Review Article

# TUBERCULOSIS AND LUNG CANCER

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**Abstract** The occurrence of pulmonary tuberculosis (PTB) and lung cancer as comorbidities has been extensively discussed in many studies. In the past, it was well known that lung cancer is a specific epidemiological successor of PTB and that lung cancer often develops in scars caused by PTB. In recent years, the relevance of the two diseases has drawn attention in terms of the close epidemiological connection and chronic inflammation-associated carcinogenesis. In Japanese case series studies, most lung cancer patients with tuberculous sequelae received supportive care alone in the past, but more recently, the use of aggressive lung cancer treatment is increasing. Many studies on PTB and lung cancer as comorbidities have revealed that active PTB is noted in 2–5% of lung cancer cases, whereas lung cancer is noted in 1–2% of active PTB cases. In such instances of comorbidity, many active PTB cases showed Type II (non-extensively cavitary disease) and Spread 2–3 (intermediate–extensive diseases) on chest X-rays, but standard anti-tuberculosis treatment easily eradicates negative conversion of sputum culture for *M.tuberculosis*; lung cancer cases were often stage III–IV and squamous cell carcinoma predominant, and the administration of aggressive treatment for lung cancer is increasing. The major clinical problems associated with PTB and lung cancer as comorbidities include delay in diagnosis (doctor's delay) and therapeutic limitations. The former involves two factors of radiographic interpretation: the principles of parsimony (Occam's razor) and visual search; the latter involves three factors of lung cancer treatment: infectivity of *M.tuberculosis*, anatomical limitation due to lung damage by tuberculosis, and drug-drug interactions between rifampicin and anti-cancer drugs, especially molecularly targeted drugs. The comorbidity of these two diseases is an important health-related issue in Japan. In the treatment of PTB, the possibility of concurrent lung cancer should be kept in mind, while in the treatment of lung cancer, the possibility of concurrent PTB should also be considered.

**Key words**: Tuberculosis, Lung cancer, Comorbidity, Epidemiology, Scar cancer, Doctor's delay, Therapeutic limitation

## 1. Introduction

The occurrence of pulmonary tuberculosis (PTB) and lung cancer as comorbidities was first described in an autopsy record by Bayle in 1810[1], followed by the first case report by Penard in 1846[2], and has subsequently been discussed in many studies[3–7]. In Japan, the comorbidity of these two diseases has drawn attention since the mid-20th century[8–12]. Japan is a middle-ranked country for PTB prevalence, and lung cancer is the leading cause of cancer death in Japan. Furthermore, the proportion of elderly patients affected by both diseases is high. Therefore, the comorbidity of these two diseases is an important issue in Japan.

In this review, we introduce epidemiological studies focusing on the relationship between previous tuberculosis and lung cancer development, as well as etiological studies investigating the relationship between tuberculosis-related lesions and lung carcinogenesis. We then document case series studies in terms of various pathological conditions related to the comorbidity of PTB and lung cancer.

## 2. Epidemiological studies

In epidemiological studies of lung cancer in patients with previous tuberculosis, long-term surveys in England/Wales and Australia since the early 1900s have shown that the overall mortality rate for "tuberculosis+lung cancer" was constant, at approximately 20%. As this close relationship was not seen between other diseases, lung cancer appears to be a specific epidemiological successor of PTB. It was assumed that the reduced number of tuberculosis deaths in young individuals may be associated with the increased incidence of lung cancer in elderly patients[13–15]. It is unclear

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that whether the association between these two diseases described in the dawn (mid-20th century) of anti-tuberculosis treatment is still established, but in recent years, it has been demonstrated that mostly in Asian countries, having a history of tuberculosis irrespective of smoking is an independent risk factor for lung cancer occurrence[16)–20)]. Furthermore, with regard to prognosis, a prospective population-based cohort study has shown that having a history of tuberculosis predicts poor prognosis in lung cancer patients[21)].

In Japan, it has been demonstrated that the risk of lung cancer among patients with active PTB is 20 times greater than that of the general population[22)], and patients with active PTB are more likely to die of lung cancer compared with other malignancies[23)].

### 3. Etiological studies

Various theories have been proposed with regard to the pathogenetic relationship between tuberculosis and lung cancer, including the antagonist theory of Rokitansky reported in 1855[24)], scar cancer theory[25)], and coincident theory[26)]. Among these, the scar cancer theory, which states that lung cancer is likely to develop in scars caused by PTB and other causes, has been widely accepted[27)–29)]. However, Shimosato et al.[30)] demonstrated that scar formation in peripheral lung adenocarcinoma is the result of cancer growth and not a pre-existing lesion, and Noguchi et al.[31)] revealed a close relationship between the degree of scarring within pulmonary adenocarcinoma and lung cancer prognosis. In an earlier report, Kageyama et al.[10)] described that tuberculosis lesions, compared with healthy lung tissue, can be an origin of lung cancer development, but this carcinogenesis has no specific relationship with the tuberculosis lesion. Aoki[23)] also reviewed reports on the comorbidity of PTB and lung cancer and indicated that scar cancer of the lung is rare in actual clinical practice. In recent years, it has been found that in various types of cancer, chronic inflammation and cancer development are closely related[32)]. Tuberculosis-induced chronic inflammation and the scarring process involves various cytokines, chemokines, and DNA damage of epithelial cells; therefore, this may lead to cancer development[33)34)].

### 4. Comorbidity of tuberculosis and lung cancer

(1) Previous tuberculosis and lung cancer

a) Tuberculosis sequela/state-after thoracoplasty

Tuberculosis sequela is the term for conditions that develop with various anatomical changes during the treatment process of PTB, such as respiratory dysfunction, cor pulmonale, and secondary infection[35)]. Patients with tuberculosis sequelae occasionally develop lung cancer, and in our earlier report[36)], we found that 15 out of 294 patients (5.1%) who died from tuberculosis sequelae between 1984 and 1995 had concurrent lung cancer. Most patients with lung cancer were male, smokers, and underwent surgical treatment for tuberculosis, whereas more than half of the patients ended up receiving supportive care alone. However, in patients with tuberculosis sequelae from 2003 to 2011[37)], performance status was good, and there were more patients receiving aggressive cancer therapy despite the increasing age of patients (Fig. 1). These changes result from not only advances in cancer treatments but also changes in the concept of tuberculosis sequelae; there are few post-surgical cases today, and the majority of tuberculosis sequelae were based on widespread lung injury due to severe PTB.

In the 1950s, prior to the development of anti-tuberculosis drug therapy, surgical treatment with thoracoplasty was widely performed in Japan, and many patients successfully recovered

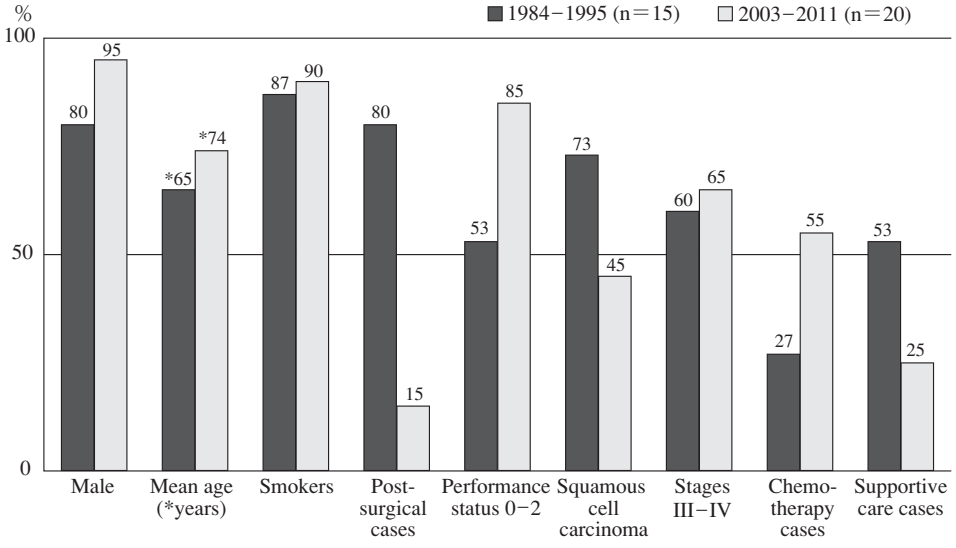


**Fig. 1** Lung cancer in patients with tuberculosis sequelae

Smokers: current and previous smokers

Post-surgical cases: patients who had a history of surgical therapy for pulmonary tuberculosis

from tuberculosis with this treatment. However, some of these patients developed tuberculosis sequelae over 20−30 years after surgery, and during management of sequelae, lung cancer was sometimes detected. During the period from 1982 to 1998, 20 of the 1,635 lung cancer patients (1.2%) seen in our hospital had a history of thoracoplasty[38]. Patients with tuberculosis sequelae and patients who had received thoracoplasty in our studies developed lung cancer in all lung lobes, irrespective of the site of the tuberculosis lesion. Yoneyama et al.[39] reported that in patients with pre-existing unilateral lung disease including tuberculosis, lung cancer predominantly developed in the healthy side of the lung. They assumed that as a result of ventilator impairment of the affected side, the healthy side may then have had increased exposure to carcinogens. From the perspective of these clinical data, it appears that most lung cancers in patients with previous tuberculosis are not scar cancers. There are few reports on such pathologies outside Japan, and only a few case reports can be found with regard to lung cancer development following surgery for tuberculosis[40)−43)].

b) Lung cancer in chronic pyothorax

The most well-known malignancy seen in patients with chronic pyothorax due to tuberculosis is pyothorax-associated lymphoma, a disease specific to Japan[44)]; its onset primarily involves *Epstein-Barr virus* infection caused by artificial pneumothorax[45)46)]. It has long been known that patients with chronic pyothorax have lung cancer[47)]. At our hospital, we found that in the 15 patients with chronic pyothorax and concurrent thoracic malignancies between 1977 and 2002, lung cancer and pyothorax-associated lymphoma occurred in four and nine patients, respectively[48)]. In a study of 12 patients with chronic pyothorax and concurrent lung cancer examined by the Japan National Hospital Organization Study Group for Lung Cancer (JNHOSGLC) between 1980 and 2005[49)], unlike lung cancer in tuberculosis sequelae and state-after thoracoplasty, lung cancer existed around the chronic pyothorax in nine patients. Lung cancer might commonly develop around chronic pyothorax because persistent chronic inflammation around the pyothorax contributes to cancer development; thus, lung cancer around chronic pyothorax can be considered to be analogous to scar cancer.

(2) Active PTB and lung cancer

Concurrent active PTB and lung cancer is a condition most commonly addressed in case series studies. Previously, Nuessle[26)] summarized past autopsy reports in which lung cancer was observed in 1.4% of active PTB cases, and active PTB was observed in 6.4% of lung cancer cases. There have been many case series studies on comorbidity of the two diseases, especially in Japan (Table 1)[22)50)−56)]. In summary, these studies indicated that lung cancer was comorbid with 1−2% of active PTB cases, while active PTB was comorbid with 2−5% of lung cancer cases. Clinical features associated with the comorbidity of these two diseases include the following: i) the comorbidity is male predominant, ii) squamous cell carcinoma is more common than adenocarcinoma, iii) the site of lung cancer often lies on the same lung side as the PTB, and iv) lung cancer is often detected at an advanced stage (stage III−IV). Furthermore, reports from the past three decades were mostly from Asian countries, whereas there have been no reports from the US and Europe, which have a low prevalence of tuberculosis.

At our hospital from 1991 to 2004, there were 56 patients with comorbid active PTB and lung cancer. Similar to patients with previous tuberculosis, there was a high rate of men, elderly individuals, and smokers among these cases; comorbid lung cancer was found in 1.2% of cases with active PTB and comorbid active PTB was found in 2.5% of cases with lung cancer[56)]. Active PTB was often sputum-smear positive, Type II (non-extensively cavitary disease), and Spread 2−3 (intermediate−extensive diseases), whereas lung cancer was frequently squamous cell carcinoma, stage III−IV, and occurred on the same lobe as PTB. This trend was comparable with a study of comorbid cases at our hospital between 2005 and 2012[57)] (Fig. 2). The comorbid cases with the two diseases may be divided into three groups according to the time of detection: the PTB preceding group, concurrent detection group, and lung cancer preceding group. In the PTB preceding group (cases with lung cancer detected during treatment for PTB), a small lung cancer shadow may be identified in many cases upon review of chest X-rays at the time of PTB diagnosis;

**Table 1** Previous studies on the comorbidity of active pulmonary tuberculosis and lung cancer

| Study | Year | Country | N | M/F | Mean age (years) | LC/APTB (%) | APTB/LC (%) | Histologic type of LC (%) | Stages III−IV (%) | Site of LC AL (SL) (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Yatsuka[50)] | 1980 | Japan | 132 | NE | NE | NE | 3.2% | SQ49%, AD21% | NE | 74% (NE) |
| Komatsu[22)] | 1981 | Japan | 17 | 16/1 | NE | 0.9% | 4.2% | SQ71%, AD24% | NE | 71% (NE) |
| Ogawa[51)] | 1990 | Japan | 39 | 35/4 | 66 | 1.3% | 4.3% | SQ51%, AD20% | NE | 83% (64%) |
| Kurasawa[52)] | 1992 | Japan | 22 | 19/3 | 73 | NE | NE | SQ59%, AD14% | 73% | 55% (27%) |
| Chen[53)] | 1996 | Taiwan | 31 | NE | 68 | NE | 0.8% | SQ65%, AD10% | 71% | 65% (10%) |
| Watanabe[54)] | 1999 | Japan | 16 | 15/1 | 66 | NE | 2.1% | SQ25%, AD56% | 69% | 67% (33%) |
| Cicenas[55)†] | 2007 | Lithuania | 46 | NE | NE | NE | 2.1% | SQ52%, AD22% | NE | NE |
| Tamura[56)] | 2007 | Japan | 56 | 47/9 | 66 | 1.2% | 2.5% | SQ46%, AD39% | 82% | 41% (25%) |

APTB: active pulmonary tuberculosis, LC: lung cancer, AL: affected-side lung, SL: same lobe, NE: not evaluated,
SQ: squamous cell carcinoma, AD: adenocarcinoma, †: surgical case study

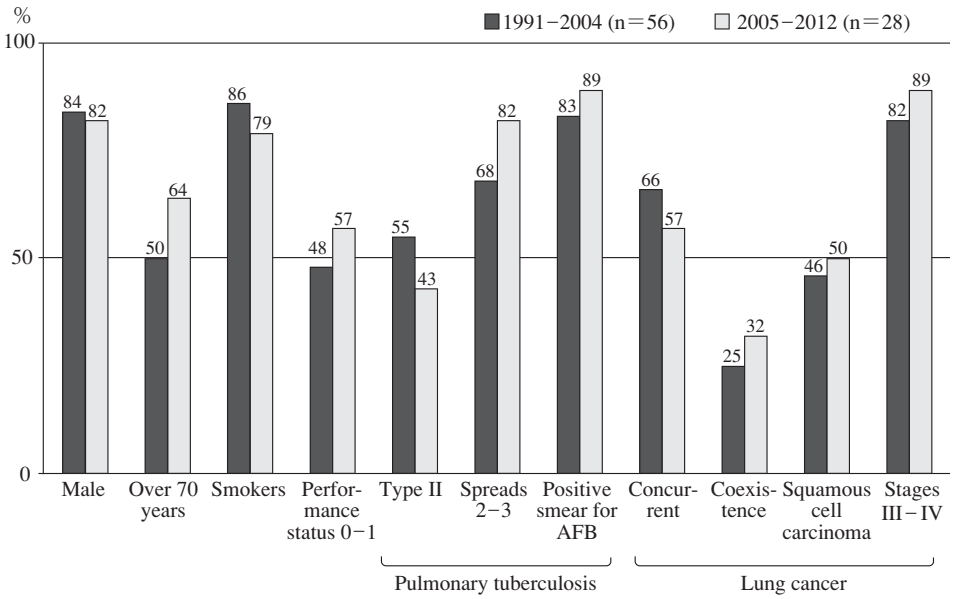


**Fig. 2** Relationship between active pulmonary tuberculosis and lung cancer

Smokers: current and previous smokers, Type II: non-extensively cavitary shadow on chest X-ray, Spreads 2−3: intermediate−extensive diseases on chest X-ray, AFB: acid fast bacilli, Concurrent: lung cancer concurrently detected with pulmonary tuberculosis, Coexistence: coexisting lung cancer and pulmonary tuberculosis in the same lobe

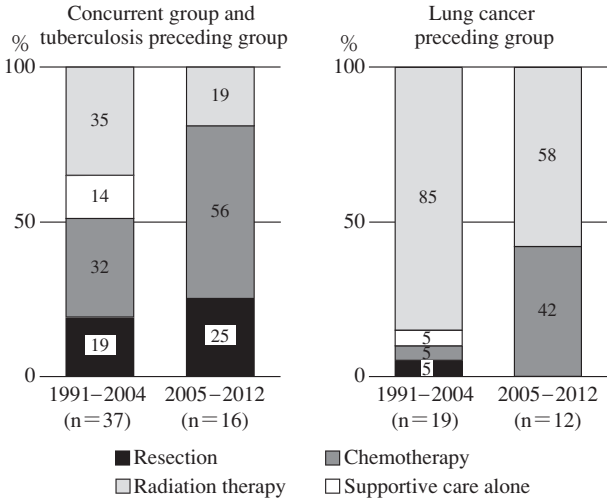


**Fig. 3** Selection of lung cancer treatment in patients with active pulmonary tuberculosis and lung cancer

thus, this group may essentially be considered to be similar to the concurrent detection group. In contrast, PTB in the lung cancer preceding group is often found when lung cancer is advanced and patients are receiving anti-cancer chemotherapy, corticosteroids for brain metastasis, or supportive care alone. Compared with other groups, patients in this group are often in poor general condition, with severe illness resulting from both diseases. With advanced age, an immunosuppressive state, and corticosteroid administration, it is commonly known that there is an increased risk of PTB arising from endogenous reactivation[58)−60)]. During the treatment of elderly patients with lung cancer in whom incidence rates of tuberculosis are high, appropriate care should be taken regarding the onset of pulmonary tuberculosis due to reactivation.

With the treatment of the two diseases in our study[56)], we found that the negative conversion rate of sputum culture with PTB treatment was good at 56% after 1 month and at 94% after 2 months in the concurrent detection group and the tuberculosis preceding group combined. In other case series studies[52)58)61)] and a case-control study[62)], it has been shown that if PTB is adequately treated, it can easily yield negative conversion of sputum culture, and anti-cancer chemotherapy is not an obstacle in the treatment of PTB. In contrast, it has been reported that in lung cancer treatment, the clinical course of each disease runs independently[61)]; however, it has also been reported that patients with concurrent tuberculosis have a worse prognosis than patients without tuberculosis[53)]. In our hospital, the lung cancer preceding group included many patients with poor performance status who were receiving supportive care alone, while in the concurrent detection and tuberculosis preceding groups, there were many patients undergoing aggressive cancer therapy, such as resection and chemotherapy. Furthermore, as shown in Fig. 2, although there has been no change in patient background, aggressive cancer therapy has been increasingly performed in all groups; there has been a remarkable increase particularly in the number of cases treated with chemotherapy, increasing from 32% to 56% in the concurrent detection group and tuberculosis preceding group, and increasing from 5% to 42% in the lung cancer preceding group (Fig. 3). Data on the detailed outcomes of patients with both active PTB and lung cancer who receive more recently developed anti-cancer chemotherapy

drugs are greatly anticipated.

Interestingly, with comorbid active PTB and lung cancer, both diseases commonly co-occur in the same lung lobe. At our hospital, we have sometimes experienced lung cancer and pulmonary mycobacteriosis coexisting in the same lobe of the lung[63]; the tuberculosis lesions were within or lied adjacent to lung cancer. Pathological findings of resected cases have revealed disruption of the fibrocaseous tuberculosis lesion wall due to lung cancer invasion and associated tuberculosis reactivation, while there were no cases of lung cancer developing within the tuberculosis lesion. Kageyama et al.[10] noted that tuberculosis lesions are prone to reactivation when there are coexisting tuberculosis lesions and lung cancer. Karnak et al.[64] also reported that bronchoscopy revealed that malignant tumors, particularly lung cancer, led to the reactivation of pulmonary tuberculosis. It is thought that the two diseases coexist in the same lobe often due to the onset of tuberculosis secondary to the progression of lung cancer. Furthermore, the coexistence of the two diseases is a condition that requires careful clinical attention, because many investigators have indicated that radiographic diagnosis of this coexistence is difficult[65)–68)].

(3) Active PTB after resection of lung cancer

Gastrectomy for gastric cancer has been found to be a risk factor for the onset of pulmonary tuberculosis[69]. However, there have been few reports focused on PTB following resection of lung cancer. Of the 4,393 patients hospitalized at our hospital for active PTB between 1996 and 2007, 14 patients (0.3%) developed PTB following lung cancer resection[70]. Patients who developed PTB were often men, elderly, within 5 years after lobectomy, with previous tuberculosis or recurrent lung cancer, and receiving corticosteroids. In the treatment of PTB, as is the case when two diseases are concurrently detected, if standard anti-tuberculosis treatment is possible then the negative conversion of sputum culture may easily be achieved.

## 5. Clinical problems

(1) Delay in diagnosis (doctor's delay)

When clinically analyzing diagnosis of tuberculosis, there is a period from the time of symptom onset to the time of diagnosis, called total delay, which is further categorized into patient's delay (from the time of symptom onset to the time of first visit to a medical institution) and doctor's delay (from the time of first visit to a medical institution to the time of diagnosis [delay in diagnosis])[71]. Total delay is a major problem for PTB in clinical practice[72]. Since patients with active PTB, previous tuberculosis, and lung cancer are typically under the management of medical institutions, patient's delay is rare in these cases; doctor's delay more than patient's delay is considered to be the primary factor contributing to total delay with regard to comorbid PTB and lung cancer.

There are two main factors that cause doctor's delay. First, in the interpretation of chest X-rays, pulmonologists attempt to classify chest shadows with various patterns as a single disease or as simply as possible — i.e., they often apply the principle of parsimony (Occam's razor) when making a diagnosis. In general, when faced with various clinical data, parsimony is useful for making a differential diagnosis and determining treatment. However, it is also well known that this tendency to simplify can result in erroneous diagnoses[73)74)]. It is thought that in concurrent PTB and lung cancer, especially in cases in which the two diseases coexist in the same lobe, this principle of parsimony can easily result in a doctor's delay[63]. Another factor is that the effectiveness of a visual search[75] depends on the number and nature of interfering objects. For example, it is difficult to detect a small lung cancer shadow (target object) among widespread previous tuberculosis shadows (interfering objects) in patients with tuberculosis sequelae[36].

To eliminate any doctor's delay caused by these factors, it is important to keep in mind the possibility of coexisting PTB and lung cancer. More specifically, the following should be noted: i) a shadow on peripheral consolidations of chest X-ray of hilar-type lung cancer should not simply be considered obstructive pneumonia, but the possibility of a tuberculosis lesion such as caseous pneumonia should be taken into consideration; ii) one should perform sputum examination for *M.tuberculosis* in patients with lung cancer, even when they are receiving supportive care; iii) it is important to carefully consider whether or not there are any growing shadows on chest X-ray during PTB treatment; and iv) pulmonologists should compare prior X-rays and assess any changes when examining patients with previous tuberculosis.

(2) Therapeutic limitations

As mentioned above, if the PTB treatment proceeds uneventfully, negative conversion of sputum culture can be easily achieved; therefore, any limitations in the treatment of comorbid PTB and lung cancer are primarily the limitations of lung cancer treatment. These include 1) postponing the timing of surgery for lung cancer due to tuberculosis infectivity; 2) limitations to treatment methods for anatomical injury due to tuberculosis, especially avoidance of surgical treatment; and 3) interference of anti-cancer chemotherapy due to anti-tuberculosis therapy, particularly the induction of CYP3A4 by rifampicin (RFP).

With regards to JNHOSGLC questionnaire survey by Hayashi et al.[76] regarding the time until lung cancer surgery for cases in which cancer and PTB were concurrently detected, it was found that the majority of respondents were of the opinion that the surgical period for lung cancer was "more than 4 weeks after the start of anti-tuberculosis treatment, and upon negative conversion of sputum smear with or without confirmation of drug-sensitivity". Although there has been no evidence regarding the appropriate timing of surgery, the opinion that takes into account tuberculosis infectivity for others before and after surgery is presumed to be valid[77]. With

**Table 2** Pharmacokinetic drug-drug interactions of molecular targeted drugs with rifampicin

| Drug | Metabolic mediator | Decrease† of $AUC_\infty$ | Decrease† of $C_{max}$ |
|---|---|---|---|
| Gefitinib[78] | CYP3A4 | 83% | 65% |
| Erlotinib[79] | CYP3A4 | 69% | 39% |
| Afatinib[80] | P-glycoprotein | 34% | 22% |
| Crizotinib[81] | CYP3A4 | 82% | 69% |
| Alectinib[82] | CYP3A4 | 73% | 51% |

$AUC_\infty$: area under the plasma concentration-time curve from time zero to infinity,
$C_{max}$: peak plasma concentration, †: Percent decrease by co-administration of rifampicin

regards to the second limitation mentioned above, when the tuberculosis lesions extensively exist in one side of the lung, it is often difficult to perform resection or radiotherapy for lung cancer in the contralateral lung. In our experience, lung cancers in the side of the lung contralateral to the thoracoplasty were unable to undergo resection, even if the lung cancer was stage I or II. This anatomical problem is difficult to solve, but early detection of lung cancer may increase treatment options, such as stereotactic irradiation. With regards to the third limitation listed above, it has been found that the induction of CYP3A4 by RFP affects the drug metabolism of anti-cancer agents. This mostly attenuates the decrease of blood concentration by increasing anti-cancer drug metabolism upon CYP3A4 induction. In particular, excluding bevacizumab, molecularly targeted drugs combined with RFP reduce the area under the plasma concentration-time curve from time zero to infinity ($AUC_\infty$) and peak plasma concentration ($C_{max}$) to a high degree; thus, caution is required (Table 2)[78)–82)]. On the other hand, with cytotoxic drugs, there is a case report in which the use of RFP lowered blood levels of irinotecan[83)]. In addition, it is possible that blood concentration levels of docetaxel, paclitaxel, and vinorelbine are also lowered by CYP3A induction[84)85)]; however, there is no evidence indicating that the degree of such attenuations reach significant levels in clinical practice. To avoid lowering blood concentrations of molecularly targeted drugs, it is thought that when choosing an anti-tuberculosis agent, RFP should be changed to rifabutin, which induces CYP3A4 to a lesser degree[86)]; however, adverse effects associated with rifabutin should be taken into consideration[87)].

## 6. Conclusion and Future Perspective

The close relationship between PTB and lung cancer has again come to light as a result of large scale epidemiological studies recently conducted in Asia. At the same time, it is thought that investigations into scar cancer will be accelerated from the perspective of chronic inflammation and cancer development. In studying the mechanisms of carcinogenesis, instead of studies regarding PTB with regional differences in prevalence rates, studies of the relationship between pulmonary nontuberculous mycobacteriosis, the prevalence of which is increasing worldwide, and lung cancer may be significant[88)–91)].

Doctor's delay is a major clinical problem related to PTB and lung cancer. To eliminate this delay, it is necessary to consider concurrent lung cancer in the treatment of active PTB and to consider concurrent active PTB in the treatment of lung cancer; it is also important to perform X-rays and sputum examination with bronchoscopy if necessary. Furthermore, when treating active PTB, it is thought that the adequate introduction of standard anti-tuberculosis treatment[92)] will be useful for early detection of lung cancer and verification of Interferon-Gamma Release Assays[93)] for elderly lung cancer patients in Japan will be useful for early diagnosis of active PTB. Anti-cancer chemotherapy, which has made remarkable developments, should be managed after fully understanding drug-drug interactions, especially the attenuation of the effects of molecularly targeted drugs as a result of CYP3A4 induction by RFP.

## Conflict of interest

The author declares that there is no conflict of interest related to this article.

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