Trends in treatment and relative survival among Non-Small Cell Lung Cancer patients in the Netherlands (1990-2014)

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

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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

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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

Table 2
Administered treatment options of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to five-year period of diagnosis, stage of disease and stratified for younger (< 70 years) and older patients (≥70 years).

		Younger patients (n = 105,417)					Older patients (n = 81,898)				
Stage	Period of diagnosis treatment***	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014
I	Surgery*	3237 (77)	3243 (80)	2758 (81)	3159 (80)	3088 (80)	1842 (45)	1918 (48)	1688 (53)	2051 (57)	1849 (55)
	RT	495 (12)	405 (10)	238 (12)	325 (16)	582 (15)	1204 (30)	1116 (28)	771 (24)	904 (25)	1164 (35)
	BSC	291 (7)	321 (8)	183 (5)	152 (4)	101 (3)	905 (22)	901 (23)	599 (19)	485 (13)	259 (8)
II	Surgery*	1064 (82)	1109 (84)	1066 (72)	989 (72)	1568 (75)	482 (62)	500 (65)	529 (52)	539 (50)	960 (50)
	RT	78 (6)	78 (6)	102 (7)	82 (6)	121 (6)	151 (19)	139 (18)	250 (25)	227 (21)	467 (24)
	BSC	47 (4)	86 (6)	64 (4)	55 (4)	87 (4)	105 (13)	111 (14)	171 (17)	167 (16)	275 (14)
III	CHRT	102 (1)	541 (7)	1674 (26)	2421 (37)	3068 (48)	14 (0)	102 (2)	520 (10)	1044 (19)	1336 (27)
	Surgery*	1181 (17)	1120 (15)	795 (12)	763 (12)	879 (14)	484 (10)	504 (9)	404 (8)	434 (8)	448 (9)
	RT	3821 (54)	3047 (42)	1199 (18)	540 (18)	389 (6)	2680 (53)	2456 (46)	1701 (32)	1017 (18)	929 (19)
	CT	322 (5)	1027 (14)	1664 (25)	1764 (27)	1164 (18)	55 (1)	172 (3)	553 (11)	905 (16)	666 (13)
	BSC	1272 (18)	1311 (18)	1041 (16)	866 (13)	647 (10)	1627 (32)	1893 (36)	1905 (36)	1927 (35)	1436 (29)
IV	CT	426 (8)	1057 (18)	2534 (32)	3924 (37)	4543 (35)	53 (2)	179 (5)	798 (16)	1499 (20)	1979 (21)
	RT**	1405 (27)	1068 (18)	776 (10)	615 (6)	551 (4)	722 (25)	663 (19)	655 (13)	552 (8)	642 (7)
	Other	275 (5)	120 (2)	128 (2)	318 (3)	519 (4)	135 (5)	73 (2)	108 (2)	288 (4)	424 (5)
	BSC	2842 (55)	3463 (58)	4044 (51)	5226 (49)	6664 (52)	1949 (66)	2448 (71)	3402 (66)	4843 (66)	6239 (66)

Numbers are displayed as number with percentages (%); Abbreviations BSC 'Best supportive care', CHRT 'Chemo-radiotherapy', CT 'Chemotherapy', n 'Number', RT 'Radiotherapy', yrs 'Years'.

* with or without (neo)adjuvant therapy.

** RT on primary tumor.

*** Patients can receive combinations of treatments; cumulated percentages could be lower than 100% as treatment options with low proportions were not included in this table.

proportion of stage IV NSCLC increased strongly from 2000 to 2004, while stage I and III decreased slightly in both age groups. Over time, curative-intent treatment was more often administered in all patients, although this remained clearly lower among elderly (Table 2). Between 1990 and 2014, five-year RS increased from 17 to 22% among younger patients, and from 12 to 16% among elderly (Fig. 1, median RS displayed in Supplementary Table 1). Also, the RER in both age groups was significantly lower in 2010–2014 as compared to 1990–1994, even after adjustment for sex, histology and treatment. These decreases in RER over time were slightly stronger for younger patients compared to elderly (Table 3). Detailed results of all stages of NSCLC are described below.

For stage I, both the application of surgery and RT increased slightly over time, whereas BSC decreased noticeably. Despite strong increases over 25 years, elderly received remarkably less surgery compared to the younger group. One-year RS increased relatively more over time among elderly, even as for five-year RS. From 2000 to 2004, the RER decreased significantly compared to 1990–1994 in both age groups. In 2010–2014, the RER was significantly lower among older (RER 0.49) compared to younger patients (RER 0.62). After additional adjustment for treatment, differences in RER between younger and older patients disappeared (Table 3, model 2).

For stage II, the proportion of patients undergoing surgery decreased from 2000 to 2004 onwards. Elderly underwent considerably less surgery, more RT, and more BSC compared to younger patients. Initially, RS increased relatively more over time among younger patients, but elderly seemed to catch up from 2005 to 2009. The RER decreased significantly from 2005 to 2009 and this decrease was more pronounced in younger compared to older patients, even after adjustment for treatment (RER 0.58 for < 70 and RER 0.73 for ≥70 (Table 3, model 2)).

For stage III, the application of CHRT increased strongly from 2000 to 2004 but remained considerably lower among elderly. The proportion of patients in both age groups undergoing surgery remained stable over time, CT increased, and RT decreased, whereas BSC decreased in younger patients only. The improvement in RS over time was more pronounced in younger compared to older patients. Although the RER decreased over time in both age groups, this was stronger among younger (RER 0.54) compared to older patients (RER 0.61 (Table 3, model 1)). This difference disappeared after adjustment for changes in treatment over time (2010–2014: RER 0.78 for < 70 and 0.81 for ≥70 (Table 3, model 2)).

For stage IV, both age groups received CT considerably more from 2000 to 2004. However, elderly received BSC more often than younger patients. Median, one-year and three-year RS increased from 2000 to 2004 in both age groups, although this increase was stronger among younger patients. Decreases in the RER over time were seen in both age groups, but were stronger among younger patients (RER 0.65 for < 70 and 0.70 for ≥70 (Table 3, model 1)). After adjustment for changes in treatment over time, the decrease in RER over time remained stronger for younger patients (RER 0.72 for < 70 and 0.82 for ≥70 (Table 3, model 2)).

4. Discussion

The aim of this study was to describe trends and disparities in treatment patterns, RS, and the contribution of treatment toward changes in RER over time between younger and older patients with NSCLC according to patient and tumor characteristics. In stage I–III, curative-intent treatment was administered more often over time, even as CT for stage IV NSCLC. Also, RS improved considerably over time, both in the total group as in all separate stages. Overall, these trends were less pronounced among elderly, [22,23] which might be explained by high-risk characteristics, [6,8] therapeutic nihilism by high age, [24] lack of evidence for treatment options due to exclusion of elderly in trials, and slow accrual in studies specifically aimed at elderly.[5,9,25] Patients could also prefer less intensive treatment, as good quality of life is cherished instead of longer survival time.[5,26] A previous population-based study found promising trends in progress for patients with NSCLC over time up to 2009.[1] Our study indicated continued progress in curative-intent treatment, RS, and RER adjusted for treatment in 2010–2014, although less profound among elderly.

The increasing incidence of NSCLC diagnoses from 2000 to 2004 could be explained by the rise in popularity of smoking 30–40 years prior.[27] However, cancer is a disease of the elderly and the expanding population as well as ageing will have contributed to higher cancer incidence over time.[28] Increases in curative-intent treatment and RS could be explained by improvements in detection and treatment options over time. Furthermore, increased awareness of worthwhile treatment options and the availability of treatment guidelines in the Netherlands

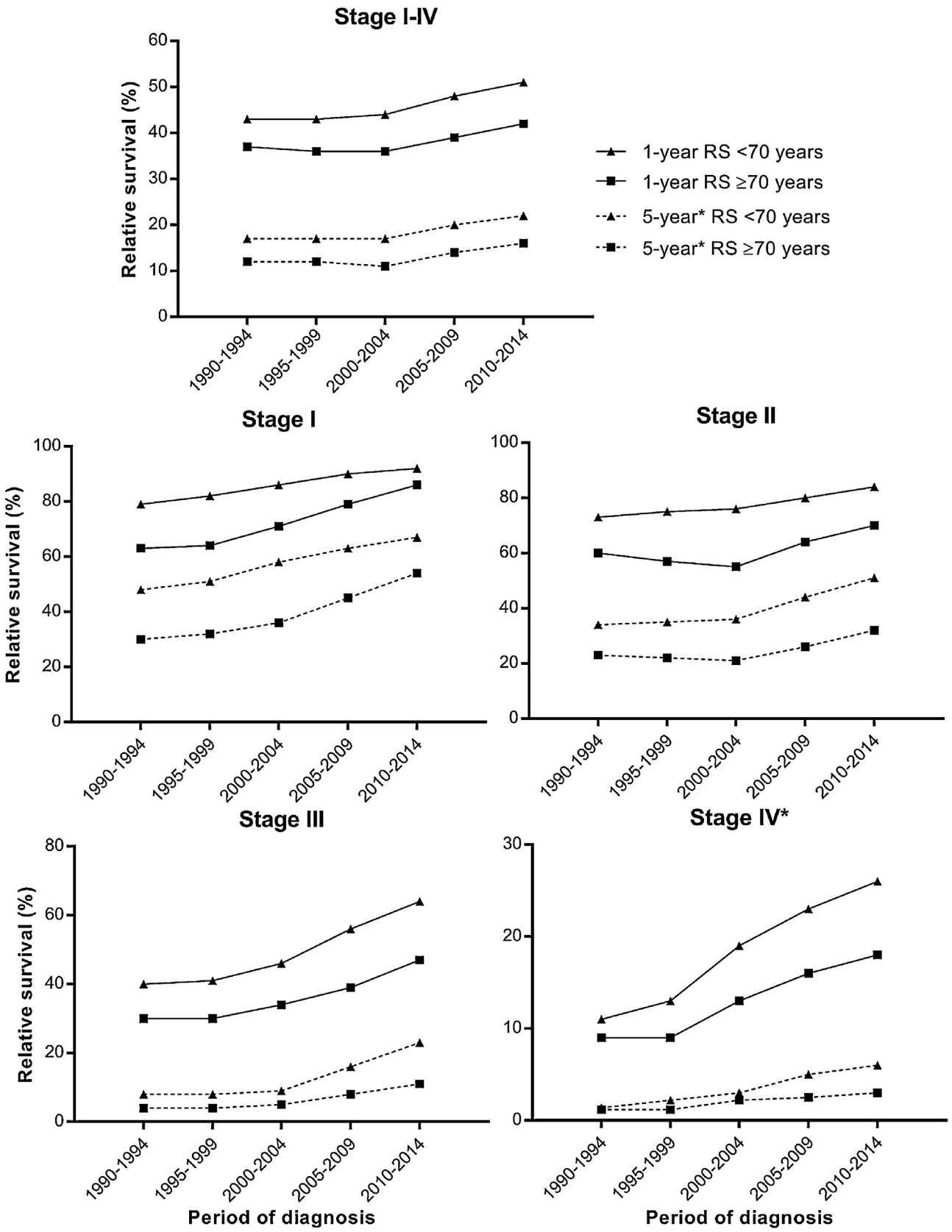

Fig. 1. Relative survival rates of all patients diagnosed with non-small cell lung cancer between 1990 and 2014 in the Netherlands according to five-year period of diagnosis, stage of disease and stratified for younger (< 70 years) and older patients (≥70 years) *three-year relative survival for stage IV.

Table 3
Multivariate relative survival with relative excess risk 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 stage of disease, and stratified for younger (< 70 years) and older patients (≥70 years).

Stage	Period of diagnosis	Younger patients (*n* = 105,417)				Older patients (n = 81,898)			
		Model 1		Model 2		Model 1		Model 2	
		RER	95% CI	RER	95% CI	RER	95% CI	RER	95% CI
All	1990–1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995–1999	0.98	0.96–1.00	0.95	0.93–0.98	0.98	0.95–1.01	1.02	0.99–1.04
	2000–2004	0.94	0.92–0.97	0.96	0.94–0.98	0.97	0.95–1.00	1.03	1.01–1.06
	2005–2009	0.82	0.80–0.84	0.81	0.79–0.82	0.82	0.80–0.84	0.91	0.89–0.93
	2010–2014	0.92	0.90–0.94	0.81	0.79–0.83	0.89	0.87–0.92	0.90	0.88–0.93
I	1990–1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995–1999	0.93	0.87–1.00	0.87	0.82–0.93	0.95	0.89–1.00	0.93	0.87–0.98
	2000–2004	0.76	0.71–0.82	0.78	0.72–0.83	0.81	0.76–0.87	0.85	0.80–0.91
	2005–2009	0.66	0.61–0.71	0.62	0.58–0.83	0.58	0.64–0.62	0.64	0.60–0.68
	2010–2014	0.62	0.57–0.67	0.54	0.50–0.58	0.49	0.45–0.53	0.49	0.45–0.53
II	1990–1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995–1999	0.95	0.86–1.05	0.84	0.76–0.93	1.04	0.92–1.19	1.04	0.92–1.19
	2000–2004	0.92	0.84–1.02	0.87	0.79–0.97	1.08	0.95–1.21	1.08	0.96–1.22
	2005–2009	0.72	0.65–0.80	0.66	0.59–0.74	0.85	0.75–0.96	0.82	0.73–0.93
	2010–2014	0.63	0.57–0.70	0.58	0.53–0.65	0.80	0.71–0.90	0.73	0.65–0.82
III	1990–1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995–1999	0.98	0.95–1.02	1.02	0.99–1.06	0.97	0.93–1.01	0.98	0.94–1.03
	2000–2004	0.86	0.83–0.89	1.07	1.03–1.12	0.86	0.82–0.90	0.97	0.93–1.01
	2005–2009	0.63	0.61–0.66	0.88	0.85–0.92	0.69	0.66–0.72	0.87	0.83–0.91
	2010–2014	0.54	0.52–0.57	0.78	0.74–0.81	0.61	0.58–0.63	0.81	0.77–0.85
IV	1990–1994	*Ref*		*Ref*		*Ref*		*Ref*	
	1995–1999	0.90	0.86–0.93	0.92	0.89–0.96	0.96	0.91–1.01	0.98	0.93–1.03
	2000–2004	0.73	0.70–0.76	0.84	0.81–0.87	0.78	0.75–0.82	0.91	0.86–0.95
	2005–2009	0.63	0.61–0.65	0.72	0.69–0.74	0.71	0.68–0.74	0.83	0.80–0.87
	2010–2014	0.65	0.63–0.67	0.72	0.70–0.75	0.70	0.67–0.74	0.82	0.78–0.86

Numbers are displayed as N 'number' with 95% CI '95% confidence interval'; Abbreviations Ref 'Reference'; Model 1 adjusted for sex and histology; Model 2 adjusted for sex, histology and treatment.

from 2000 to 2004, could partly explain these increases as well. Nevertheless, stage migration (the so-called Will Rogers phenomenon) might also play a role, [29,30] and could lead to selection of good prognosis patients and upstaging of those with worse prognosis. This could result in seemingly more curative-intent treatment and improved survival for separate stages. However, RS in the current study increased for all patients independent of stage. This was somewhat more pronounced for younger patients (5% increase in five-year RS over time) as compared to elderly (4% increase in five-year RS over time). Furthermore, changes in the classification of stage of NSCLC by TNM guidelines over 25 years may also have impacted available treatment options and prognosis for each stage and both age groups.[31]

For stage I, the application of surgery and RT among elderly increased over time, even as RS. Extensive collaboration between medical specialties for treatment decision-making and the influence of patient's wishes could have contributed.[32] Also, stage migration and revisions by the seventh edition of TNM guidelines could have resulted into selection of patients with a predominantly good prognosis, as those with stage IB and worse prognosis were upstaged to stage IIA, leading to seemingly more curative-intent treatment and improved RS. [33] Although advances in treatment options like the rising application of Video Assisted Thoracic Surgery and Stereotactic Ablative Radiotherapy[34] could explain improved RS, especially for older patients, this could not be confirmed yet.[35] Together, elderly seem to be catching up on younger patients and disparities became smaller over time for patients with stage I NSCLC.

For stage II, surgery decreased but remained the most often-administered treatment option for both age groups. The application of RT and BSC were higher among elderly as compared to the younger group. Patients migrated up to stage II from stage IB since 1999, [36] and down from stage IIIA since 2010, [33] leading to a heterogeneous patient group. This could explain lower resection rates, [1] and increased application of CHRT up to 9 and 7% among younger and older patients in recent years, respectively. Although younger patients showed earlier improvements in one-year RS, elderly seem to catch up modestly, whereas the contribution of treatment for changes in RS remains uncertain in both age groups. Nevertheless, disparities did not change over time for stage II NSCLC.

For stage III, the introduction and increasing application of CHRT could have led to improved RS and decreased RER in younger patients, as implementation increased sharply from 2000 to 2004 onwards. Although the application of CHRT also increased among elderly, this remained considerably lower compared to younger patients. Awareness of treating older patients is rising in recent years, whereas treatment options remain limited in vulnerable patients.[11,37] This might be explained by lack of evidence for treatment options in older and vulnerable patients,[38] patients not being fit enough, fear of adverse events or patients' refusing therapy.[37] Also, the implementation of the PET/CT-scan and upstaging of stage IIIB could have led to migration of those with worse prognosis to stage IV and thus contributed to improved survival for patients with stage III and IV over time. [30,33,39] Together, increased use of curative-intent treatment seemed to contribute to improved RS and RER. However, less improvement was seen for treatment and RS among elderly, leading to widening disparities between age groups for stage III NSCLC.

For stage IV, BSC remained the most common administered treatment for both age groups. The application of CT increased strongly over time, although considerably less among elderly. This could be explained by CT becoming standard treatment for stage IV NSCLC in Dutch guidelines since 2004, with elderly benefiting slightly later.[40] Previous increases in the administration of CT could be assigned to positive results in clinical trials, leading to earlier application in clinical practice. Still, the proportion of CT was expected to be higher in younger patients, as was seen in a previous study of the Netherlands Cancer Registry.[41] Our results affirm that decreased RER over time seems to be explained partially by increased application of CT.

However, it should be considered that diagnosis by PET/CT scan were recommended by Dutch guidelines for the diagnosis and treatment of lung cancer since 2004 in order to identify previously undetected metastases, [42] and together with changing TNM-guidelines [31,33] considerably more patients with stage IV and a relatively good prognosis were diagnosed.[31]This might partially explain increased one-year RS among stage IV patients as well.[43] Better survival could also be explained by those with single organ metastases having a favorable prognosis, especially in case of low TN status.[44] Nevertheless, improvements in three-year RS were scant in both age groups. As poor performance status and comorbidities can contraindicate CT, it was expected that elderly showed less improvements over time.[2] Targeted therapies and other promising treatments are emerging, but concern a small proportion of patients and were not further issued in this study. Although increases in the administration of CT and improvements in one-year RS were seen for younger patients, disparities between age groups were widening for treatment, RS, RER and the RER adjusted for treatment among those with stage IV NSCLC.

Strengths of this study are the nationwide coverage of Dutch patients diagnosed with NSCLC from 1990 to 2014 and the large number of patients included (n = 187,315), without exclusion of specific subgroups. Also, this is the first population-based study describing treatment patterns and RS focusing on disparities between patients aged < 70 years and ≥70 years with NSCLC over a period of 25 years. Nevertheless, certain limitations should be mentioned. Some information could not be extracted from the medical records. For instance, smoking habits, and social factors were unknown and comorbid conditions and performance status were unavailable for most patients, which could provoke unknown biases.[2,37] Treatment details like start and end dates, type of CT and type of RT were often lacking, especially in earlier years. As a result, concurrent and sequential CHRT as well as conventional RT and stereotactic RT could not always be distinguished. In earlier years, CHRT was coded by CT and RT separately. In more recent years, a distinctive code for CHRT was implemented at the Netherlands Cancer Registry. As acquired treatment was retrieved and toxicity data were not available, it is possible that combined treatments such as CHRT were intended in clinical practice, while toxicities inhibited further treatment, leading to the administration of CT only instead of (intended) CHRT in clinical practice. This could explain the relatively high rate of CT as compared to CHRT for patients with stage III NSCLC, as treating these patients by CT only is uncommon practice and not logical.[37,45] Also, TNM classification guidelines could have been adopted earlier for treatment decision-making in clinical practice (the fifth and seventh editions became available in 1997 and 2009, respectively), than they were implemented at the Netherlands Cancer Registry (in 1999 and 2010, respectively). Nevertheless, it was assumed that this equally impacted older and younger patients. Follow-up was completed until February 2016, leading to smaller proportions of patients diagnosed in 2012–2014 with complete five-year follow-up. Also, censoring could occur more among younger patients with stage I and II NSCLC.

In order to maximize treatment effects and continue progress in curative-intent treatment and RS for all patients in the future, vulnerable patients within the older and entire population of NSCLC should be distinguished more carefully. Upcoming prospective studies should include older and vulnerable patients as well, and incorporate predictive patient and tumor factors such as comorbidity and additional geriatric information for older patients. This is essential to optimize treatment selection and survival for all patients with NSCLC.

In conclusion, this population-based study gained insights into age-specific trends in clinical practice and subsequent disparities between older and younger unselected patients with NSCLC. The application of curative-intent treatment and RS increased over time for all patients, but remained less profound among elderly. Although improvements in RS for specific stages could be explained by alterations in staging procedures and guidelines for treatment over time, significant improvements in both RS and RER were seen for the whole patient group. Disparities between older and younger patients in patterns of treatment and RS over time seemed to narrow for patients with stage I NSCLC, did not change for stage II, and became wider for patients with stage III and IV at the expense of elderly. Future prospective studies should specifically focus on predictive factors to optimize selection of elderly for curative-intent treatment in order to improve survival.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2017.04.005.

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