Original Study

Comorbidity in Patients With Small-Cell Lung Cancer: Trends and Prognostic Impact

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Abstract

The present study is the first on the trends in comorbidity among patients with small-cell lung cancer. In particular, hypertension and pulmonary, cardiac, and vascular disease have become more common. Multimorbidity and cardiac and digestive disease have affected survival in those with limited-stage disease, and cardiac and cerebrovascular disease have decreased the survival of patients with extensive disease. These data are relevant for treatment decisions and patient communication in daily clinical practice.

Introduction: We evaluated the trends in the prevalence of comorbidity and its prognostic impact in a cohort of unselected patients with small-cell lung cancer (SCLC). **Patients and Methods:** All patients (n = 4142) diagnosed with SCLC from 1995 to 2012 were identified from the population-based Netherlands Cancer Registry in the Eindhoven region. **Results:** The prevalence of comorbidity increased from 55% in 1995 to 1998 to 76% in 2011 to 2012 and multimorbidity (ie, ≥ 2 concomitant diseases) from 23% to 51%. The prevalence of a comorbidity increased with age. Among the men, hypertension, cardiac disease, and diabetes, in particular, became more common (increased from 11% to 35%, from 19% to 36%, and from 7% to 18%, respectively). In the women, the rate of pulmonary disease, hypertension, and cardiac disease increased the most (increased from 18% to 30%, from 12% to 28%, and from 11% to 24%, respectively). Multimorbidity was associated with a slightly increased hazard of death, independent of treatment in those with limited-stage SCLC (hazard ratio [HR] for ≥ 2 comorbidities vs. no comorbidities, 1.2; 95% confidence interval [CI], 1.0-1.4). The prognostic effects of multimorbidity resulted from treatment in those with extensive-stage SCLC (HR for ≥ 2 comorbidities vs. no comorbidities, final model, 1.2; 95% CI, 1.0-1.2). The prognostic impact of the specific comorbidities varied, with digestive disease reducing the hazard and cardiac disease increasing the hazard in those with limited-stage SCLC (HR for digestive disease vs. no digestive disease, 0.7 [95% CI, 0.5-0.9], and HR for cardiac vs. no cardiac disease, 1.2 [95% CI, 1.0-1.3]). Also, cardiac and cerebrovascular disease increased the hazard in those with extensive-stage SCLC (HR 1.2 [95% CI, 1.0-1.3] and HR 1.3 [95% CI, 1.1-1.6], respectively). **Conclusion:** Comorbidity among patients with SCLC is very common and has been increasing. Multimorbidity was associated with a slightly increased hazard of death in those with limited-stage SCLC, independent of treatment. However, the prognostic effects in those with advanced-stage SCLC resulted from treatment. Digestive disease favorably affected survival and cardiac disease negatively affected the prognosis for those with limited-stage SCLC, and cardiac and cerebrovascular diseases had a negative prognostic effect for those with extensive-stage SCLC. With the burden of comorbidities in patients with SCLC increasing, more attention to individualized treatment approaches is needed.

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Introduction

Worldwide, lung cancer is the most common cancer in men (1.2 million cases annually) and the fourth most common cancer among women (583,000 cases annually).[1] It is the leading cause of death from cancer. Lung cancer is commonly classified as small-cell lung carcinoma (SCLC) and non–small-cell lung carcinoma (NSCLC). SCLC is a highly aggressive neoplasm and is often diagnosed in the presence of other chronic medical conditions. These comorbidities can complicate the therapeutic options because of, among others, decreased life expectancy, interactions between the comorbidity and the cancer therapy, polypharmacy, and, in the elderly, age-related physiologic changes.[2] The presence of a comorbidity was associated with less aggressive treatment or abstaining from treatment in patients with SCLC.[3] Whether the presence of a comorbidity also affects the prognosis of patients with SCLC is not yet clear, because both negative prognostic effects and the absence of an effect have been reported.[3-5]

The presence of a comorbidity in patients with cancer has not only been associated with increasing age, but also with sex and socioeconomic status.[5-7] Furthermore, the prevalence of a comorbidity could change over time owing to the aging of patients, improved life expectancy, and changing lifestyle habits. Monitoring the presence of comorbidities will improve the awareness of the effect of these diseases, among both clinicians and researchers. However, data on the trends in the prevalence of comorbidities in patients with SCLC are scarce.

In the present study, we evaluated the trends in the prevalence of comorbidities in a large cohort of unselected patients with SCLC during an 18-year study period. We also studied the prognostic effect of comorbidities in these patients and investigated whether these effects resulted from differences in treatment.

Materials and Methods

All patients newly diagnosed with SCLC from 1995 to 2012 in the Eindhoven region of the population-based Netherlands Cancer Registry were included. The Cancer Registry in the Eindhoven region records the data from all patients with cancer in the southern Netherlands, an area with approximately 2.4 million inhabitants (about 15% of the Dutch population) and no academic hospitals. Trained registry personnel actively collected data from the medical records on the patient characteristics, such as sex, birth date, postal code, and comorbidities, and the tumor characteristics, such as the date of diagnosis, tumor type, subsite ("International Classification of Diseases for Oncology"),[8] histologic type, tumor grade, and initial treatment. The stage was recorded according to the TNM classification[9] and the system developed by the Veterans Administration Lung Cancer Study Group (VALSG). In the present study, we classified the tumors as limited (tumor confined to 1 hemithorax, including the contralateral hilus lymph nodes, mediastinum, ipsilateral supraclavicular lymph nodes, and metastases to the ipsilateral lung) and extensive (all other tumors and, among other factors, distant metastases, except for metastases to the ipsilateral lung). This staging was primarily referenced using the VALSG classification and supplemented with the clinical TNM stage (N3 and M1 were classified as extensive and M0 as limited). The quality of the cancer registry data is high owing to thorough training of the registration clerks and a variety of computerized consistency checks at the regional and national levels. Completeness has been estimated to be $\geq$ 95%.[10] Information on the vital status of the patients was obtained from the population registries network, which provides virtually complete coverage of all deceased citizens of The Netherlands. The follow-up data were complete until January 1, 2014. We included all patients diagnosed at 1 of the 10 hospitals in the Eindhoven region.

Socioeconomic status, determined from the individual fiscal data on the economic value of the home and household income, was provided at an aggregated level for each postal code.[11] The socioeconomic status was categorized into tertiles. A separate class was used for postal codes in areas with a long-term care-providing institution.

Treatment was classified as surgery with or without adjuvant therapy (for limited disease), chemotherapy plus radiotherapy, chemotherapy alone, no therapy, prophylactic cranial irradiation, and other (including radiotherapy to the primary tumor, metastasis-directed therapy, and other).

Since 1993, information on the presence of comorbidities was routinely collected for the Eindhoven region of the Netherlands Cancer Registry by screening the patients' previous admissions, letters of referral from and discharge to general practitioners, the

Table 1 Disease Categories for Comorbidity Registered by The Netherlands Cancer Registry in the Eindhoven Region

Disease Category	Comorbid Conditions
Other malignancy	Other malignancy; excluded: basal cell carcinoma and carcinoma in situ of the cervix
Pulmonary disease	Obstructive and restrictive pulmonary disease, lung fibrosis, lung transplantation
Cardiac disease	Myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty of the heart, heart decompensation, angina pectoris, heart valve disease, heart failure, heart transplantation, heart rhythm disorder, pericarditis, cardiomyopathy, pacemaker
Vascular disease	(Deep venous) thrombosis, lung embolus, generalized arterial atherosclerosis, peripheral arterial disease, percutaneous transluminal angioplasty, abdominal aneurysm, abdominal aortic surgery
Cerebrovascular disease	Cerebrovascular accident, hemiplegia, hemiparesis, quadriplegia, carotid surgery (TIA excluded)
Hypertension	Systemic hypertension, portal hypertension
Diabetes mellitus	Insulin dependent, oral medication dependent, diet dependent
Infectious disease	HIV, AIDS, tuberculosis
Digestive tract disease	Ulcer disease, reflux esophagitis, (partial) stomach resection, chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis, inflammatory bowel disease), liver disease, liver transplantation, diverticulitis. Excluded: polyposis coli
Genitourinary disease	Chronic glomerulonephritis, kidney failure, nephrotic syndrome, kidney transplantation, dialysis, pregnant at diagnosis
Muscle, connective tissue and joint disease	Connective tissue disease, sarcoidosis, Wegener's disease, polyarteritis nodosa, systematic lupus erythematosus, rheumatoid arthritis
Central and peripheral nervous system	Dementia, Alzheimer's disease, Parkinson disease, serious psychiatric disease (severe depression, admittance to a psychiatric unit, psychosis, schizophrenia)

Abbreviations: AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; TIA = transient ischemic attack.