Role of Comorbidity on Survival after Radiotherapy and Chemotherapy for Nonsurgically Treated Lung Cancer

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Background: Comorbidity, such as diseases of the cardiovascular, pulmonary, and other systems, may influence prognosis in lung cancer and complicate its treatment. The performance status of patients, which is a known prognostic marker, may also be influenced by comorbidity. Due to the close link between tobacco smoking and lung cancer, and because lung cancer is often diagnosed in advanced ages (median age at diagnosis in Denmark is 70 years), comorbidity is present in a large proportion of lung cancer patients.

Methods: Patients with any stage lung cancer who did not have surgical treatment were identified in the Danish Lung Cancer Registry. Danish Lung Cancer Registry collects data from clinical departments, the Danish Cancer Registry, Danish National Patient Registry, and the Central Population Register. A total of 20,552 patients diagnosed with lung cancer in 2005 to 2011 were identified. Comorbidity data were extracted from the Danish National Patient Registry, which is a register of all in- and outpatient visits to hospitals in Denmark. By record linkage, lung cancer patients who had previously been diagnosed with comorbid conditions were assigned a Charlson comorbidity index. Initial cancer treatment was categorized as chemotherapy, chemoradiation, radiotherapy, or no therapy. Data on Charlson comorbidity index, performance status, age, sex, stage, pulmonary function (forced expiratory volume in 1 second), histology, and type of initial treatment (if any) were included in univariable and multivariable Cox proportional hazard analyses.

Results: Treatment rates for chemotherapy and chemoradiation declined with increasing comorbidity and in particular increasing age. Women received treatment more often than men. In a univariable analysis of all patients combined, stage, performance status, age, sex, lung function, and comorbidity were all associated with survival. Apart from excess mortality among patients with unspecified histological subtypes (hazard ratio), there was no clear difference between the specified subtypes. When adjusting for the other factors, particularly age, sex, performance status, and stage proved to be robust while risk estimates for comorbidity were attenuated somewhat. When grouped by the three types of cancer treatment or no treatment, there was no influence of comorbidity on radiation therapy and modest influence on survival after chemotherapy and chemoradiation. In contrast, age remained a strong negative prognosticator after multivariate adjustment as did stage and performance status.

Conclusion: Comorbidity has a limited effect on survival and only for patients treated with chemotherapy. It is rather the performance of the patient at diagnosis than the medical history that prognosticates survival in this patient group.

Key Words: Lung cancer, Comorbidity, Performance status.

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The simultaneous presence of cancer and other medical conditions (comorbidity) is frequent. Cigarette smoking is the major risk factor for lung cancer (LC), and other tobacco-related diseases are particularly frequently found in patients with LC.[1] Comorbidity affects outcome in several ways, such as reluctance toward diagnosis and therapy and impaired tolerance to treatment.[2,3] Furthermore, comorbidity may affect the performance status (PS) of the individual, thereby reducing the efficacy and increasing the side effects of treatment. Anticancer treatment may worsen a number of common comorbid conditions such as diabetes and kidney failure, and comorbid diseases may directly shorten life expectancy. Comorbidity has been shown to be associated with suboptimal chemotherapy and with poor survival in clinical trials, and guidelines recommend that comorbidity be considered when planning treatment for patients with LC.[4,5] In general, outcome of therapy is dependent on multiple factors, which in LC includes sex, stage, age, and PS. However, the magnitude of the effect of comorbidity and the interaction with PS and age are unknown, and we therefore conducted this study to determine the role of comorbidity on treatment rates and survival for patients with advanced (nonsurgical) LC.

METHODS

Newly diagnosed patients with LC were identified in the Danish Lung Cancer Registry for the period 2005 to 2011. The register covers all hospital departments in Denmark and collects information on diagnostic procedures, stage, Eastern Cooperative Oncology Group PS, and first treatment.[6] This information was supplemented by record linkage to the Central Population Register for information on survival,

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the National Pathology Register for pathology information, and the National Patient Registry for information on previous illnesses.[7,8] The latter register contains coded discharge diagnosis and interventions related to diagnostic evaluation and treatment for all somatic patient admissions in Denmark. Information on comorbidity was included up to 10 years before LC diagnosis. Comorbidity was classified according to the scores from the weighted Charlson comorbidity index (CCI), however, leaving out information on cancer-related contact within 150 days before the date of LC diagnosis.[9] If an individual had a disease coded more than once with a difference in severity (uncomplicated versus complicated or mild versus severe), the most severe score was used. The CCI is an extensively validated comorbidity measure and is calculated from 19 different disorders, which can be grouped in seven broader groups.

Patients were categorized in four age groups based on age at diagnosis. Lung function was based on forced expiratory volume in 1 second (FEV_1) as percentage of predicted value and grouped in four groups. Clinical stage was based on clinical information on tumor, lymph nodes, and metastasis (TNM) and recoded according to the seventh edition of TNM. The nonsurgical treatment was coded as no treatment, chemotherapy only, radiotherapy only, or chemoradiation. Only the initial treatment was considered.

Multivariable logistic regression was used to calculate odds ratio (OR) and 95% confidence intervals for having chemo- or radiotherapy and chemoradiation according to comorbidity and age, sex, stage, histological subtype, FEV_1, and PS. Univariable and multivariable Cox proportional hazard analyses were used to calculate hazard ratios (HRs) and 95% confidence intervals for survival of the various categories. χ^2 tests were used to estimate the p value for trend and heterogeneity, excluding missing value categories.

RESULTS

A total of 20,552 patients were identified, four had missing data on comorbidity and were excluded leaving 20,548 for the analysis. Slightly more men than women were included (53% versus 47%), and the median age at diagnosis was 69 years. For some variables, there were missing data: lung function (FEV_1) was missing for 35%, for cTNM 14% was missing, and histological subtype was missing for 14% of patients (Table 1).

Of the 20,548, 10,270 (50%) had no comorbidity (CCI = 0), 4727 (23%) had a CCI of 1, 3359 (16%) had a CCI of 2, and 2192 (11%) had a CCI of 3 or more. Comorbid conditions and thus CCI appeared to increase with age although low CCI was found in the oldest age group of 80 years or older. The majority of patients had advanced stage disease IIIa (14%), IIIB (13%), and IV (46%). Adenocarcinoma was the most frequent histology (26%) although the number of patients in unspecified categories of non–small-cell lung cancer was high (31%). The most frequent type of initial treatment was radiotherapy (33%) followed by chemotherapy (17%) and chemoradiation (13%). No treatment was recorded as initial treatment for 7563 (37%) patients (Table 1). Frequencies of the various comorbid conditions are shown in Table 2. The most frequent comorbidity was chronic obstructive lung disease found in 10% in LC patients. Also, a history of another cancer than LC was observed in a substantial number (9%).

Table 3 presents ORs for having a specific treatment in relation to CCI, age, and sex, and further adjusted for PS, FEV_1, stage, and histology. With increasing CCI, the odds of having radiotherapy and especially chemotherapy and chemoradiation was significantly reduced. For patients with a CCI of 3 or more, the ORs of having chemotherapy or chemoradiation were 0.54 or 0.61, respectively. For patients older than 70 years, the odds of having chemotherapy or chemoradiation was significantly reduced to such a degree that the ORs for having chemotherapy or chemoradiation for those aged 80 years or more were 0.11 and 0.10 compared with patients younger than 60 years. A slight difference was found for sex with higher chemotherapy and chemoradiation treatment rates for women. In Table 4, odds of receiving radiotherapy is shown by intent of treatment. CCI significantly affected the odds of having curative but not palliative radiotherapy.

Survival was highly influenced by CCI with increasingly poor survival for patients with comorbidity (p for trend < 0.001; Table 5). However, after multivariable adjustment, the difference was attenuated so that the HR for CCI of 3 or more of 1.31 in the univariable analysis was reduced to an HR of 1.10 in the multivariable analysis. Likewise, a strong negative impact of age on survival was found although attenuated when controlled for other factors. Women had a significantly better survival than men ($HR_{univariable} = 0.87$), and this difference was actually more pronounced in the multivariable model ($HR_{multivariable} = 0.81$). PS was strongly associated with survival (p for trend < 0.001), so that patients with a PS of 4 had an $HR_{univariable}$ of 6.54, which was somewhat reduced when adjusted for other factors ($HR_{multivariable} = 4.31$). Some histological subtypes were found to be associated with higher death rates compared with adenocarcinoma, non–small-cell LC, large cell, and not otherwise specified and unknown subtype LC with $HR_{univariable}$ of 1.27, 1.19, and 1.36, respectively. These estimates were attenuated but remained significant after adjustment for other factors. Finally, as expected, stage was a very strong and robust indicator for survival. $HR_{univariable}$ for survival increased gradually up to 4.09 for stage IV (p_{trend} <0.0001). The estimates remained virtually unchanged after adjustment.

Table 6 examines HR for survival for the three treatment categories by CCI and the other main prognostic factors: age, sex, PS, and stage. For patients with radiotherapy as initial treatment, there was actually a trend toward better survival for increasing comorbidity ($p_{trend} = 0.09$) and higher age ($p_{trend} = 0.003$). Again, a significantly better survival was seen in women. Conversely, a worse survival was seen with poor PS and higher stages. Although stage remained very robust after adjustment, somewhat attenuated HRs were seen when PS was adjusted. For chemotherapy, there was a clear trend for poor prognosis being associated with high degree of comorbidity, age, PS, and stage ($p_{trend} \leq 0.001$ for all variables). As earlier, women had better survival than men. For chemoradiation, a modest effect of comorbidity ($p_{trend} = 0.44$) and age ($p_{trend} = 0.02$) was found. Advanced PS and stage were highly strongly

