Lung Cancer 108 (2017) 198–204

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Trends in treatment and relative survival among Non-Small Cell Lung Cancer patients in the Netherlands (1990–2014): Disparities between younger and older patients

Elisabeth J. Driessen[a,*], Mieke J. Aarts[b], Gerbern P. Bootsma[c], Judith G. van Loon[d], Maryska L. Janssen-Heijnen[a,e]

[a] Department of Clinical Epidemiology, VieCuri Medical Centre, Venlo, the Netherlands
[b] Netherlands Cancer Registry, Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands
[c] Department of Pulmonology, Zuyderland Medical Centre, Heerlen, the Netherlands
[d] MAASTRO Clinic, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands
[e] Department of Epidemiology, Maastricht University Medical Centre, GROW School for Oncology and Developmental, Maastricht, the Netherlands

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Age
Treatment
Survival
Healthcare
Benefit
Elderly
Trends

ABSTRACT

Background: This study aimed to describe trends over time regarding disparities in treatment and relative survival (RS) between younger and older patients with non-small cell lung cancer (NSCLC).
Methods: All patients diagnosed with pathologically verified NSCLC in 1990–2014 were included from the Netherlands Cancer Registry (n = 187,315). Treatment and RS (adjusted for sex, histology and treatment) were analyzed according to age group (< 70 years versus ≥70 years), stage and five-year period of diagnosis.
Results: Between 1990 and 2014, five-year RS increased from 17 to 22% among younger patients and from 12 to 16% among elderly. The application of surgery increased over time for elderly with stage I NSCLC, decreased for elderly with stage II, and was stable but higher for younger patients. Disparities in RS between age groups with stage I became smaller since 2000–2004, but did not change over time for stage II. For stage III and IV, both age groups showed strong increases over time in chemoradiotherapy and chemotherapy from 2000 onwards, although considerably less among elderly. One-, three- and five-year RS increased more strongly over time for the younger group leading to larger disparities between age groups with stage III or IV NSCLC.
Conclusion: More curative-intent treatment and improved RS for NSCLC were seen over time, but were less profound among elderly. Disparities herein between age groups seemed to become smaller over time for stage I NSCLC, did not change for stage II, and were widening for stage III and IV at the expense of elderly. Future prospective studies should focus on optimizing treatment selection and outcomes for elderly.

1. Introduction

Survival of non-small cell lung cancer (NSCLC) has improved significantly between 1989 and 2009.[1] A Dutch population-based study found that more than 60% of patients with NSCLC younger than 75 years received standard treatment, whereas this was only 20% for those aged 75 years and older.[1] Elderly with NSCLC suffer particularly from smoking-related comorbidities, poor performance status, and inactivity.[2–4] As these factors can affect patient mobility, treatment tolerance and survival, [5–8] older and high-risk patients are often excluded from standard therapy and clinical trials.[9] Therefore, evidence is scarce for curative-intent treatment options in elderly. [10–12] It is unclear whether older patients with NSCLC have taken advantage of new detection and treatment options over time in the same way as younger patients.

This study focuses on describing trends and disparities over time in treatment, relative survival (RS), and the contribution of treatment toward changes in relative excess risk of mortality (RER) between younger and older patients with NSCLC over the last 25 years in the Netherlands, according to patient and tumor characteristics.

2. Methods

Population-based data from the nationwide Netherlands Cancer Registry were used. Since 1989, almost all newly diagnosed cancer patients were included, with a completeness rate of > 95% and

* Corresponding author at: Department of Clinical Epidemiology, VieCuri Medical Centre, P.O. Box 1926, 5900 BX, Venlo, the Netherlands. Tel.: +31 773205093.
E-mail address: research@viecuri.nl (E.J. Driessen).

http://dx.doi.org/10.1016/j.lungcan.2017.04.005
Received 18 January 2017; Received in revised form 13 March 2017; Accepted 7 April 2017

Table 1
Characteristics of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to five-year period of diagnosis and stratified for younger (< 70 years) and older patients (≥70 years).

	Younger patients (n = 105,417)					Older patients (n = 81,898)				
Period of diagnosis demographics	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014
Total *n*	18,484	19,219	19,723	22,703	25,288	14,255	14,667	15,178	17,911	19,887
Sex *n (%)*										
Male	14793 (80)	14147 (74)	12959 (66)	13339 (59)	14793 (80)	12652 (89)	12423 (85)	11928 (79)	13109 (73)	13655(69)
Female	3691 (20)	5072 (26)	6764 (34)	9364 (41)	3691 (20)	1603 (11)	2244 (15)	3250 (21)	4802 (27)	6232 (31)
Median age yrs	62	62	60	61	62	75	75	75	75	76
Histology *n(%)*										
Squamous CC	8709 (47)	7575 (39)	6270 (32)	5699 (25)	6153 (24)	8179 (57)	7156 (49)	6066 (40)	6113 (34)	7152 (36)
Adenocarcinoma	5540 (30)	6567 (34)	7162 (36)	9553 (42)	14399 (57)	2886 (20)	3632 (25)	4179 (28)	5866 (33)	8877 (45)
Large CC	2608 (14)	3782 (20)	4410 (22)	4392 (19)	2064 (8)	1866 (13)	2775 (19)	3377 (22)	3477 (19)	1559 (8)
Other NSCLC	1627 (9)	1295 (7)	1881 (10)	3059 (13)	2672 (11)	1324 (9)	1104 (8)	1556 (10)	2455 (14)	2299 (12)
Stage *n (%)*										
I	4219 (23)	4079 (21)	3426 (17)	3940 (17)	3881 (15)	4077 (29)	3998 (27)	3181 (21)	3621 (20)	3355 (17)
II	1298 (7)	1325 (7)	1471 (7)	1379 (6)	2099 (8)	781 (5)	770 (5)	1020 (7)	1074 (6)	1934 (10)
III	7043 (38)	7252 (38)	6522 (33)	6540 (29)	6354 (25)	5053 (35)	5330 (36)	5261 (35)	5574 (31)	4942 (25)
IV	5199 (28)	5968 (31)	7970 (40)	10621 (47)	12843 (51)	2935 (21)	3455 (24)	5138 (34)	7354 (41)	9481 (48)
Unknown	725 (4)	595 (3)	334 (2)	223 (1)	111 (0.5)	1409 (10)	1114 (8)	578 (4)	288 (2)	175 (1)

Abbreviations % 'Percentage', CC 'Cell carcinoma', *n* 'Number', NSCLC 'Non-small cell lung cancer', yrs 'Years'.
All demographics differed significantly between periods of diagnosis within age groups ($P < 0.0001$).

complete national coverage. Trained registrars routinely collect data from medical records such as patient and tumor characteristics and primary treatment. According to the Central Committee on Research involving Human Subjects (CCMO), this type of study does not require approval from an ethics committee in the Netherlands. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry.

Information on all patients with primary invasive lung cancer between 1990 and 2014 was retrieved. Patients with small cell lung cancer, carcinoid tumors, absence of pathological verification, or incidental diagnosis at autopsy were excluded (Supplementary Figure 1). The International Classification of Disease for Oncology (ICD-O) was used to code topography (C34) and morphology (invasive 8010-8020, 8022-8035, 8046-8230, 8243-8246, 8250-8576, 8972, 8980-8982 and 9110). Between 1986 and 1992, the first edition was used, [13] and between 1993 and 1994 an adapted version for the Netherlands became available (ICD-O "N").[14] The second edition was also adapted for the Netherlands and handled between 1995 and 2000 (ICD-O2).[15] Since 2001, the third edition adapted for the Netherlands was handled, including the updates to the International Classification of Diseases for Oncology since 2012 (ICD-O3).[16,17] Tumor Node Metastases (TNM) guidelines [18] were used for tumor staging and derived from the postsurgical TNM and supplemented with the clinical TNM. At the Netherlands Cancer Registry, edition 4 of the TNM guidelines was applied up to 1992, edition 4 (second edition) from 1993 to 1998, edition 5 from 1999 to 2002, edition 6 from 2003 to 2009 and edition 7 from 2010 onwards. Stage of disease was classified as I, II, III, IV or unknown. Unknown stage of disease was not further issued for analyses. Histology was sub-classified as adenocarcinoma, squamous cell carcinoma, large cell carcinoma and other NSCLC (including not otherwise specified NSCLC).[19] Age was categorized as younger patients (< 70 years), and older patients or elderly (≥70 years). This demarcation point was chosen since the incidence of age-related changes sharply increases in those aged 70 years and older.[20] Years of diagnosis were divided into five-year periods from 1990 to 2014. Primary treatment was categorized as surgery with or without (neo)adjuvant therapy, radiotherapy (RT), chemotherapy (CT), chemoradiotherapy (CHRT, including radiotherapy with sensitizer, CT prior to RT, or RT prior to CT), best supportive care (BSC), other (including targeted therapy) and unknown. Concurrent and sequential CHRT could not be distinguished for analyses, as time between treatments was often unavailable, especially in earlier years. Curative-intent treatment included surgery (with or without (neo)adjuvant therapy) and CHRT. RT has not been included as curative-intent treatment as radical and palliative RT could not be distinguished for all patients. Information on vital status was initially obtained from municipal registries and hospitals and since 1995 from the nationwide population registries network. Follow-up was completed and calculated from the time of diagnosis until death or until February 1, 2016. RS was displayed as median, one-year and five-year RS rate. For stage IV NSCLC, three-year instead of five-year RS rate was displayed. RS was considered a proxy for lung cancer-specific survival, as it is divided by age and sex-specific overall survival of the general Dutch population, thereby eliminating the effect of other causes of death.

Multivariable RS analyses, using Poisson regression modeling, [21] were performed to calculate the specific Relative Excess Risk (RER) of death estimates with corresponding 95% Confidence Intervals (95% CI). The RER displays trends of the risk of mortality for the given period compared to the reference period 1990–1994. These trends are compared between younger and older patients and stratified by stage. Adjustments for the influence of sex and histology were performed in model 1. Additional adjustment for treatment was performed in model 2 in order to investigate the effect of treatment on the RER of mortality over time. When model 1 and 2 are compared, and the RER moves more toward 1.0 by ≥ 0.10 after additional adjustment for treatment, differences in RER became smaller compared to the reference group and might be explained by treatment. This means that treatment might have contributed to decreased excess risk in the given time period. Whether disparities between age groups are widening or narrowing over time was determined by comparing age groups with respect to trends in proportions of curative-intent treatment, improvements in RS, changes in RER (model 1), and the contribution of treatment on these changes (model 2). All analyses were performed using SAS 9.4.

3. Results

In the Netherlands, 187,315 patients were diagnosed with NSCLC between 1990 and 2014 of whom 44% was aged ≥70 years. Over time, the proportion of males was highest and decreased less in older compared to younger patients (Table 1). Squamous cell carcinoma occurred more frequently among elderly and decreased in both age groups over time, whereas adenocarcinoma increased over time. The