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Temporal trends and spatial variation in stage distribution of non-small cell lung cancer in the Netherlands

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Abstract

Introduction

To explore regional and temporal variation in clinical stage distribution of non-small cell lung cancer (NSCLC) and link the observations to the introduction of positron emission tomography (PET).

Method

All NSCLC patients diagnosed between 1989 and 2007 were selected from the Netherlands Cancer Registry (n=126,962). Maps of smoothed percentage distribution of clinical stage NSCLC were conducted by period of diagnosis. Join point regression analyses were performed to detect trends over time. Geographic variation in stage distribution was evaluated using spatial scan statistic. To evaluate the impact of PET in regions proportions of stage IV and Estimated Annual Percentage of Change (EAPC) were calculated for two regions in which PET was introduced between 1995 and 2000 and for two regions without a PET scanner during this period.

Results

The percentage of stage I and unknown decreased with 7.4% and 13.3% between 1989 and 2007, while the percentage of stage IV increased with 23.4%. The most rapid increase in stage I and IV were observed between 1997 and 2003. In two regions with a PET scan the proportion of stage IV increased annually with 10.3 and 8.5% compared to 5.4 and 6.4% in two regions without a PET scan.

Conclusion

The most rapid changes towards more stage IV NSCLC diagnoses correspond with the implementation of PET. However, trends were already visible before PET was introduced and regions without PET also showed considerable increases in stage IV diagnose, suggesting other factors or improvements in diagnostics also contributed substantially.

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Introduction

More than 8.000 new patients are diagnosed with non-small cell lung cancer (NSCLC) in the Netherlands each year [1]. NSCLC accounts for approximately 80% of the total number of all newly diagnosed lung cancer cases.

Accurate staging is essential for choosing the optimal treatment strategy and estimating prognosis. Most patients with NSCLC are diagnosed in an advanced stage, conferring a poor prognosis. In the Netherlands the overall five-year relative survival rate, survival compared to the survival of the general population of corresponding sex and age, for NSCLC was 16% for patients diagnosed between 2004 and 2008. The five-year relative survival ranged from 65% when diagnosed at TNM stage IA to 2% when diagnosed with TNM stage IV NSCLC[1, 2].

Stage at diagnosis of lung cancer is associated with several factors. Men and young patients are more likely to present with advanced lung cancer than women and older patients. Less advanced stage diagnosis in elderly might be the result of less accurate diagnosis as invasive diagnostic techniques are less frequently used in elderly compared to younger patients [3,4]. In several countries rural patients are more likely to be diagnosed with advanced stages of lung cancer [5,6,7], whilst a higher socio-economic status (SES) is associated with more local stage disease [3]. Furthermore, lung cancer stage at diagnosis has been associated with tumour histology, smoking status, education level, and screening behaviour [4, 8,9,10].

The accuracy of staging strongly depends on the available diagnostic methods. A major improvement in diagnostics of NSCLC during the last decades has been the implementation of PET (Positron Emission Tomography) scanning. Currently, PET has an important role in mediastinal preoperative staging in NSCLC which is described in the guidelines for preoperative lymph node staging in NSCLC [11,12]. The widespread use of FDG-PET has been linked to shifts in stage distribution of NSCLC. Several studies indicated a higher accuracy of FDG-PET in detecting lymph-node involvement as well as distant metastases, resulting in the detection of more advanced stage diagnoses [13]. In the Netherlands the first PET scanner was implemented in the University Medical Centre

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Groningen in 1991. In the first years this scanner was mainly used for scientific research. Around 1996 the scanner was used for patient care. In 1997 a second PET-scanner came available in Amsterdam (VU University Medical Centre) and in 1998 the University Medical Centre of Nijmegen also implemented a PET-scanner for clinical use. Between 2000 and 2007 the number of PET-scanners in the Netherlands increased from 3 to 25.

In the United States stage shifts towards more advanced stage lung cancer have been observed, which were linked to the introduction of PET [14,15]. Due to the variation in the time of implementation of PET in the different Dutch regions we hypothesized that regional variation in clinical stage distribution is present due to the distribution of PET scanners. Within this study we provide an overview of changes and geographical differences in clinical stage distribution of NSCLC in the Netherlands over the years and relate this to the implementation of new imaging techniques in clinical practice.

Materials and Methods

Netherlands Cancer Registry (NCR)

The Netherlands Cancer Registry (NCR) is a population-based registry in which almost all newly diagnosed tumours are registered (completeness>95%) [16]. The NCR has a complete national coverage since 1989. Notification is mainly obtained from the Automated Pathology Archive (PALGA) and completed by the National Registry of Hospital Discharge and Radiotherapy Departments, which accounts for up to 8% of all new cases [17]. After notification, specially trained registrars collect data from patient files in the hospital. Information on patient characteristics (e.g. gender, date of birth, residence), tumour characteristics (e.g. localisation, histological type, tumour stage) and treatment are recorded. Topography and morphology are coded according the International Classification of Disease for Oncology (ICD-O) [18] and tumours are staged according to the TNM-classification [2].

Patient selection

All patients diagnosed with NSCLC in the Netherlands between 1989 and 2007 were selected from the NCR. Non-small cell lung tumours were classified as squamous cell carcinoma, adenocarcinoma, large cell carcinomas, adenosquamous carcinoma, sarcomatoid carcinoma and salivary gland carcinoma, according the WHO classification [18].

Geographical mapping

For each municipality in the Netherlands in 2007 (n=443) the percentage share of all clinical stages to the total number of NSCLC patients was calculated by sex and year of diagnosis. The percentages were mapped according to the mapping method developed by the Finnish Cancer Registry. The smoothing method was used aimed at deleting the random variation typical to observations based on small populations by showing their floating averages [19]. Cities with more than 100,000 inhabitants were presented as coloured circles on the maps. The radius of the circle indicates the size of the population and the colour indicates the percentage. For each 500m by 500m grid, a weighted average of the percentages of the neighbouring municipalities within a 100km radius was calculated to define the colour of that grid. The rates were directly weighted with the population size of the municipality and inversely weighted in relation to the distance. The percentage share of all stages was mapped for four different time periods (1989-1994, 1995-1998, 1999-2002 and 2003-2007).

Statistical analyses

Changes in tumour and patient characteristics over time were evaluated using chi-square tests.

Changes in proportional stage distribution in the Netherlands were evaluated calculating the estimated annual percentage change (EAPC) and the corresponding 95% confidence interval (CI). Estimated annual percentage

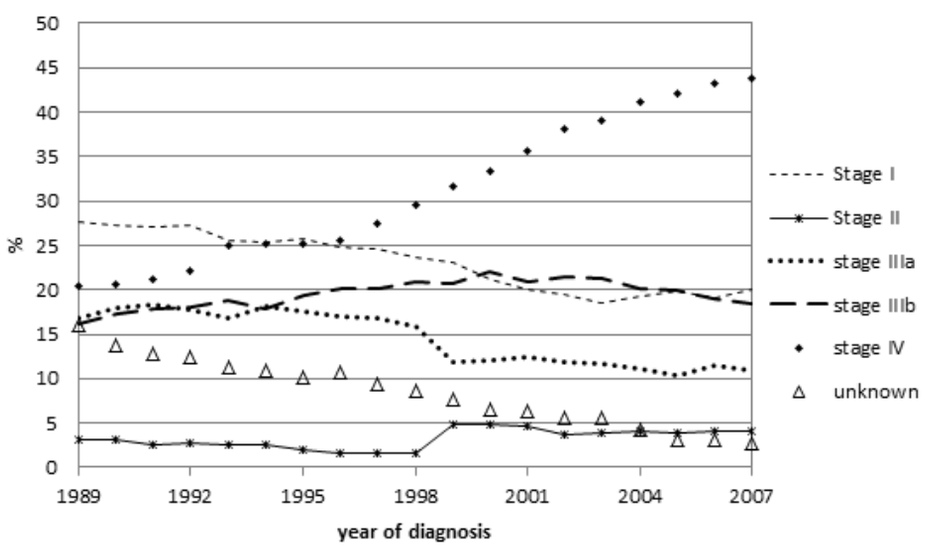

Figure 1: stage distribution of NSCLC in the Netherlands 1989-2007.

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changes were calculated for the whole Netherlands. Changes were also calculated for the period 1995-2001 for two regions where PET was introduced during this time period (Groningen region and Amsterdam region) and for two regions which did not have a PET scanner during this time period. Analyses were performed for each stage separately. The join point regression models were performed using the Joinpoint Regression Program (version 3.5) from the Surveillance Research Program of the US National Cancer Institute (http:surveillance.cancer.gov/joinpoint/). Spatial Scan Statistic's (SaTScan) Bernouilli model was used to identify clusters of municipalities in the Netherlands with high or low proportion with a specific clinical stage of NSCLC 20. The null hypothesis of complete spatial randomness was tested against the hypothesis of one of more areas with a higher or lower percentage of a specific stage of NSCLC. Patients with a certain stage were defined as cases, while all patients with other stages were defined as controls. The test was considered to be significant at the 0.05 level. The maximum spatial cluster size was set to 25% of all cases and controls and the minimum size was at least one municipality. The tests were performed for all stages separately.

Results

Between 1989 and 2007 126,962 patients (96,357 men and 30,605 women) were newly diagnosed with NSCLC in the Netherlands. Table 1 shows the tumour and patients characteristics by time of diagnosis. The median age was 68 years during all time periods, but the proportion of patients aged 60-74 years decreased and the proportion of patients younger than 60 increased. The median age at time of diagnosis for women was 5 years lower than for men during all periods. Relatively more women were diagnosed with NSCLC over time, the proportion of women has been doubled between 1989-1994 and 2003-2007 (15.7 versus 32.8%, p=<0.001). The distribution of histological subtypes has also changed over the years, the proportion of squamous cell carcinoma decreased with 22.9% between 1989-1994 and 2003-2007, while adenocarcinoma and large cell carcinoma increased with 10.4% and 13.3% respectively.

Temporal changes in stage distribution

Figure 1 shows the proportional distribution of the clinical stages of NSCLC between 1989 to 2007 for men and women together. The results of the join point regression analyses are presented in Table 2.

The proportion of stage I tumours declined from 27.6% in 1989 to 18.3% in 2007. From 1989 to 2003 the proportion of stage I declined significantly, with the strongest decline between 1997 and 2003 (EAPC -4.5 ;95%CI:-5.8 to -3.2). Since 2003 the proportion of stage I did not decline anymore. A rapid but not statistically significant increase in proportion of stage II and decrease in proportion of IIIA was seen between 1998 and 1999. The proportions of both

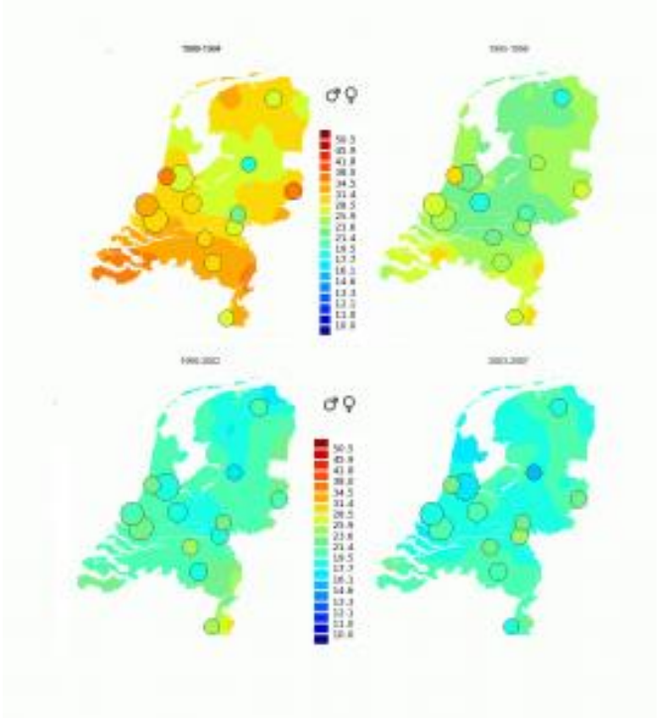

Figure 2: spatial pattern of proportion of NSCLC stage I in the Netherlands, by period of diagnosis.

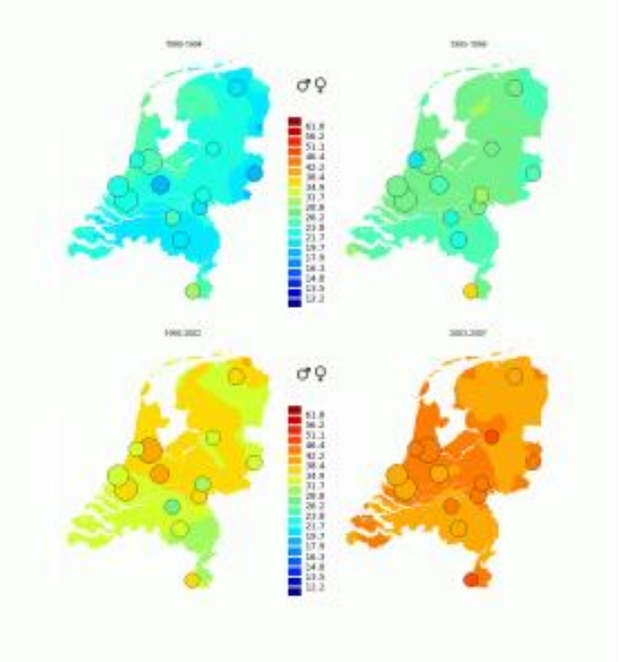

Figure 3: spatial pattern of proportion of NSCLC stage IV in the Netherlands, by period of diagnosis.

stage II and stage IIIA declined during the other years. The percentage of stage IIIB increased slightly till 2000 when it presented 22.0% of all patients. Afterwards a slight decrease has been observed. Both trends were statistically significant. The proportion of stage IV tumours increased from 20.4% in 1989 to 43.9% in 2007. Between 1997 and

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2002 the proportion of stage IV tumours increased most rapidly (EAPC 6.8%; 95%CI:4.4 to 9.4). Finally, the percentage of patients for whom clinical stage could not be determined decreased continuously (16.0% in 1989 and 2.7% in 2007). Although between 1989 and 1999 a statistically significant decrease was seen, the proportion of tumours classified as stage unknown decreased most dramatically after 1999 with an annual percentage change rate of -12.5% (95%CI: -15.2 to -9.9).
No differences in time trends between men and women were observed (data not shown). However, women presented with a higher percentage of stage IV over the years (38.4 versus 29.7% overall years), while men generally revealed a somewhat higher percentage of the lower stages.

Regional variation in stage distribution
Figures 2-4 show maps of the geographic distribution of stage I, IV and unknown stage for the different time periods. We will further focus on these stages as they showed most prominent changes.
For all stages significant clusters were identified. Higher proportions of stage I NSCLC were observed in the southern part of the Netherlands during the first time periods. In the middle of the country lower proportions of stage I were observed. Spatial variation seemed to become smaller over the time.
The proportion of stage IV tumours seemed to be higher in the north-western region of the Netherlands and in the southern part of Limburg during the first time period. Lower proportions of stage IV were observed in the east and in the south of the Netherlands. The statistically lower proportions of stage IV in the south were observed during all time periods. The areas around the larger cities Utrecht and Amsterdam showed higher proportions of stage IV tumours during 1999-2002 and 2003-2007, respectively. During all time periods clusters of higher proportions of stage unknown were observed in the southern region, while in the north-western part clusters of lower proportions of stage unknown were detected. In the west-southern region clusters with lower than expected ratios of stage unknown were observed between 1989-1994 and 1995-1998, while between 1989 and 2002 the eastern region showed higher proportions of stage unknown.
The EAPCs for clinical stage IV NSCLC between 1995 and 2000 were 10.3% (95%CI: 3.2 to 17.8) and 8.5% % (95%CI: 2.7 to 14.5) for the regions of Amsterdam and Groningen, respectively (regions were PET was implemented during this period), while two regions which did not have a PET scanner (Rotterdam and The Hague) showed EAPCs of 5.4% (95%CI: 0.9 to 10.1) and 6.4% (95%CI: 2.5 to 10.4).

Discussion
In this study an overview of percentage stage distribution of NSCLC throughout the Netherlands was provided. A shift in stage distribution towards relatively more advanced

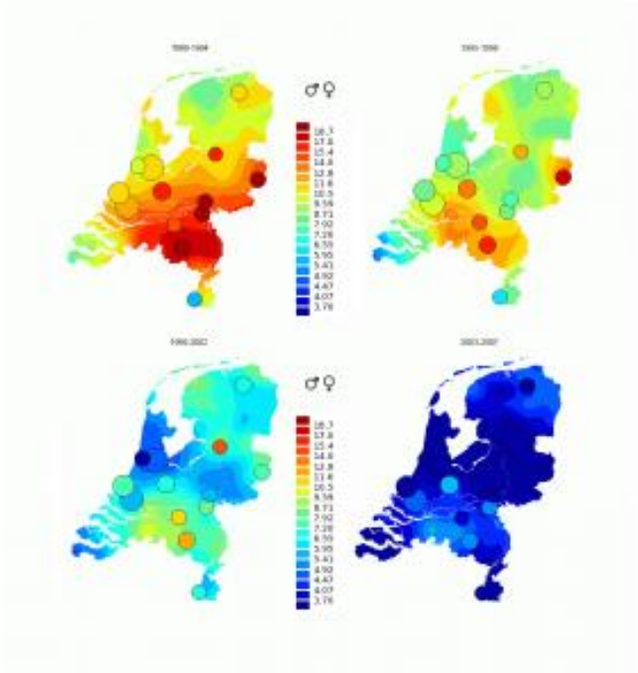

Figure 4: spatial pattern of proportion of NSCLC stage unknown in the Netherlands, by period of diagnosis.

stage NSCLC in the Netherlands between 1989 and 2007 was revealed. A continuous decrease in stage I NSCLC was observed, while relatively more patients had clinically confirmed metastases (stage IV) at the time of diagnosis. The proportion of patients with an unknown clinical stage decreased considerably during the same time period. Furthermore, an obvious increase in clinical stage II was observed between 1998 and 1999, while simultaneously a decline of stage IIIA was observed. These changes in proportional distribution are a consequence of a change in TNM staging. Before 1999 a tumour staged T3N0M0 was classified as stage III while after the change in TNM staging this is considered as a stage IIB tumour 2. When all tumours were reclassified according to the 5th edition of the TNM classification of Malignant Tumours (T3N0M0 is classified as stage IIB) we observed a decrease in proportion stage II tumours from 7.6% to 4.1% and a decrease in stage IIIa tumours from 12.4% to 10.9% (data not shown).
Several studies have indicated a higher sensitivity and specificity of FDG-PET in detecting distant metastases and metastases to mediastinal lymph nodes compared to conventional CT-scan [13, 21, 22]. This would result in a shift in stage distribution towards more advanced disease diagnoses [14,15] and consequently less futile thoracotomies [22]. The most rapid changes in stage I and IV revealed in this study correspond with the introduction of PET in the Netherlands. We also looked at the concordance between clinical and pathological stage and found that half of the patients with clinical stage I NSCLC also had a pathological stage I tumor. As this percentage increased over time, this could also be an indication of improved staging accuracy. Besides, a higher percentage of pathological stage

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unknown was observed over time, which possibly indicates that fewer (futile) surgeries were performed over time (data not shown).

Nonetheless, since the observed trends in stage distribution were already visible before PET was implemented, although to a lesser extent, other improvements in diagnostics may also have played a role.

Various studies showed an association between histology and stage at diagnosis. Squamous cell carcinomas are more likely to be diagnosed in an early stage compared to adenocarcinomas, probably because squamous cell carcinomas usually arise near the central parts of the lung, whereas adenocarcinomas usually occurs in a peripheral location [4, 23]. A tumour on a peripheral location is more likely to give late signs. In our study relatively more adenocarcinomas were detected over time while the proportion of squamous cell carcinoma decreased. When comparing the clinical stage distribution of both subtypes, a higher proportion of stage I was seen in patients diagnosed with squamous cell carcinoma (29.5 versus 22.0%), while the proportion of stage IV was considerably lower compared to adenocarcinomas (19.6 versus 38.4%, data not shown). The relative increase in incidence of adenocarcinomas compared to squamous cell carcinomas could therefore also have contributed to the increase in proportion of stage IV diagnoses.

The increase in proportion of adenocarcinomas over time might be due to changes in smoking habits such as the increase in use of low tar filter cigarettes which is associated with adenocarcinoma. Mainly women smoked low tar filter cigarettes and the increasing proportion of women with lung cancer therefore might have resulted in the increase of adenocarcinomas. A study in the Netherlands showed indeed a higher proportion of adenocarcinomas in women compared to men [24].

Factors that caused the decrease in stage unknown are not exactly known. It might be the result of improvements in diagnostic techniques as well as improved registration methods. To obtain an estimation of the tumour spread of tumours classified as stage unknown at time of diagnosis we performed relative survival analyses (data not shown). Relative survival rates of patients with clinical stage unknown were compared to those with known stage with respect to overall five-year survival rates. The rates of patients with clinical stage unknown were higher than overall survival rates which might indicate an overrepresentation of patients with lower stages of NSCLC. As stage unknown decreased considerably over the years,

Table 1: Patient and tumour characteristics of patients with Non-small cell lung cancer by period of diagnosis.

	Period of diagnosis								
	1989-1994		1995-1998		1999-2002		2003-2007		
	N	%	N	%	N	%	N	%	*P*
Total	36,516		26,602		26,548		37,296		
Sex									<0.001
Male	30,789	84.3	20,925	78.7	19,574	73.7	25,069	67.2	
Female	5,727	15.7	5,677	21.3	6,974	26.3	12,227	32.8	
Age at diagnosis									<0.001
<60	7,825	21.4	6,120	23.0	6,663	25.1	9,738	26.1	
60-74	19,725	54.0	14,054	52.8	13,398	50.5	18,116	48.6	
≥75	8,966	24.6	6,428	24.2	6,487	24.4	9,442	25.3	
Histology									<0.001
Squamous cell	19,615	53.7	11,708	44.0	10,110	38.1	11,471	30.8	
Adenocarcinoma	8,858	24.3	7,911	29.7	8,378	31.6	12,951	34.7	
Large cell	7,416	20.3	6,631	24.9	7,741	29.2	12,442	33.4	
Adenosquamous carcinoma	493	1.4	267	1.0	221	0.8	234	0.6	
Sarcomatoid carcinoma	94	0.3	63	0.2	72	0.3	171	0.5	
Salivary gland carcinoma	40	0.1	22	0.1	26	0.1	27	0.1	
Clinical stage									<0.001
I	9,722	26.6	6,560	24.7	5,555	20.9	7,222	19.4	
II	1,009	2.8	438	1.6	1,193	4.5	1,504	4.0	
III	12,901	35.3	9,839	37.0	8,833	33.3	11,485	30.8	
IV	8,218	22.5	7,168	26.9	9,225	34,7	15,697	42.1	
Unknown	4,666	12.8	2597	9.8	1,742	6.6	1,388	3.7	

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Table 2: Joinpoint analyses for proportional clinical stage distribution of NSCLC in the Netherlands 1989-2007
Abbreviation: EAPC= Estimated Annual Percent Change *EAPC is significantly different from 0 (p< 0.05).

stage	Years	EAPC (95%CI)	Years	EAPC (95%CI)	Years	EAPC (95%CI)
I	1989-1997	-1.5* (-2.0;-0.9)	1997-2003	-4.5* (-5.8;-3.2)	2003-2007	1.7 (-0.2;3.7)
II	1989-1998	-8.3* (-11.3;-5.3)	1998-1999	204.6 (-)	1999-2007	-2.3 (-4.8;0.3)
IIIa	1989-1998	-0.8 (-1.8;0.1)	1998-1999	-27.0 (-)	1999-2007	-1.5* (-2.8;-0.1)
IIIb	1989-2000	2.6* (2.0;3.2)	2000-2007	-2.2* (-3.2;-1.2)	-	-
IV	1989-1997	4.0*(2.9;5.1)	1997-2002	6.8*(4.4;9.4)	2002-2007	3.0*(1.7;4.4)
Unknown	1989-1999	-5.9* (-7.2;-4.7)	1999-2007	-12.5* (-15.2;-9.9)	-	-

this could have led to an attenuation of the decreasing trend observed in early stage NSCLC.

Two other population-based studies observed a similar stage shift as observed in our study, although they examined a smaller time period [14,15]. Both studies linked these shift to the increasing use of PET scanning. When patients are upstaged due to improved staging this might results in improved survival for all stage groups (Will Rogers phenomenon). A recent study in the Netherlands revealed improvements in stage specific survival rates. Improvements in stage specific survival could be related to an increased accuracy of staging procedures such as the use of PET. However, as overall survival improved slightly during the same period the authors suggested also other factors as changes in treatment would have contributed to the improvements in survival rates [25].

Regional differences in clinical staging procedures might have led to spatial differences. In 2004 the first Dutch national guideline on NSCLC was introduced, earlier only regional guidelines were available. According to the national guideline every patient eligible for curative surgery needs to have a PET scan. Although regional variation in guideline adherence regarding treatment has been observed[26], it is not known whether there is variation in guideline adherence regarding diagnostics. However, PET scanning was introduced gradually in the Netherlands and the available PET scanners were distributed unequally, which might affect spatial variation in stage distribution. Due to changes in referral patterns is it difficult to relate areas with higher proportions of advanced stage NSCLC to the implementation of PET.

As most dramatic change in stage distribution as consequence of the introduction of PET was expected in clinical stage IV, we calculated the proportion stage IV diagnoses of total NSCLC diagnoses and EAPC between 1995 and 2000 in regions were PET scanning was implemented around 1997 and regions which did not have a PET scan during this whole period. We observed larger changes in regions were the PET was implemented during this period. Nonetheless, confidence intervals are wide and regions without a PET scanner also showed a statistically significant increase of proportion of stage IV. These results also suggest that PET might have played a role in the observed stage shift, but also other factors or improvements in diagnostics probably contributed substantially to the observed stage shift.

Other factors that can influence stage distribution are the distribution of SES, smoking status, age and attitudes towards seeking help. In line with a study on stage distribution of CRC we did not clearly observe more advanced stages in rural areas or areas with lower SES [27]. Also regions with an older population do not clearly show higher proportions of advanced stage diagnoses. The high proportion of male cigar smokers in the past might have contributed to the statistically lower proportion of stage IV in the south of the Netherlands which was observed during all time periods [28].

Conclusion

We observed several time trends and spatial differences in stage distribution of NSCLC in the Netherlands. Relatively more patients were provided with a clinical stage at diagnosis and a shift towards more advanced stage disease has been observed. As more patients are diagnosed with a clinical stage IV this would probably have resulted in less futile thoracotomies performed over the years in the Netherlands. Improvements in diagnostics, especially the implementation of the PET scan have probably contributed to these shifts. Nonetheless, the proportion of clinical stage IV diagnoses increased already before the implementation of PET and regions without a PET scanner also showed a considerable increase in stage IV NSCLC, suggesting also other factors or improvements in diagnostics might have contributed substantially. Knowledge about space and time trends can provide an estimate about the improvements made in diagnostics and also help policy makers in planning of health care interventions and resources.

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