0.025
Veteran				
Yes	987 (44.8)	956 (44.4)	31 (64.5)	0.075
Cell type				0.24
Adenocarcinoma	1728 (78.6)	1688 (78.5)	40 (83.3)	
Signet-ring cell carcinoma	262 (11.9)	260 (12.1)	2 (4.2)	
Mucinous adenocarcinoma	19 (0.9)	18 (0.8)	1 (2.1)	
GIST	36 (1.6)	35 (1.6)	1 (2.1)	
Others	154 (7.0)	150 (7.0)	4 (8.3)	
Cancer stage on diagnosis				0.12
Ia	270 (12.3)	263 (12.2)	7 (14.6)	
Ib	162 (7.4)	158 (7.3)	4 (8.3)	
II	203 (9.2)	193 (9.0)	10 (20.8)	
IIIa	235 (10.7)	231 (10.7)	4 (8.3)	
IIIb	126 (5.7)	124 (5.8)	2 (4.2)	
IV	814 (37.0)	803 (37.3)	11 (22.9)	
Missing data	389 (17.7)	379 (17.6)	10 (20.8)	
Primary treatment for gastric cancer				0.1
Surgery without chemotherapy	1007 (45.8)	976 (45.4)	31 (64.6)	
Surgery + chemotherapy	407 (18.5)	399 (18.5)	8 (16.7)	
Chemotherapy alone	339 (15.5)	336 (15.67)	3 (6.3)	
Local	13 (0.6)	13 (0.6)	0 (0)	
Palliative treatment	433 (19.7)	427 (19.9)	6 (12.5)	
Comorbidity				
DM	266 (12.1)	257 (11.9)	9 (18.8)	0.093
Solid tumor	169 (7.7)	164 (7.6)	5 (10.4)	0.489
Hematologic malignancy	4 (0.2)	4 (0.3)	0 (0)	
CXR finding on diagnosis				0.099
Abnormal				0.003
Old TB pattern	182 (8.3)	170 (7.9)	12 (25.0)	
Others	98 (4.5)	96 (4.5)	2 (4.2)	
Mix	85 (3.9)	85 (4.0)	0 (0)	
Metastatic	165 (7.5)	164 (7.6)	1 (2.1)	
Unilateral pleural effusion	47 (2.1)	46 (1.2)	1 (2.1)	
Normal	1298 (59.0)	1276 (59.3)	22 (45.8)	
Not available	324 (14.7)	314 (14.6)	10 (20.8)	

GIST gastrointestinal stromal tumor, *DM* diabetes mellitus, *CXR* chest X-ray

^a *p* value of 2-sided χ^2 test or Fisher-Freeman-Halton exact test for categorical data, or Student's *t*-test for continuous data (i.e., age)

Incidence of TB and treatment method as risk factors for TB

As shown in Fig. 1, in patients with gastric cancer without a history of gastrectomy, the incidence of TB was 457 per 100,000 person-years at the time of diagnosis of gastric cancer. Of the 2177 patients without previous anti-TB treatment, the overall incidence was 788 per 100,000 person-years, and it was 8421 per 100,000 person-years among patients with previous anti-TB treatment, with a recurrence rate of 18.2% (4/22).

The age and sex-specific active TB incidence for the 2199 patients is demonstrated in Fig. 2, which shows that the incidence of active TB in gastric cancer patients was slightly higher than that in the general population. Figure 2b shows the overall age-specific TB incidence according to treatment method. Both gastrectomy and chemotherapy had similar trends of a higher incidence than on diagnosis of gastric cancer or the general population.

The age-sex standardized incidence is shown in Table 2. For the 2199 gastric cancer patients, the overall standardized incidence of active TB was higher than that in the general population (134.3/100,000; 95% confidence interval [CI] 80.9–187.6, SIR: 2.11, $p < 0.05$). Comparing the standardized TB incidence to that in the general population, patients who received palliative treatment had the lowest incidence (75.7/100,000; 95% CI 16–135; SIR: 1.19, $p > 0.05$), and the patients who received gastrectomy had a significantly higher incidence (159.1/100,000; 95% CI 80.4–237; SIR: 2.5, $p < 0.05$). Patients receiving adjuvant chemotherapy or chemotherapy alone also had a trend of an increasing standardized incidence of active TB, although this trend was without statistical significance.

Data for patients without previous anti-TB treatment and the age-sex standardized incidence of active TB were recalculated (Table 3). In general, the overall standardized incidence of active TB in patients with gastric cancer was higher than that in the general population in Taiwan (SIR: 2.03, $p < 0.05$). Patients who received gastrectomy still had a significantly higher standardized incidence than the general population (SIR: 2.46, $p < 0.05$).

Chest film pattern and interaction with treatment method for gastric cancer

When the chest films were categorized into old TB patterns, non-old TB patterns, and normal chest films, there was a difference in TB incidence between treatment methods (Table 4). Among patients with old TB patterns, treatment with chemotherapy alone had a trend of higher incidence of TB than treatment with surgery

Fig. 2 Age- and sex-specific incidence of TB, compared to that in the general population in 2006 in Taiwan from the Centers for Disease Control (CDC) data. **a** Age- and sex-specific TB incidence. **b** Age-specific TB incidence by treatment for gastric cancer

alone (5681 vs. 2435, respectively, CIR = 2.3, 95% CI = 0.3–17.3). This relationship was not present if the chest film showed other patterns (CIR = 0.87, 95% CI 0.1–6.0). Furthermore, in patients who received palliative treatment, a slightly higher incidence of TB [crude incidence: 3514 vs. 2435, CIR = 1.4, 95% CI = 0.2–11.2] but without statistics significance was found.

When the chest film images were categorized into normal, abnormal, and not available, there were no significant differences in the incidence of TB (data not shown).

Multivariate analysis

A multivariate logistic regression model for active TB was calculated (Table 5). After adjusting for the effects of age

Table 2 Tuberculosis in patients after gastric cancer treatment ($n = 2199$)

Treatment for gastric cancer	<i>N</i>	Mean follow-up (years)	Person-years	<i>n</i>	Crude incidence	CIR	<i>p</i> ^a	Standard incidence (95% CI) ^b	SIR
Palliative treatment	432	1.04	451.9	6	1327.7	1.6	0.27	75.7 (16–135)	1.19
Local treatment	13	1.06	13.76	0	0			0	
Gastrectomy	1007	3.985	3883.5	31	798.2	1	–	159.1 (80.4–237)	2.50*
Had chemotherapy	744	1.74	1297.1	11	861.5.0	1.06	0.84	185.1 (27.65–342)	2.91
Gastrectomy + CT	407	2.35	957.9	8	835.2	1.04	0.88	163.3 (–6 to 132)	2.56
CT alone	339	0.96	323.99	3	940.9	1.15	0.75	793.9 (–49 to 2836)	12.46
Total	2192	2.56	5625.7	48	853.2			134.3 (80.9–187.6)	2.11*

Incidence: cases per 100,000 person-years

CT chemotherapy, CIR crude incidence ratio, crude incidence compared to that in patients with gastric cancer after gastrectomy, SIR standardized incidence ratio, standardized incidence divided by incidence (63.7) in the general population, CI confidence interval

^a *p* value of CIR, 2-sided Mantel-Haenszel test, * *p* value <0.05

^b Age-sex standardized incidence, general population in Taiwan in 2006 as the reference group, by direct method. Use of Poisson model, improved approximate (Dobson) method for 95% confidence interval

Table 3 Tuberculosis in patients after gastric cancer treatment without known previous anti-TB treatment ($n = 2177$)

Treatment for gastric cancer	<i>N</i>	Mean follow-up (years)	Person-years	<i>n</i>	Crude incidence	CIR	<i>p</i> ^a	Standard incidence (95% CI) ^b	SIR
Palliative treatment	418	1.05	438.5	3	684.2	0.56	0.35	39.8 (8.2–116)	0.62
Local treatment	13	1.04	13.8	0	0.0	–	–	0	
Gastrectomy	1001	3.84	3850.5	30	779.1	1	–	157 (85–251)	2.46*
Had chemotherapy	744	1.72	1296.4	11	862.4	1.08	0.79	185.2 (50–397)	2.91
Gastrectomy + CT	406	2.36	973.0	8	835.6	1.05	0.86	163.4 (22–403)	2.57
CT alone	338	0.94	318.4	3	942.2	1.2	0.7	794 (–49 to 2836)	12.46
Total	21876	2.6	5578.2	44	788.8			129.5 (80–191)	2.03*

Incidence: cases per 100,000 person-years

CIR crude incidence ratio, crude incidence compared to that in patients with gastric cancer after gastrectomy, SIR standardized incidence ratio, standardized incidence divided by incidence (63.7) in the general population, CI confidence interval

^a *p* value of CIR, 2-sided Mantel-Haenszel test, * *p* value <0.05

^b Age-sex standardized incidence, general population in Taiwan in 2006 as the reference group, by direct method. Use of Poisson model, improved approximate (Dobson) method for 95% confidence interval

and sex, both previous anti-TB treatment and gastrectomy were significant factors ($p < 0.05$) regarding active TB. There was no increased risk when considering the gastric cancer stage ($p > 0.5$); however, both gastrectomy ($p = 0.03$, relative risk [RR] = 3.3, 95% CI 1.13–9.7) and old TB pattern on chest film were still significant risk factors ($p < 0.001$, RR = 3.6, 95% CI 1.76–7.4, data not shown). Compared to the patients who received palliative treatment, patients who received adjuvant chemotherapy showed a borderline relationship to active TB ($p = 0.058$). Subgroup analysis for patients without previous anti-TB treatment was also performed. The results showed that the chest film pattern was still related to the presence of TB (Supplement 1), and gastrectomy and adjuvant chemotherapy remained significant factors for active TB.

Discussion

The present study was a retrospective cohort study of the incidence of active TB among patients with gastric cancer. Of particular note is that this study introduced the method of age-sex standardized incidence compared to that in the general population, and analysis of the interaction of chest film findings and treatment was performed.

According to a previous survey of the health insurance database in Taiwan, the crude incidence of TB among patients with gastric cancer was 324 per 100,000 person-years [19]. Our baseline incidence was 457 per 100,000 person-years and the follow-up incidence of newly active TB after gastric cancer diagnosis was 788 per 100,000 person-years overall among patients without previous anti-TB treatment (Table 3). There are several reasons for the

Table 4 Interaction between chest plain film images on diagnosis and treatment method for gastric cancer ($n = 2199$)

CXR finding	<i>N</i>	Person-years	<i>n</i>	Incidence	CIR	(95% CI)	Standard incidence (95% CI)	SIR
Non-old TB pattern on CXR								
Gastrectomy	811	3183.6	17	534.0	1	—	122.8 (48.5–230)	1.93
Have chemotherapy				616.9	1.15	(0.5–2.9)	157.1 (18–415)	2.47
Gastrectomy + chemotherapy	321	740.4	5	675.3	1.26	(0.5–3.4)	137.9 (3.3–403)	2.16
Chemotherapy	259	232.2	1	430.6	0.87	(0.1–6.0)	813.1 (20.6–4530)	12.76
Palliative treatment	293	243.5	3	1232.3	2.3	(0.7–7.6)	89.8 (18.5–262)	1.41
Old TB on CXR								
Gastrectomy	100	369.5	9	2435.8	4.56	(2.1–9.5)*	192.7 (77–397)	3.03*
Have chemotherapy				3037.5	6.7	(1.9–23.8)*	488.8 (59–1765)	7.67
Gastrectomy + chemotherapy	19	48.2	1	2072.9	3.88	(0.6–25.2)	861.9 (21–4802)	13.53
Chemotherapy	26	17.6	1	5681.8	10.6	(2.1–53)*	799.4 (20–4454)	12.55
Palliative treatment	36	28.5	1	3514.4	6.5	(1.1–37.7)*	902.2 (22–5026)	14.16

p value: univariate analysis, obtained by the 2-tailed Mantel-Haenszel test

CIR crude incidence ratio, *CI* confidence interval, *SIR* standardized incidence ratio, standardized incidence divided by incidence (63.7) in the general population

* *p* value <0.05

Table 5 Multivariate logistic regression model for identification of active TB after gastric cancer treatment ($n = 2199$)

Variable	<i>N</i>	aRR	95% CI		<i>p</i>
			Lower	Upper	
Sex					
Male	1671	2.32	0.81	6.6	0.117
Female	528	–	–	–	–
Age	2199	1.03	1.01	1.06	0.041*
History of anti-TB treatment					
No	2177	–	–	–	–
Yes	22	8.1	2.2	29.6	0.002*
CXR finding					
Old TB pattern	182	3.15	1.5	6.6	0.002*
Non old TB pattern	1693	–	–	–	–
Not available	324	2.5	1.17	5.35	0.18
Treatment for gastric cancer					
Gastrectomy alone	1007	3.76	1.43	9.9	0.007*
Local	13	0	0		0.99
CT alone	339	1.06	0.25	4.5	0.93
Gastrectomy + CT	407	3.12	0.96	10.0	0.058
Palliative surgery or no treatment	433	–	–	–	–
DM	266	1.5	0.79	3.2	0.28
Malignancy	173	1.04	0.38	2.8	0.94

aRR adjusted risk ratio estimated by the logistic regression model, *CI* confidence interval, *CT* chemotherapy, *DM* diabetes mellitus

* *p* value <0.05

high incidence: (1) the source of our database was patients older than the general population; more than 75% of the patients were older than 60 years of age, and older age is a risk factor for TB [20]. (2) There were more males (75.6%) in this study, and male gender is also related to a high

incidence of TB. (3) Our population was limited to patients with gastric cancer, leading to a variable and higher range of incidence.

Our results showed that the patients who underwent gastrectomy had a significantly higher incidence of TB than the general population [SIR 2.5 (95% CI 1.26–3.72)], and chemotherapy alone had a similar trend [SIR 12.46 (95% CI –0.76 to 44.5)]. When patients with previous anti-TB treatment were excluded, the relationship between gastrectomy and TB was unchanged [SIR 2.46 (95% CI 1.33–3.94)]. This suggests that gastrectomy is an independent risk factor for TB that might not be affected by the history of previous anti-TB treatment. This result is compatible with previous studies in which gastrectomy [14] and chemotherapy for malignancy had an increased risk of TB [21]. However, the small sample size in our study limits the statistical inference, and further studies with large populations should be considered.

Some studies have shown conflicting conclusions about short-term intensive cyclic chemotherapy for hematological malignancy not being related to TB reactivation [22]. Previous studies have included all TB patients with non-specific solid-organ malignancy, or only cohorts with hematologic malignancy with TB and concurrent chemotherapy. The present study focused on gastric cancer patients and was limited to new-onset (or recurrent) TB diagnosed two months after gastric cancer treatment, rather than concurrent TB, which is more specific in patients with gastric cancer.

An interaction between old TB patterns on chest films and chemotherapy was found in our study. This result is also compatible with previous research. One case-controlled study showed that chronic renal failure, old healed

TB on chest X-ray, and anti-cancer chemotherapy were risk factors for TB in patients with malignancy [21]. That study also found an interaction between old healed TB on chest X-ray and chemotherapy for malignancy. However, in our study, the age-standard incidence ratio revealed conflicting findings (i.e., no difference in incidence ratio [SIR] between patients who received chemotherapy with or without old TB patterns on chest film). This could be explained by the limited case numbers and because the standardized incidence was diluted by the normal distribution in the general population. When the patients who received chemotherapy (adjuvant chemotherapy or chemotherapy alone) were combined, the bias appeared to be diminished and the age-standardized incidences (95% CI) were 157.1 (18–415) and 488.8 (59–1765), and SIRs were 2.47 and 7.47, respectively. Among patients without a previous history of anti-TB treatment who had old TB chest X-ray patterns, the interaction between TB and chemotherapy remained (Supplement 2). This may indicate that asymptomatic or latent TB is a risk for TB incidence after chemotherapy for gastric cancer. However, a lack of evidence for latent status is a limitation of the present study. Further immunological tests, including interferon gamma release assay (IGRA) tests [23–27] and follow-up should be conducted, although the role of interferon-gamma in high-burden areas remains controversial [28].

In the present survey, 14.5% of the patients did not have available chest film images, and 8 of them had TB after gastric cancer treatment. Chest films were not routinely checked during the early years of the hospital, and 70% (227/324) of them were diagnosed before the end of 2002. Because an old TB pattern on chest film was a significant risk factor for TB and risk of incidence after chemotherapy, routine chest X-ray check-ups are necessary and further prospective studies should be performed.

There were some limitations to the present study with regard to the risk of chest film pattern and TB incidence. First, not all patients were routinely checked for sputum acid-fast stains, due to either a lack of symptoms or signs or because of the invasive nature of the diagnostic procedure (i.e., bronchoalveolar lavage). This lack of routine checking may have caused bias in the incidence of active TB. In addition, in patients with old healed TB patterns, sputum check-ups might have been performed more aggressively than in those without old healed TB patterns, which may have led to an earlier detection of active TB and a lead time bias and a higher incidence (lower observation person-years under risk) than that in patients without old healed TB patterns on chest X-ray.

The stage of the disease was a confounding factor with choice of treatment. In our study, multivariate analysis

showed no increased risk among different cancer stages ($p \geq 0.5$). Sub-population analysis according to clinical TNM stage should be done to adjust for the confounding effect; however, this analysis was not performed due to the limited sample size in our study. Further investigations such as multicenter studies might solve this problem.

Some patients with poor clinical status may have received palliative treatment. The incidence of active TB among these patients is indicated in Tables 2 and 3; there was no difference between the group with palliative treatment and general population ($p > 0.05$). This finding indicates that the neoplasm itself may be not associated with active TB itself. The lack of a European Cooperative Oncology Group (ECOG) score and information on nutritional status in our database were limitations, and such information should be included in future investigations.

A decrease in immunity has been hypothesized to be a risk factor for symptomatic TB and reactivation, by reducing the expression of gamma interferon, tumor necrosis factor alpha, and other mycobactericidal substances which may selectively compromise portions of the cell-mediated response that are important for containing and restricting TB [29, 30]. Gastrectomy can cause a poor nutritional status leading to poor immunity, and TB also leads to a poor nutritional status [31]. Micronutrients, including vitamins A, C, E, B, and folic acid, and minerals zinc, copper, selenium, and iron have key roles in metabolic pathways, cellular function, and immune competence [32]. The concentrations of these entities may play a role in the host defense against TB [33]. There have been few studies on the influence on TB exerted by specific chemotherapy agents such as 5-fluorouracil (5-FU)/platinum-based regimens for gastric cancer [34]. Because 5-FU is an antagonist of folic acid metabolism and because platinum may influence the cell cycle, both types of agents might play a role in immunity to TB, and the mechanism needs to be investigated further.

Some risk factors were not available for examination in this retrospective study, such as advanced HIV infection, chronic renal failure, infliximab therapy, poorly controlled diabetes, underweight (<10% below normal), malnutrition, use of glucocorticoids, general condition (i.e., ECOG score), and silicosis. Due to the limited sample size, detailed gastrectomy methods (subtotal, total, partial gastrectomy) showed no influence on TB (data not shown), and subgroup analysis of different chemotherapy agents was also not performed. In order to differentiate the risks for TB reactivation after chemotherapy, more gastric cancer patients should be enrolled in future multicenter investigations. Newly developed screening methods such as IGRAs should also be conducted to verify the status of latent TB and reactivation after gastric cancer treatment.

Conclusions

In summary, this study demonstrated a higher incidence of TB infection after gastrectomy than that in the general population. Surgery might be an independent risk factor for the incidence of TB. Patients with previous anti-TB treatment also had a higher risk of reactivation after chemotherapy. Among patients with gastric cancer at the time of the diagnosis of TB, a chest X-ray is necessary to identify old healed TB patterns, as these patterns might increase the risk of TB incidence during the management of gastric cancer.

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