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Risk factors for postoperative pneumonia after lung cancer surgery and impact of pneumonia on survival

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ABSTRACT

Objective: Little is known about risk factors and prognosis for postoperative pneumonia (POP) in patients undergoing therapeutic lung cancer (LC) surgery.
Methods: We followed a nationwide population-based cohort of 7479 patients with LC surgery in Denmark 1995–2011. We used logistic regression analysis to examine risk factors for POP within 30 days after surgery. Subsequent survival in patients with POP was analyzed with Cox regression.
Results: We identified 268 (3.6%) patients with POP. Important risk factors included advanced age (age ≥80 years: (adjusted odds ratio [aOR] = 3.64; 95% CI: 2.17–6.12) as compared to patients aged 50–59 years), previous pneumonia (aOR = 2.68; 95% CI: 2.02–3.56), obesity (aOR = 1.91; 95% CI: 0.99–3.69), chronic pulmonary disease (aOR = 1.90; 95% CI: 1.40–2.57), alcoholism (aOR = 1.56; 95% CI: 0.81–3.01), and atrial fibrillation (aOR = 1.42; 95% CI: 0.82–2.45). Overall thoracoscopic surgery halved the risk of POP and the highest risk of POP was seen in pneumonectomy performed in open thoracotomy. Among patients surviving the 30-day postoperative period, 31–365 day mortality was 21.6% in POP patients vs. 16.8% in non-POP patients, and 1–5-year mortality was 62.2% vs. 53.0%. Adjusted 31–365 day hazard ratio (HR) of death with POP was 1.31 (95% CI: 1.00–1.73), and 1–5 year HR was 1.22 (95% CI 0.98–1.53).
Conclusion: Major risk factors for POP following LC surgery are advanced age, previous pneumonia, obesity, chronic pulmonary disease, alcoholism, and atrial fibrillation. POP is a clinical marker for decreased LC survival.

1. Introduction

Postoperative pneumonia (POP) is one of the most common complications in patients with lung cancer (LC) undergoing therapeutic surgical resection [1–3]. In recent studies the reported incidence of POP following LC surgery has ranged from 2.9 to 10.7% [4–9]. Older age and advanced malignancy have been the risk factors for POP most consistently reported [4,5,10,11]. Other suggested risk factors include male sex, chronic obstructive pulmonary disease (COPD), low FEV_1%, tobacco-smoking, obesity, diabetes mellitus, extent of LC surgery, induction therapy, right sided pulmonary surgery, and preoperative airway colonization by potential pathogenic microorganisms [5,10,12,13]. Robust data from large population-based studies on risk factors for POP are sparse however, and important patient-related potential risk factors including cardiovascular disease [14] and a history of previous pneumonia [15,16] have not been studied.

Occurrence of POP may be a marker of increased long-term mortality in patients with LC surgery, but we are aware of only one previous population-based study examining this topic. This Canadian study followed 4033 LC patients from day 90 after surgery in the years 2000–2004 and found a decreased 5-year overall survival associated with occurrence of any major postoperative infectious complication (including pneumonia, mediastinitis, and pleural empyema) with an adjusted death hazard ratio (HR) of 1.67 (95% confidence interval (CI), 1.39–2.01) [6]. To prevent pneumonia in LC patients and understand its impact on the disease course of LC, up-to-date data on POP risk factors and prognosis are necessary. We therefore did a population-based cohort study to examine patient-related risk factors for POP following therapeutic LC

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surgery and to assess the impact of POP on subsequent patient survival.

2. Materials and methods

The universal Danish health care system provides tax-supported health care services to all residents, guaranteeing free access to hospitals and primary medical care. The civil registration number (CPR number), a unique identifier assigned to every Danish citizen at birth or immigration, allows for accurate linkage among all medical databases used in this study [17].

2.1. Patients with lung cancer surgery

We used the Danish Cancer Registry (DCR) and the Danish National Registry of Patients (DNRP) to identify all patients in Denmark (current population, 5.6 million) who had a diagnosis of LC and a lung resection date within 180 days following the diagnosis date from January 1, 1995 through December 31, 2011 (n = 7479). The 180-day-time window was chosen in order to maximize the probability that the lung resection (i.e. LC surgery) was related to the preceding LC diagnosis and not due to some other lung disease. The DCR contains nationwide data on cancer incidence in Denmark since 1943 and is 95–98% complete and valid [18]. We excluded patients with a previous diagnosis of LC before 1995. We classified LC stage prior to surgery as localized (cTNM-stage with N = 0, and M = 0), regional (cTNM-stage with N > 0 and M = 0), metastasized (cTNM-stage with M > 0), or unknown. In order to identify the complete history of surgical procedures and a 5-year record of comorbidities at the time of LC surgery, we linked the LC patients to the DNRP. The DNRP, a nationwide registry established in 1977, contains computerized records on 99.4% of all discharges from Danish hospitals. From 1995 onwards, data on hospital specialist outpatient clinics is also included [19].

2.2. Predictors of POP risk and LC prognosis

From the DNRP, we assessed data on individual diseases apart from LC. We used Charlson Comorbidity Index (CCI) scores to assess overall comorbidity levels in the study cohort [19,20]. The CCI score was computed as the sum of points (between 1 and 6) assigned to each of the 19 diseases included in the index (see Table 5 in Online Material). Patients were classified into three levels according to their CCI score: 0 points ("low comorbidity"); 1–2 points ("moderate comorbidity"); and ≥3 points ("severe comorbidity"). We excluded LC from the CCI as it represents the index disease under study and consequently should not be adjusted for. We assessed the following groups of frequent (prevalence ≥ 5%) CCI comorbidities as potentially important risk factors for POP: chronic pulmonary disease (including COPD, chronic bronchitis, asthma and bronchiectasis), cardiovascular disease (including myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease), diabetes mellitus (including diabetes mellitus type I and II, and diabetes with end end-stage organ damage), and any other solitary tumor. We also analyzed the following conditions not included in the CCI as preoperative risk factors; presence or absence of-atrial fibrillation, hypertension, obesity (BMI ≥30 kg/m^2), alcoholism, a history of previous pneumonia (within the last 5 years), sex (M/F), age group (<50, 50–59, 60–69, 70–79, ≥80), cancer stage (localized, regional, metastatic, unknown), marital status (married vs. un-married), time from diagnosis to surgery exceeding 60 days (yes/no), calendar period (1995–2000, 2001–2006, 2007–2011), overall surgery type (open thoracotomy vs. thoracoscopic), individual thoracoscopic procedures (lobectomy, wedge resection, segment resection, bilobectomy and pneumonectomy). Individual procedures in open thoracotomy (lobectomy, wedge resection, segment resection, bilobectomy, extended lobectomy, and pneumonectomy). (See diagnosis codes in Online Material).

2.3. Information on POP

Data on POP was obtained through the DNRP. We defined an episode of POP as either a hospital discharge date, a new hospital admission date, a hospital outpatient clinic visit date or an emergency department visit date with a primary or secondary diagnosis code of pneumonia occurring within 0–30 days after the date of surgery (index-admission with surgery included). We included both viral and bacterial pneumonias along with pneumonia NOS (pneumonias of any infectious etiology) (See diagnosis codes in Table 5 in Online Material).

3. Statistical analysis

We calculated proportions of POP according to the predefined potential risk factors. We then used logistic regression to compute crude and adjusted ORs with 95% CIs as a measure of the relative risk of POP within 30 days after LC surgery among patients with a given risk factor, compared with patients without the risk factor, adjusting for sex, age group, CCI score, and cancer stage (excluding patients with unknown cancer stage from the regression model). Estimates for the aforementioned groups of frequent CCI comorbidities were adjusted for the rest CCI score level excluding the given comorbidity from the index. We systematically tested variables for statistical interaction. The size of the dataset did not allow for the logistic regression model to be stratified on calendar period. It can also be argued that especially patient related risk factors for POP are somewhat stable across calendar periods; eliminating the need for said stratification.

For the prognosis analysis, patients were followed from day 31 (end of the postoperative period) after LC surgery until death, migration, or end of follow-up, whichever came first. This was done in order to eliminate immortal person-time bias [21]. We estimated and plotted 31–365 day, and 31 day-5 year cumulated mortality as well as mortality rates according to presence or absence of POP for all LC surgery patients, using the Kaplan–Meier method. Subsequently, we used Cox proportional hazards regression model to compute 31–365 day, and 1–5 year HRs with 95% CIs as a measure for the relative risk of death for LC patients with POP. HRs associated with POP were adjusted for sex, age, CCI level, cancer stage, and time from LC diagnosis to LC surgery exceeding 60 days.

All statistical analyses were performed using STATA software (version 12.0 StataCorp LP, College Station, TX). The study was approved by the Danish Data Protection Agency (number 1-16-02-1-08).

4. Results

4.1. Patient characteristics

We identified 7479 patients (3502 [46.8%] women and 3977 [53.2%] men) with a first time diagnosis of LC and LC surgery between 1995 and 2011 (Table 1). Of these 268 (3.6%) had a diagnosis of POP; and 4.3% of men vs. 2.8% of women experienced POP. The risk of POP increased substantially with advanced age; POP developed in 1.1% of patients <50 years, compared with 4.4% in patients aged 70–79 years, and 9.7% in patients aged ≥80 years. The proportion of patients with recorded POP increased from 2.0% in 1995–2001 to 4.2% in 2007–2011. In 94% of POP cases no etiologic agent was registered in the DNRP (Table 4). In total, 41.9% of the LC