Variation in causes of death in patients with non-small cell lung cancer according to stage and time since diagnosis


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Background: Many patients with non-small cell lung cancer (NSCLC) die within the first few years of diagnosis, and considerable excess mortality remains even after 5 years. We investigated the death rate and the distribution of causes of death for NSCLC patients by age and stage at diagnosis during long-term follow-up.

Patients and methods: All 72,021 patients aged 45–89 years diagnosed with stage I–III NSCLC between 1989 and 2008 in the Netherlands and who died up till 2011 were derived from the Netherlands Cancer Registry and linked with the database of Statistics Netherlands for underlying causes of death. Mortality ratios and proportional distribution of causes of death were calculated during 5 time periods after diagnosis of NSCLC (up to 15 years).

Results: Median follow-up was 9.6 years (range: 0–23 years). Lung cancer was the predominant cause of death in the first 6 years after diagnosis (being 80%–85% and ∼90% up to 3 years for localized and locally advanced disease, respectively, and ∼60%–75% and ∼75%–85% during years 4–6 for both stage groups, respectively). Thereafter, lung cancer as cause of death proportionally decreased with time since diagnosis, but remained over 30%. Hence, cardiovascular diseases and chronic obstructive pulmonary diseases (COPD) became more important causes of death, especially for patients aged >60 years at diagnosis (up to 34% for cardiovascular diseases and up to 19% for COPD).

Conclusions: With time, the relative contribution of cardiovascular and COPD causes of death increased, although the absolute contribution of lung cancer remained high in non-metastatic NSCLC. Therefore, managing morbidity of these diseases remains relevant.

Key words: causes of death, conditional survival, excess mortality, long-term, non-small cell lung cancer

Introduction

Lung cancer is still the most important cause of cancer death, representing almost 20% of cancer deaths [1, 2]. More than two-thirds of all lung cancers are non-small cell lung cancer (NSCLC). In the Netherlands, a country with about 16 million inhabitants, almost 9000 new NSCLC cases are diagnosed annually [3]. Five-year relative survival is about 17% [3]. Since NSCLC is very lethal, most studies focus only on the first 5 years after diagnosis, whereas little is known about the proportionally few (but absolutely many) patients who survive the first 5 years. Prognosis for NSCLC patients improves with every additional year survived up to 4–5 years after diagnosis, but an excess mortality of 20–40% compared with the general population remains [4–9]. Since NSCLC mainly occurs in the elderly, and smoking is the crucial risk factor in most patients [10], excess mortality is likely to be due to smoking-related comorbidity, such as chronic obstructive pulmonary diseases (COPD), cardiovascular diseases (CVD) and (other) cancers in the upper respiratory tract. Insights into competing causes of death may help define both treatment policies and surveillance of patients.

We investigated variation in long-term mortality and the distribution of causes of death in patients diagnosed with non-metastatic NSCLC according to stage and time since diagnosis in order to underpin policies for surveillance.

Methods

data collection

Population-based data were used from the nationwide Netherlands Cancer Registry (NCR), which was started in 1989 and is maintained and hosted by
the eight Comprehensive Cancer Centres (which were unified since 2014). The NCR is based on notification of all newly diagnosed malignancies in the Netherlands by the automated pathological archive (PALGA). Although the national registry of hospital discharge diagnoses, which account for up to an extra 8% of new cases is an additional source, unfortunately the causes of death statistics are not. Information on patient and tumour characteristics is obtained routinely directly from the medical records in hospitals and radiotherapy institutes about 6–9 months after diagnosis. The quality of the data is excellent due to thorough training of the registrars and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95% [11]. In addition to passive follow-up via the hospitals, date of death is also retrieved through linkage with the Municipal Personal Records Database (GBA). This database contains all deaths or emigrated persons in the Netherlands since October 1994. For patients diagnosed before October 1994, follow-up was completed by merging with municipality death records or with the Central Bureau for Genealogy, which registers deaths in the Netherlands. Date of death was completed until 31 December 2011. For patients who had died in the study period, causes of death were retrieved by merging the database from the NCR with the causes-of-death database from Statistics Netherlands. Causes of death were classified as lung cancer, another cancer, CVD, pulmonary disease, and other. Data handling of the unidentifiable data from the NCR was done according to the specifications of the officially recognized Code of Conduct Use of data in health research (www.federa.org).

For the present study, all patients aged 45–89 years and diagnosed with primary NSCLC stage I–III in the period 1989–2008 in the Netherlands were included (N = 85 265, of whom N = 73 450 (86%) deceased during follow-up). This study focused on stage I–III patients, because stage IV patients generally had a limited survival (1-year survival about 20% [3]). Patients <45 and >89 years were excluded from the analysis as only 4% of all patients were diagnosed below age 45 and causes of death might be unreliable at older age. After linking our data with the database of Statistics Netherlands, causes of death could be retrieved for 72 021 (98%) of deceased patients (Table 1).

Patients were divided into three groups according to their age (45–59, 60–74 and 75–89 years). The tumour-node-metastasis (TNM) classification according to the edition valid at the time of diagnosis was used. Stage was based on the pathological TNM in patients who underwent surgery. Otherwise, clinical stage was used. Stage was classified as localized (stage I or II) for which mostly surgery and sometimes adjuvant chemotherapy was given and locally advanced (stage III) disease that was most often treated with chemo-radiotherapy, radiotherapy or sometimes with chemotherapy and surgery. The 5 periods after diagnosis were classified as the first year (days 0–364), years 2–3 (days 365–1094), years 4–6 (days 1095–2189), years 7–11 (days 2190–4014) and years 12–16 (days 4015–5839) after diagnosis.

### statistical analyses

For the five periods after diagnosis, the proportional distribution of causes of death and the death rates were assessed according to age and stage. The death rates, as an estimator of death incidence, were computed by dividing the number of deaths by the number of person-years. Person-years were used to correct for censored patients and different lengths of follow-up intervals. With this method, each patient contributes to all time intervals up to and including the one in which they died or were censored (i.e. patient X who died after 2.6 years contributed 1 person-year to the first period and 1.6 person-years to the second period). The death rates were accompanied by 95% confidence intervals (CIs). Calculations were performed with SAS software (SAS system 9.3, SAS Institute, Cary, NC).

#### Results

Median follow-up for the total study population was 9.6 years (5%–95% quantile range: 3.5–17.6 years, total range: 0–23 years). The proportional distribution of causes of death for males and females, respectively, were: 81% versus 83% for lung

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cancer, 5.5% versus 6.9% for another tumour, 5.3% versus 3.6% for cardiovascular, 2.5% versus 2.0% for pulmonary and 5.3% versus 4.6% for other causes. Because gender distribution is almost similar and subgroup analyses would include too small numbers, results of age- and stage-specific analyses were presented for males and females combined. The numbers of deaths as well as the death rates in each interval after diagnosis, according to age and stage, are shown in Table 2. Death rates by sex can be found in the supplementary table, available at Annals of Oncology online. Death rates were highest up to 2 years after diagnosis, being higher for elderly and for locally advanced disease.

**Localized disease (stage I–II)**

Lung cancer was the major cause of death up to 3 years after diagnosis (83% <1 year after diagnosis and 85% in period 2–3 years for patients aged 45–59 and 80% <1 year and 79% 2–3 years for patients aged 60–74 and 82% <1 year and 79% 2–3 years for patients aged 75–89 years) (Figure 1A–C). Lung cancer as the cause of death decreased proportionally with time since diagnosis, but remained important, even after 6 years (varying between 30% and 56% for the different age groups). CVD and COPD became more important causes of death for those who died a longer time after diagnosis, especially for elderly patients (up to 24% for CVD in patients aged 60 or older at diagnosis and up to 19% for COPD).

**Locally advanced disease (stage III)**

As expected, lung cancer comprised a bigger proportion of causes of death up to 3 years after diagnosis (~90%) when compared with localized disease and also remained the major cause of death during period 4–6 years after diagnosis (73%–85%); it decreased thereafter (Figure 1D–F), but remained higher than among patients with localized NSCLC up to 11 years after diagnosis. Again, CVD and COPD became more important for those who died longer after diagnosis (up to 34% for CVD and up to 19% for COPD).

**Discussion**

In our population, almost 30% of all patients with localized NSCLC and more than 60% of patients with locally advanced NSCLC died within 1 year after diagnosis and lung cancer was the overwhelming cause of death during the first 6 years after diagnosis. CVD and COPD became more lethal after longer follow-up, especially among elderly.

Because NSCLC is very common, large absolute numbers of patients survive their primary cancer despite a relatively poor survival rate (about 25 000 prevalent cases in the Netherlands; www.cijfersoverkanker.nl). As such, knowledge about health status during follow-up including the causes of death is important to design rational follow-up schedules in this group of patients who often have serious comorbidity [12].

A previous study has shown that about 90% of cancer patients died of lung cancer [13], as we found in the first years after diagnosis. A study with SEER (Surveillance, Epidemiology and End Results) data has shown that ~50% of deaths in 5-year NSCLC survivors were due to lung cancer [14]. In our study, a similar
outcome was observed, although this proportion was lower among the elderly. As more than 90% of lung cancer patients had contributing causes of death, e.g. emphysema, infection and organ failure, saving a patient from one cause may only lead to another immediate cause of death [15].

The prevalence of comorbidity is high among NSCLC patients [12, 16–21], especially of tobacco-related diseases, such as cardiovascular (25%–30%), COPD (25%–30%) and previous malignancies (~20%) [12, 18, 22, 23]. Therefore, an excess mortality due to comorbidity might play a major role, even though this is probably

Figure 1. Proportional distribution of causes of death for NSCLC patients by disease stage, age and interval after diagnosis. N represents the total number of deaths in the respective interval after diagnosis. Note: Numbers do not add up to 72,021 because period 12–16 years is excluded for age group 75–89 years (number of patients aged 75–89 in years 12–16 after diagnosis too small for reporting valid proportions).
of less importance in the case of a relatively lethal disease as lung cancer [12, 16, 17, 24]. Most patients probably die from NSCLC before they die from the comorbid condition.

Two studies among early-stage NSCLC patients have shown that the probability of dying from lung cancer decreased over time [25, 26] and became equivalent to CVD if patients survived up to 7 years after lobectomy [26]. This point was reached earlier at higher age. We found the same in our study for localized disease. Since mortality from CVD has been decreasing in the Netherlands [27], this point will probably be reached later in more recently diagnosed patients.

Second tumours occur in up to 10% of NSCLC survivors [25, 28, 29], the majority being diagnosed within 2 years [30]. In our study, 4%–6% of patients who died within the first year died due to another cancer, but this proportion increased with time since diagnosis. Ever smokers had about a double risk for second smoking-related cancers when compared with never smokers [31]. As NSCLC survivors are thus at very high risk to develop a second primary [32], it seems logical to offer them surveillance similar to other high-risk patients [33]. This may include low-dose CT screening [34–36].

Because COPD, CVD and second cancers are often smoking-related, as is NSCLC [10, 31], it does not come as a surprise that these disorders account for a substantial proportion of deaths. Smoking cessation programs thus remain essential [37].

**strengths and limitations**

Variations in coding the underlying cause of death could make the attribution of observed causes of death more arbitrary, especially in elderly with comorbidity. However, the reliability of cause of death in the Netherlands was high (>90%) for major causes of death such as cancers and acute myocardial infarction [38].

For evaluating the influence of late side effects of treatment (especially chemotherapy and radiotherapy) on causes of death, it would be interesting to stratify analyses according to treatment. However, in addition to stage and age, this would lead to subgroups that are too small to estimate valid proportions. Many patients received more than one treatment. In addition, most late side effects of treatment might be primarily functional and would often not be lethal and might therefore not be detected by evaluating causes of death. For the interpretation of results, one should take stage migration, changes in TNM classification over time and trends in treatment into account. In the Netherlands, during the included period, surgery increased from 84% to 89% among younger patients (<75 years) and from 35% to 49% among elderly (≥75 years) with stage I; for stage II, this proportion decreased from 80% to 70% in younger patients and remained 25% in elderly patients [3]. Adjuvant chemotherapy for stage II increased from 0% to 24% in younger patients, but remained <5% among the elderly. Chemoradiation increased from 8% to 43% among younger patients with stage III and from 1% to 13% among elderly. In stage IV, chemotherapy in younger patients increased from 10% to 54%, and in elderly from 5% to 21%.

The strength of this study is that all registered Dutch patients with a diagnosis of NSCLC were included, including frail patients and those with poor performance status. We therefore could document cause-specific mortality in a large series of unselected patients reflecting everyday clinical practice. A limitation is that our data are not comparable to studies that have used 5 years (1825 days) as a boundary. In our study, patients who had died during the complete 5th year after diagnosis were included in period 4–6 years after diagnosis. Unfortunately, it was not possible to repeat the analysis using <5 years as boundary for technical reasons. In addition, our study was limited to the use of descriptive statistics as a first approach. Regression analyses are recommended in a second step.

In conclusion, although most patients with NSCLC died within the first few years after diagnosis, long-term excess mortality remained important. Other smoking-related diseases become important competing causes of death with increasing time since diagnosis. Therefore, managing morbidity of these diseases remains relevant.

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**disclosure**

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**references**


