Trends of bacterial colonisation and the risk of postoperative pneumonia in lung cancer patients with chronic obstructive pulmonary disease

Yoshito Yamada, Yasuo Sekine, Hidemi Suzuki, Takekazu Iwata, Masako Chiyo, Takahiro Nakajima, Kazuhiro Yasufuku, Shigetoshi Yoshida

Department of Thoracic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

Department of Thoracic Surgery, Tokyo Women's Medical University Yachiyo Medical Center, Chiba, Japan

Received 7 January 2009; received in revised form 3 May 2009; accepted 7 May 2009; Available online 12 August 2009

Abstract

Background: Lung cancer patients with chronic obstructive pulmonary disease (COPD) have a high risk of developing postoperative pneumonia (POP). This study aims to investigate the impact of COPD on POP and the trends for perioperative bronchial colonisation by micro-organisms.

Methods: A retrospective chart review was made for 626 patients who underwent lung cancer surgeries at the Chiba University Hospital between 1996 and 2005. The patients were categorised as non-COPD (n = 475) and COPD (FEV1/FVC < 70%; n = 151). All the patients had sputum and bronchial bacterial cultures examined for potentially pathogenic micro-organisms (PPMs). Risk factors for POP and mortality were analysed.

Results: Patients with COPD had a significantly higher incidence of POP (23/151, 15.2%) than those without COPD (17/475, 3.6%) (p < 0.0001). Preoperative bronchial bacterial examinations showed that 50 of 475 patients without COPD (10.5%) had positive cultures, while the results for 30 of 151 patients with COPD (19.9%) were positive (p = 0.0111). Only 31 of 548 patients (5.7%) who did not show any preoperative PPMs had POP, while nine of 78 patients (11.5%) who presented preoperative PPMs had POP (p = 0.0469). The PPMs that emerged postoperatively were primarily Staphylococcus aureus (94.4% of PPMs), while they were seen less frequently preoperatively (46.5% of PPMs). Multivariate analysis demonstrated that advanced age and FEV1/FVC were independent risk factors for POP. Patients with POP had significantly worse long-term survivals than those without POP (p = 0.0004).

Conclusion: COPD was a risk factor for POP. Staphylococcus aureus and Gram-negative bacilli should be targets for postoperative prophylactic antibiotic selection. Patients with POP had poor long-term survivals.

Keywords: Postoperative pneumonia; Micro-organism; Lung cancer; Chronic obstructive pulmonary disease

1. Introduction

Owing to the increases in the incidence of both lung cancer and chronic obstructive pulmonary disease (COPD), surgeries for lung cancer in patients with COPD have been increasing. It is estimated that 20—45% of patients who underwent lung cancer surgeries had COPD [1,2].

Postoperative pulmonary infection is one of the main causes of mortality [3]. This may be due to perioperative bacterial colonisation [4]. Cabello et al. reported that 42% of patients with lung cancer had bronchial colonisation with either commensal or potentially pathogenic micro-organisms (PPMs) [5]. Postoperative pneumonia (POP) is seen more frequently in patients with COPD than in those without COPD [2]. It is well known that COPD patients are likely to have bacterial colonisation of the respiratory tract [6]. Monso et al. reported a colonisation rate of 25% in patients with stable COPD [7]. However, there are few reports with regard to the association between bacterial colonisation and the risk of POP in patients with COPD [8]. This study aimed to investigate the impact of COPD on POP as well as the trends of bronchial micro-organisms and the influence of POP on long-term survival.

2. Patients and methods

This study was approved by the local Institutional Review Board of the hospital. Informed consent from the patients was waived as this was a retrospective study. We performed a chart review for 883 patients with lung cancer who had undergone pulmonary resections at the Chiba University Hospital between January 1996 and March 2005. We routinely
examined the sputum cultures for 3 consecutive days coinciding with the time of hospital admission and collected bronchial secretions for culture during bronchoscopic examinations. All the study participants met the following criteria: (1) preoperative spirometry had been performed, (2) preoperative bacterial examination of the bronchial secretions had been done and (3) no antibiotics had been prescribed for the 2 weeks preceding surgery. Thus, 626 of 883 patients (70.9%) met these criteria during the study period.

The functional definition of COPD was the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) <70%; [9] 151 of 626 (24.1%) had a diagnosis of COPD, and 475 (75.9%) did not meet the criteria for COPD. We routinely introduced rehabilitation for patients with moderate-to-severe COPD. All current smokers were encouraged smoking cessation. A few patients were administered inhalation of bronchodilators and steroid perioperatively.

For pulmonary bacterial examination, all patients had submitted at least one sample of spontaneous sputum or bronchial secretions had been obtained using a bronchoscopic brushing technique. All samples were obtained within the 2 weeks preceding the operation.

We used a qualitative test for the examination of sputum samples. We examined a Gram’s stain of a sample in an area of maximal purulence for polymorphonuclear leucocytes and epithelial cells. Samples were considered suitable for culture when <10 squamous cells and >25 leucocytes per low-power magnification field were seen. Samples were processed for quantitative microbiological study in accordance with accepted laboratory methods. Using a microbiological loop, 0.01-ml samples were seeded onto the following culture media: blood agar, MacConkey agar, chocolate agar and Sabouraud’s agar with chloramphenicol. Incubation was at atmosphere contained 5—7% carbon dioxide (CO2). A first reading was taken after 24 h, and a second, final reading was taken after 48 h of culture. Micro-organisms were regarded as 'colonised' when they reached growths >10^4 colony-forming units (cfu) per millilitre.[4,10]

Potentially pathogenic micro-organisms (PPMs) were surveyed in this study. The PPMs were considered as possible agents causing respiratory infections irrespective of whether or not they belonged to the gastrointestinal or oropharyngeal flora. *Streptococcus pneumoniae* (*S. pneumoniae*), *Haemophilus influenzae* (*H. influenzae*) and *Moraxella catarrhalis* were considered as PPMs related to community-acquired pneumonia: PPMs-CAP. *Staphylococcus aureus* (*Staph. aureus*), *Psuedomonas aeruginos* (*P. aeruginosa*), *Stenotrophomonas maltophilia*, non-fermenting Gram-negative bacilli (NF-GNB) and Enterobacteriaceae were considered as PPMs related to nosocomial pneumonia; PPMs-NP [5].

Postoperative pneumonia was considered a pulmonary complication. Pneumonia was defined by the presence of infiltrative shadows on chest X-ray, body temperature ≥37.5 °C and white blood cell count >10 000 per microlitre prior to discharge from the hospital.

We also performed postoperative respiratory microbiological examinations when patients had at least one of the following conditions: (1) frequent yellowish sputum, (2) difficulty with expectorating sputum that required bronchoscopic aspiration, mini–tracheotomy or tracheostomy, (3) continuous infiltration on chest X-ray after surgery or (4) showing any symptoms indicative of pulmonary infection, such as high-grade fever.

The first choices for prophylactic antibiotics were ampicillin with β-lactamase inhibitor (ABPC/SBT) (n = 265), first-generation cephalosporin (primarily cefazolin) (n = 146), second-generation cephal (primarily cefotiam hydrochloride) (n = 133) and others (n = 82). When no infection was confirmed, antibiotics were discontinued on the second postoperative day. When infection was suspected or diagnosed, antibiotics were accordingly selected based on sensitivity tests.

3. Statistical analysis

The data were analysed using Stat View version 5.0 (Statistical Analysis Systems; Cary, NC, USA). To compare the non-COPD and COPD groups, the Mann–Whitney U-test was used for continuous variables and the Fisher’s exact test was used for categorical variables. The data were presented as mean ± standard deviation. A multiple logistic regression model was used to determine factors that were independently associated with POP. Survival curves were estimated by the Kaplan–Meier method, and any difference in survival times between the two groups (POP positive vs negative) was calculated by the log-rank test. Overall survival was defined as the time elapsed from the date of surgery either to death from any cause or to the last follow-up. Cox’s proportional hazards model was used for identifying prognostic factors. A p-value <0.05 was considered significant.

4. Results

Patient characteristics are summarised in Tables 1 and 2. Male gender and a positive smoking history were more frequent in the COPD group than in the non-COPD group. Age, smoking index and several pulmonary function parameters, including FVC, FEV1, % predicted FEV1, FEV1/FVC and PaO2, were considered as risk factors for POP. Respiratory infections were more frequent in the COPD group than in the non-COPD group. Smoking index and several pulmonary function parameters were significantly different from those in the non-COPD group. Squamous cell carcinoma and advanced cancer stages were more frequently seen in the COPD group than in the non-COPD group.

Postoperative pneumonia occurred in 40 patients (6.4%). In the non-COPD group, 17 of the 475 patients (3.6%) had POP and 23 of the 151 patients (14.3%) in the COPD group suffered from POP (p < 0.0001). The 30-day mortality was 0.4% (2/475) in the non-COPD group and 1.3% (2/151) in the COPD group (p = 0.247).

In the preoperative bacterial examinations of pulmonary secretions, positive cultures for PPMs were obtained from a total of 80 patients (12.8%); 50 of the 475 patients (10.9%) in the non-COPD group, 30 of the 151 patients (19.9%) in the COPD group (p = 0.011). A total of 99 strains of PPMs were obtained preoperatively (Fig. 1). The isolated PPMs were: 19 cases of *S. pneumoniae* (3.0%), 21 of *H. influenzae* (3.4%), 13 of *M. catarrhalis* (2.1%), 13 of *S. aureus* (2.1%), six of *P. aeruginosa* (1.0%), four of *S. maltophilia* (0.6%), 11 of NF-GNB (1.8%) and 12 of Enterobacteriaceae (1.9%).
Nine of the 78 patients with preoperative PPMs (11.5%) had POP, while 31 of the 548 patients who were negative for preoperative PPMs (5.7%) had POP (**p** = 0.047). In particular, non-COPD patients without preoperative PPMs had a significantly lower incidence of POP than COPD patients with or without preoperative PPMs (**p** < 0.0001; Fig. 2).

Postoperative microbiological examinations of pulmonary secretions were performed for 212 patients (33.9%): 136 of the 475 patients (28.6%) in the non-COPD group and 76 of the 151 patients (50.3%) in the COPD group (**p** < 0.0001). Positive cultures for postoperative PPMs were obtained in 63 patients (29.7%): 34 of the 136 patients (25.0%) in the non-COPD group and 29 of the 76 patients (38.2%) in the COPD group (**p** = 0.06). Nineteen of the 63 patients who were positive for postoperative PPMs (30.2%) had POP, and 18 of the 149 patients who were negative for postoperative PPMs (12.1%) had POP (**p** = 0.003).

A total of 87 strains of PPMs were obtained from 63 patients postoperatively (Fig. 3). In the non-COPD group, 29 of 121 patients (24.0%) who underwent postoperative bacterial examinations and did not have POP had 35 strains of PPMs and five of 15 patients (33.3%) who developed POP had eight strains of PPMs (**p** = 0.527). By comparison, in the COPD group, 16 of 53 patients without POP (30.2%) showed 16...
strains of PPMs and 13 of 23 patients with POP (56.5%) had 28 strains of PPMs ($p = 0.041$). The rate of PPMs emergence in patients with POP was higher than in those without POP ($p = 0.0299$). The emergent PPMs were mostly PPMs-NP (94.4% of PPMs).

With regard to postoperative antibiotics usage, 482 of 570 patients (84.5%) without POP received single antibiotics. In contrast, only nine of 38 patients (24%) who had POP received single antibiotics, and 74% received multiple antibiotics. Aminoglycosides and/or carbapenems were mainly selected as the second-line antibiotics.

To identify independent risk factors for POP, we conducted univariate and multivariate analyses. Based on univariate analyses, male, advanced age, positive smoking history, preoperative PPMs, lower % predicted FEV1 and lower FEV1/FVC were depicted as risk factors, while multivariate analysis demonstrated that higher age and lower FEV1/FVC were independent risk factors (Table 3).

Fig. 4 shows that patients with POP had significantly worse long-term survivals than those without POP ($p = 0.0004$). Five-year overall survivals for patients without POP and those with POP were 67.3% and 47.2%, respectively. Major lung resections, advanced pathological stages and POP were identified as significant prognostic factors by a proportional hazards model (Table 4).

5. Discussion

Postoperative pneumonia is one of the most critical medical complications following thoracic surgery and is associated with high mortality [11]. In this retrospective study, we determined that perioperative examinations for PPMs should be performed for patients with COPD. Patients who are preoperatively positive for PPM should be carefully watched and broad-spectrum antibiotics that target PPMs-NP should be given.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>3.39 (1.31–8.77)</td>
<td>0.012</td>
<td>1.00 (0.26–3.89)</td>
<td>0.997</td>
</tr>
<tr>
<td>Age</td>
<td>1.09 (1.04–1.14)</td>
<td>0.0002</td>
<td>1.07 (1.02–1.19)</td>
<td>0.006</td>
</tr>
<tr>
<td>Smoking history</td>
<td>4.64 (1.63–13.22)</td>
<td>0.004</td>
<td>2.87 (0.65–12.8)</td>
<td>0.162</td>
</tr>
<tr>
<td>Preoperative PPMs</td>
<td>2.08 (1.01–4.56)</td>
<td>0.05</td>
<td>1.55 (0.67–3.61)</td>
<td>0.306</td>
</tr>
<tr>
<td>% Predicted FEV1</td>
<td>0.98 (0.96–0.96)</td>
<td>0.011</td>
<td>1.01 (0.98–1.03)</td>
<td>0.616</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>0.93 (0.90–0.96)</td>
<td>&lt;0.0001</td>
<td>0.95 (0.91–0.98)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

PPMs, potentially pathogenic micro-organisms; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.
Several causes may lead to POP in lung cancer patients with COPD, including: (1) decreased forced expiratory volume, (2) weakened clearance system with microvillus movements on bronchial epithelium due to chronic bronchitis, (3) deterioration of the local immune barrier and fragile tolerance against micro-organism infection, (4) decreased cough reflex due to nerve injury and (5) silent aspiration due to a weakened nasopharyngeal reflex.

In the preoperative bronchial bacterial examinations, positive cultures were more frequently obtained from the COPD group than from the non-COPD group. This result is consistent with the reports from Nan et al. [12] and Schussler et al. [8]. Cabello and colleagues [5] showed that distal airways were frequently colonised in clinically stable populations with bronchogenic carcinoma (42%), COPD (83%), bronchiectasis (88%) and in long-term tracheostomised patients (47%). Monso´ et al. [7] showed that 25% of 40 stable COPD patients had colonisations of the distal airways, which was confirmed using fibre-optic protected specimen brush (PSB) samples. However, they did not distinguish potential pathogenic micro-organisms from non-potential pathogenic micro-organisms. The study of Belda and colleagues [4] also showed that distal airways were frequently colonised in clinically stable patients with mild or moderate COPD suffering with bronchogenic carcinoma.

In this study, postoperative bacterial examinations were performed for 33.9% of the enrolled patients. Patients who had positive postoperative PPMs had significantly higher morbidity with POP than the patients without PPMs. These results demonstrate that a postoperative bacterial examination was related to POP, and that isolated PPMs were regarded as pathogens. In the non-COPD group, the ratio of each emergent PPM for patients with POP was higher than for those without POP. In the COPD group, the emergent ratio was much higher for patients with POP than for patients without POP.

In either group, PPMs-NP, such as S. aureus and Gram-negative bacilli, were the main causative pathogens for POP. From this analysis, it is clear that appropriate prophylactic antibiotics against PPMs-NP should be used. Several studies have reported the microbiological aetiology for POP. Sok et al. reported that Gram-negative pathogens were responsible for 71% of POP and Streptococcus species were found in only 10% [13]. This was consistent with the results of our study. In contrast, Schussler et al. reported that in most instances pathogenic bacteria were H. influenzae (41.7%), S. pneumonia (25%) and other streptococci (12.5%). Enterobacter and Pseudomonas species were responsible for 8.7% and 25% of cases, respectively [8]. Bernard et al. also reported that Streptococcus species and H. influenzae were responsible for 50% of all POP and Gram-negative pathogens (other than Haemophilus spp.) accounted for 31% [14].

What is most unclear is why postoperative pathogens isolated in patients with POP are frequently different from those isolated in the preoperative studies for patients with COPD. In this sense, although this study was not designed to establish a relationship between prior colonisation and micro-organisms isolated in patients with POP, Belda and colleagues [4] found a partial or total coincidence between preoperative colonisation and postoperative microbiology of respiratory infections only in the 42% cases of infection. The decision regarding the choice of a suitable prophylactic antibiotic and the duration of administration is important to prevent postoperative respiratory infections. The reasons for these differences for colonisations from our results are not clear. The use of different prophylactic antibiotics may be one reason. Schussler et al. [8] reported that Gram-negative bacteria were detected postoperatively in 37.5% of patients, while these bacteria were detected only in 19.3% of patients preoperatively. Sethi et al. [15] compared sputum samples of COPD patients with stable conditions and those with exacerbations. They demonstrated that acquisition of new strains of bacterial pathogens was associated with COPD exacerbations. They speculated that strain-specific protective immune responses had developed and that the patients were susceptible to infections by other strains.

There are many reports suggesting the first choices for prophylactic antibiotics during and after thoracic surgery. In general, second-generation cephalosporin or penicillin is recommended [13,16,17]. We have used second-generation cephalosporin (primarily cefotiam hydrochloride; 1990–2000), ampicillin with β-lactamase inhibitor (ampicillin-sodium/sublactam sodium (ABPC)/SBT; 2000–2005) or first-generation cephalosporin (primarily cefazolin sodium; 2000–2005) for prophylaxis. On the other hand, patients with POP had received multiple antibiotics. The selection of antibiotics for the second or third line was determined based on the sensitivity tests of bacterial cultures. However, when pathogens cannot be detected, we have to empirically select antibiotics. According to the American Thoracic Society (ATS) guidelines for hospital-acquired pneumonia (HAP) in adults, [18] postoperative pneumonia is thought to be 'severe HAP with risk factors'. In these cases, the recommended antibiotics are aminoglycoside or ciprofloxacin plus one of the following: anti-pseudomonal penicillin, β-lactam/β-lactamase inhibitor, ceftazidime, cefoperazone or imipenem and, if needed, vancomycin. We usually use aminoglycoside (mainly amikacin) or carbapenem (primarily imipenem/ cilastatin sodium) for postoperative PPMs.

Several risk factors have been reported for POP, including FEV1, low body mass index (BMI), increased age, active smoking, carbon monoxide diffusing capacity (DLCO) less than 70% and bronchial obstruction [19–21]. Our results were similar to these previous reports. By multivariate analysis, higher age and lower FEV1/FVC were independent risk factors. Patients with POP had significantly worse prognoses than patients without POP. This may be because the postoperative pulmonary condition was severely deteriorated and chronic bronchitis and frequent pulmonary infection occurred. From these results, careful prophylactic treatments of COPD patients are critical for prolonging survival after surgery.

This retrospective study has certain limitations. First, the validity of the diagnosis of POP from discharge data is based on our clinical database for lung cancer. We assumed that the diagnoses of POP were valid, as the patients in this study had elective lung cancer surgeries and no preoperative pulmonary infections. Second, this study is a single-centre surveillance. Therefore, a larger sample of patients from multiple centres is needed to validate our results. Third, postoperative bacterial examinations were performed for only 33.9% of patients. There is a possibility for colonised...
patients without POP, and the distributions for the colonised bacterial types might be different from these results when all patients are examined postoperatively. Fourth, video-assisted thoracic surgery (VATS) was introduced into early-stage lung cancer since 2000. VATS lobectomy or segmentectomy was done by thoracotomies with small skin incisions (5—8 cm) under thoracoscopy. It has been reported that this less-invasive approach is associated with a significantly lower rate of POP [22]. However, since the sizes of the skin incisions depended on the surgeons and the severity of the pleural adhesion, it is a confounding variable. Therefore, the influence of surgical approach on POP could not be considered in this study.

In conclusion, COPD was a risk factor for POP. A preoperative bacterial examination has an association with these complications only for patients without COPD. The preoperative bacterial test was not reflective of the microorganisms for postoperative infections. The pathogens for these complications were primarily S. aureus and Gram-negative bacilli.

References