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Variation in treatment and outcome in patients with non-small cell lung cancer by region, hospital type and volume in the Netherlands☆

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Abstract

Background: Care processes for patients with NSCLC can vary by provider, which may lead to unwanted variation in outcomes. Therefore, in modern health care an increased focus on guideline development and implementation is seen. It is expected that more guideline adherence leads to a higher number of patients receiving optimal treatment for their cancer which could improve overall survival.
Objective: The aim of this study was to evaluate variations in treatment patterns and outcomes of patients with NSCLC treated in different (types of) hospitals and regions in the Netherlands. Especially, variation in the percentage of patients receiving the optimal treatment for the stage of their disease, according to the Dutch national guideline of 2004, was analyzed.
Methods: All patients with a histological confirmed primary NSCLC diagnosed in the period 2001–2006 in all Dutch hospitals ($N = 97$) were selected from the population-based Netherlands Cancer Registry. Hospitals were divided in groups based on their region ($N = 9$), annual volume of NSCLC patients, teaching status and presence of radiotherapy facilities. Stage-specific differences in optimal treatment rates between (groups of) hospitals and regions were evaluated.
Results: In the study period 43 544 patients were diagnosed with NSCLC. The resection rates for stage I/II NSCLC patients increased during the study period, but resection rates varied by region and were higher in teaching hospitals for thoracic surgeons (OR 1.5; 95%CI 1.2–1.9, $p = 0.001$) and in hospitals with a diagnostic volume of more than 50/year (OR 1.3; 95%CI 1.1–1.5, $p = 0.001$). Also the use of chemoradiation in stage III patients increased, though marked differences between hospitals in the use of chemoradiation for stage III patients were revealed. Differences in optimal treatment rates between hospitals led to differences in survival.
Conclusion: Treatment patterns and outcome of NSCLC patients in the Netherlands varied by region and the hospital their cancer was diagnosed in. Though resection rates were higher in hospitals training thoracic surgeons, variation between individual hospitals was much more distinct. Hospital characteristics like a high diagnostic volume, teaching status or availability of radiotherapy facilities proved no guarantee for optimal treatment rates.

Keywords: Non-small cell lung cancer; Variation; Quality of care; Hospital volume; Resection rate; Guideline adherence

Introduction

In literature a plethora of studies describes hospital volume as an important predictor of surgical outcomes. Most of these studies evaluate the inverse relationship between volume and adverse surgical outcomes, like postoperative

☆ Study performed by the 'Quality of cancer care' taskforce of the Signalling Committee Cancer of the Dutch Cancer Society (the committees full report is available on www.kwfkankerbestrijding.nl).

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complications and mortality.[1] Only few authors address the mechanisms which lead to these differences. Intermediate outcomes, like the percentage of patients receiving potentially curative treatment for their cancer, could explain differences in survival. Moreover, other hospital characteristics reflecting the setting in which care is delivered to cancer patients, could be equally important predictors of outcome as hospital volume.

The variation of care processes by caregiver is widely recognized and can sometimes lead to unwanted variation in patients outcomes. Therefore, in modern health care an increased focus on guideline development and implementation is seen. It is expected that more guideline adherence leads to a higher number of patients receiving optimal treatment for their cancer which could improve overall survival. Moreover, evaluating differences in guideline adherence between hospitals can reveal the reasons behind the differences in outcome and can identify best practices with better outcomes.

Differences in guideline adherence have been described for patients with Non-small cell lung cancer (NSCLC) in several countries.[2–5] In the Netherlands, lung cancer is the second common tumour in men and the third in women, with an incidence of 71 and 31 per 100 000 person years in 2007, respectively (European Standardized Rate).[6] In 2007, 10 533 patients were diagnosed with lung cancer and in eighty percent it concerned NSCLC. Only 14% of patients diagnosed with NSCLC in the Netherlands survive 5 years. Unfortunately, these survival figures have not improved in the last decades.[6] While the incidence of NSCLC in men is decreasing since the early eighties, it has been rising in women until 1999. Fortunately, recent reports predict the end of this lung cancer epidemic in women, meaning an overall decrease in lung cancer patients in the near future.[7]

In 2004 the first Dutch National Guideline on NSCLC was introduced (www.oncoline.nl). The main reasons for development of this evidence-based guideline were the introduction of PET-scanning in staging NSCLC, induction chemotherapy in locally advanced NSCLC, and concurrent chemoradiation in stage III NSCLC. According to this guideline surgical resection is the preferred treatment in patients with stage I or II NSCLC, who are fit to undergo surgery. Under the guidelines valid in our study period, surgery is also the treatment of choice in patients with limited stage III disease (T1-3N1). Patients with more advanced stage III NSCLC (cT4 and/or cN2 or cN3) should be treated with a combination of radiation therapy and chemotherapy (chemoradiation), if their performance score is sufficient (WHO-score 0–1). Chemoradiation is given in a concurrent regimen or sequentially. In general, stage III patients with malignant pleural effusions or tumour volumes too extensive for radiation treatment are no candidates for this combined modality therapy and are treated like stage IV patients with a platinum based chemotherapy regimen and/or best supportive care.

The aim of this study was to evaluate variations in treatment patterns and outcomes of patients with NSCLC treated in different (types of) hospitals and regions in the Netherlands. Especially, variation in the percentage of patients receiving optimal treatment for the stage of their disease, according to the Dutch national guidelines, was analyzed.

Patients and methods

Netherlands cancer registry

In the Netherlands, all newly diagnosed malignancies are registered in the nationwide population-based Netherlands Cancer Registry (NCR). The automated pathological archive (PALGA) and the Haematology Departments are the main sources of notification. The National Registry of Hospital Discharge Diagnosis is an additional source, which accounts for up to 8% of new cases.[8] Data are collected from the medical records by specially trained registrars and are coded according to a national manual. Information on patient characteristics, tumour characteristics, treatment, hospital of diagnosis, hospital of treatment and follow-up is recorded. For coding tumour site and morphology the International Classification of Diseases for Oncology (ICD-O) is used.[9] Cancers are staged according the TNM classification.[10] Quality of the data is high[11] and completeness is estimated to be at least 95%.[12]

Patients

All patients with a histological confirmed primary NSCLC diagnosed in the period 2001–2006 were selected from the NCR. Excluded from analysis were clinical diagnosis (no pathology), autopsy findings, sarcomas, lymphomas, neuro-endocrine and carcinoid tumours. Moreover, patients living abroad and cases with an incomplete registration status in the NCR (<1%) were excluded from analyses. Stage grouping was done according to TNM classification, 6th edition.

Hospitals and regions

Patients treated in all 97 hospitals in the Netherlands were included in this analysis. Hospitals were divided in groups based on their teaching status, availability of radiotherapy facilities, annual amount of NSCLC diagnoses (hospital volume) and their region. For the analyses concerning treatment, type of hospital was based on the hospital where the tumour was diagnosed reasoning that referral of patients is good care as well. For the analyses on postoperative mortality and survival, type of hospital was based on the hospital where the resection was performed.

Hospitals were categorized in three groups: non-teaching, teaching and academic. A teaching hospital was defined as a hospital which provides medical training to residents.

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A distinction was made between a teaching hospital for chest physicians and thoracic/lung surgeons. In the group of teaching hospitals for thoracic/lung surgeons all academic hospitals were included in the teaching hospital group. Academic hospitals are teaching hospitals affiliated with a university. The one specialized oncology centre in the Netherlands was classified as an academic hospital as well.

Radiotherapy is an essential part of the treatment of patients with stage III NSCLC. In the Netherlands there are 24 hospitals with radiotherapy facilities and 73 hospitals without a radiotherapy department. These hospitals are affiliated with a radiotherapy department on a different location. All radiotherapy departments treat patients with NSCLC. Hospitals were categorized as having radiotherapy facilities in the same location or not.

Hospital volume stands for the mean number of NSCLC diagnoses per year or for the mean number of lung resections per year. Hospital volume was categorized in 3 groups: less than 50, 50–100 and more than 100 diagnoses per year. In the period 2005–2006, 88% of the patients were operated in the hospital were the tumour was diagnosed.

In addition, hospitals were categorized according to their Comprehensive Cancer Centre region (9 groups). These Comprehensive Cancer Centres (CCCs) are non-hospital organizations that facilitate provision of consultancy services, implementation of national guidelines, coordinate organisation of cancer care, palliative care and host the cancer registry. Each CCC serves a region that includes five to twenty hospitals. Hospitals are affiliated to one CCC.

Stage grouping

Since clinical stage determines treatment policies for NSCLC, the cTNM was used in the analysis concerning the treatment policies. For the analysis concerning the outcome after resection the pathological stage (pTNM) was applied. During the study period PET-scanning was introduced gradually as an addition to traditional clinical staging in NSCLC patients. Effectiveness and stage migration effects of PET-scanning were reported in a Dutch randomized study.[13] A report on cost-effectiveness and availability of PET-scanning showed an unequal distribution across the Netherlands in 2005–06 of mobile units aimed especially for staging of localised lung cancer.[14]

Treatment

Treatment was categorized by resection (pneumonectomy, lobectomy or segmentectomy), radiation therapy, chemotherapy or combined modality treatment (chemoradiation). Chemoradiation was defined as radiation therapy combined with chemotherapy given concurrent or sequentially. Treatment was described as percentages per clinical stage and age group (<75 years and ≥75 years).

The optimal treatment ratio was defined as the percentage of patients receiving optimal treatment by stage of the disease according to the Dutch guideline of 2004[15]: resection for stage I and II patients, chemoradiation (possibly followed by resection) for stage III patients and chemotherapy for stage IV patients. Resection ratios of stage IIIa patients, usually part of combined modality therapy was investigated separately.

Statistical analyses

Logistic regression analysis was performed to examine the influence of age at diagnosis (<60, 60–74, 75+), gender, tumour size and invasion (cT), type of hospital of diagnosis (academic, teaching, general), radiotherapy facilities (same versus different location), hospital volume (<50, 50–100, >100), CCC-region and year of diagnosis on the odds of receiving optimal treatment per stage as described above.

Performance of the individual hospitals for these optimal treatment rates was exhibited in funnel plots using 95% control limits calculated around the mean.[16] Each hospital was displayed as a scatter point presenting the rates of optimal treatment, i.e., resection for patients with stage I and II disease (adjusted for age, gender and tumour size) and chemoradiation for those with stage III disease (adjusted for age, gender, tumour size and nodal involvement).

Furthermore, logistic regression analysis was used to investigate the influence of age at diagnosis (<60, 60–74, 75+), gender, tumour size and invasion (cT), type of hospital of surgery (academic, teaching, general), hospital volume of resections (<10, 10–19, 20–29 and ≥30/year) and CCC-region on the odds of postoperative mortality, defined as death within 30 days after resection. Patients with stage IV disease were excluded from this analysis. Postoperative mortality was determined for patients diagnosed in 2005 and 2006 only.

Follow-up was calculated as the time from diagnosis to death or to 1st January 2008. Cox proportional hazard modelling was used to investigate the relation between resection and survival in patients with stage I and II disease, adjusted for age at diagnosis, gender, T-stage and year of diagnosis. Furthermore, this analysis was used to determine the relation between the resection rate of hospitals and overall survival. The hospitals were split into 3 groups based on their resection rate in the funnel plot: higher than the 95% control limit, within the 95% control limits or below the 95% control limit.

STATA (version 10.0) was used and a p-value of 0.05 was considered as being significant.

Results

In the period 2001–2006, 43 544 patients (69% male) were diagnosed with primary NSCLC (Table 1). During the study period the annual number of new NSCLC

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Table 1
Patient and tumour characteristics of patients diagnosed with Non Small Cell Lung Cancer in the Netherlands 2001–2006.

	N	%
Total		
Patients	43 544	100%
Age (years)		
<60	11 357	26%
60–74	21 403	49%
≥75	10 784	25%
Gender		
Male	30 172	69%
Female	13 372	31%
Year of diagnosis		
2001	6774	16%
2002	6954	16%
2003	7108	16%
2004	7395	17%
2005	7460	17%
2006	7853	18%
Histology		
Adenocarcinoma	14 454	33%
Squamous cell carcinoma	14 310	33%
Large cell carcinoma	14 332	33%
Other histology	448	1%
Clinical stage		
In situ	78	0%
Stage I	9544	22%
Stage II	1930	4%
Stage III	13 715	32%
Stage IV	17 231	40%
Unknown	1046	2%
Pathological stage (in case of surgery)		
In situ	13	0%
Stage I	5681	13%
Stage II	2002	5%
Stage III	1749	4%
Stage IV	389	1%
Unknown	56	0%

diagnoses increased from 6774 patients in 2001 to 7853 in 2006 (16%). The rise in incidence was much higher in women than in men, 45 and 5% respectively and occurred largely at middle age, contrasting the situation in males. Twenty-five percent of NSCLC patients were older than 75 years at the time of diagnosis. During the study period there has been a minor shift from clinical stage I and II disease to the more advanced stages, especially stage IV (Fig. 1a). Table 2 shows the distribution of patients between the different types of hospitals and their CCC region. The majority of the patients with NSCLC were diagnosed in general hospitals without training status for chest physicians (68%) or thoracic surgeons (84%). Only 18% of the patients were diagnosed in a centre with radiotherapy facilities and 9% in an academic centre. About 54% of the patients were diagnosed in 32 hospitals with an annual diagnostic volume of more than 100 cases with NSCLC.

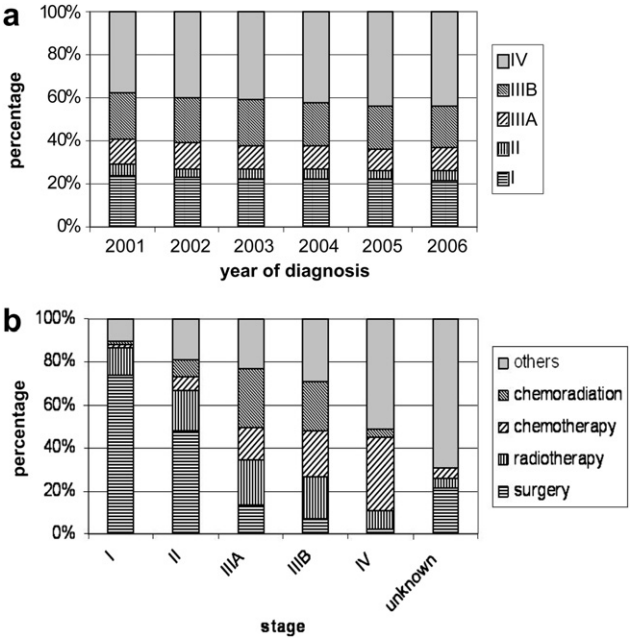

Figure 1. a. Stage migration in patients diagnosed with Non Small Cell Lung Cancer during the study period. b. Treatment characteristics according to stage of Non Small Cell Lung Cancer patients.

Treatment

Primary surgery i.c. resection of the tumour through pneumonectomy, lobectomy or segmentectomy, was performed in 23% of all NSCLC patients, being 60% for patients with clinical stage I or II (Fig. 1b). The others received radiotherapy, either with or without chemotherapy. A substantial number of patients received no oncological therapy at all, being 25% in stage I and II patients older than 75 years. In only 43% of these elderly the tumour was resected. This percentage increased only slightly during the study period. In the younger patient group (<75 years), a resection was performed in 79% of the patients.

Stage I and II

Logistic regression confirmed this role of age in the chance of a resection; in stage I and II patients older than 75 years the OR of a resection is 0.09 (95%CI 0.08–0.11, $p = 0.000$). Also, the size of the tumour, expressed in T stage, was important. Nevertheless, the chance of resection did not only depend on patient- and tumour characteristics (Table 3). Patients with clinical stage I or II disease more often had a resection of their tumour in hospitals with a teaching status for thoracic surgeons (OR 1.5; 95%CI 1.2–1.9, $p = 0.001$) and in hospitals with a diagnostic volume of more than 50 NSCLC patients a year (OR 1.3; 95%CI 1.1–1.5, $p = 0.001$). Marked differences in resection rates appeared between groups of hospitals and regionally. The chance of a resection for stage I or II NSCLC ranged from a OR of 2.0 in one region (95%CI; 1.6–2.4,

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Table 2
Number of Non Small Cell Lung Cancer patients per hospital volume category, teaching status, radiotherapy facility and region 2001–2006.

	N	%
Total		
Patients	43 544	100%
Hospital volume		
<50 (23 hospitals)	3910	9%
50–100 (44 hospitals)	16 209	37%
>100 (32 hospitals)	23 425	54%
Teaching status (chest physician)		
Non-teaching hospital	29 582	68%
Teaching hospital	9889	23%
Academic hospital	4019	9%
Teaching status (lung-/thoracic surgery)		
Non-teaching hospital	36 622	84%
Teaching hospital (incl. academic hospitals)	6922	16%
Radiotherapy facilities		
No	35 538	82%
Yes	8006	18%
Regions		
I	5888	13%
II	3732	9%
III	3172	7%
IV	7868	18%
V	4245	10%
VI	6271	14%
VII	6411	15%
VIII	2908	7%
IX	3049	7%

Hospital characteristics in this table are based on the hospital where the patient is diagnosed with NSCLC.

$p = 0.000$) to 0.77 in another (95%CI 0.63–0.91; $p = 0.004$). Fig. 2 shows differences in resection rates between *individual* hospitals from 75 to 93% for hospitals with accredited training of thoracic surgeons and from 54 to 97% for hospitals without training facilities.

The postoperative mortality rates after a resection for NSCLC were based on data from 2005 to 2006. Within 30 days after the resection 111 of 3206 patients died (3.3%), being 7.5% for patients older than 75 years. Tumour size (pT) and operative procedure also proved important factors. Patients operated in the 63 hospitals with less than 20 resections a year exhibited a similar postoperative mortality rate as in a higher volume hospital with 20 or more NSCLC resections annually (34 hospitals). Patients with stage I or II NSCLC operated in the academic centres had a significantly lower postoperative mortality (1.3%, $p = 0.012$). Logistic regression showed that this reduced risk of dying postoperatively in academic centres is statistically significant in multivariate analysis (OR 0.25; 95%CI 0.06–0.93, $p = 0.038$).

Stage III

During the study period 13 744 patients were diagnosed with stage III NSCLC, 4938 stage IIIa and 8806 stage IIIb patients. In the whole group of stage III patients 24% received combined modality treatment (Fig. 1b), 30% of the younger patients (<75 years, $n = 10\,069$) and 9% of the older patients (>75 years, $n = 3675$). The percentage of patients receiving chemoradiation went from 18% in 2001–29% in 2006 ($p < 0.001$). Higher age and advanced

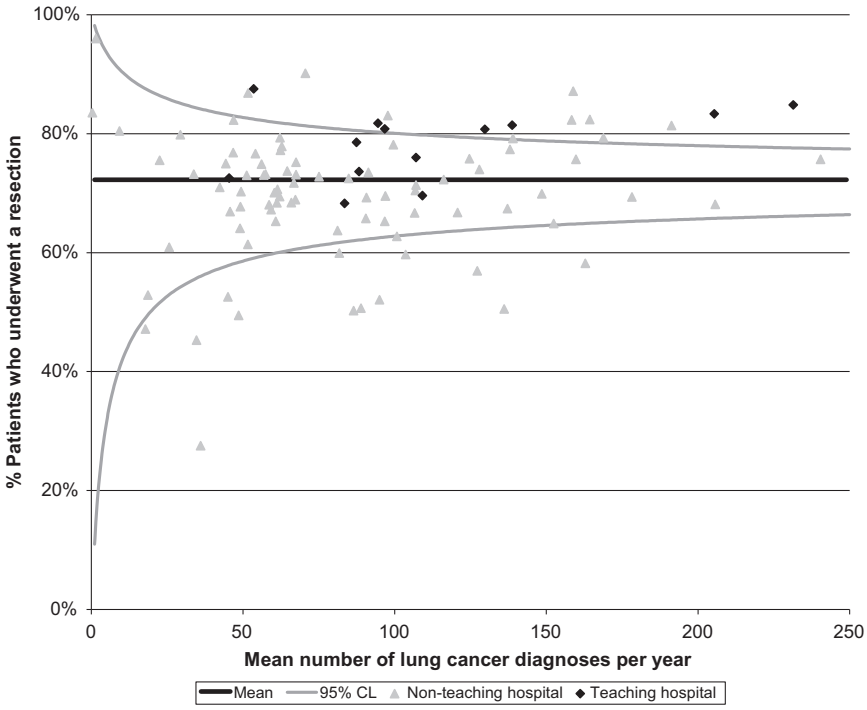

Figure 2. Percentage of stage I or II NSCLC patients in who a resection is performed for non-teaching, and teaching hospitals (adjusted for differences in age, gender and T-stage).

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tumour size were the most important factors to abandon chemoradiation (Table 4). The odds of receiving chemoradiation were lower when a patient was diagnosed in an academic centre. Chemoradiation rates were not higher in high volume hospitals (>100 diagnoses a year) or in hospitals with radiotherapy facilities, except for hospitals training thoracic or lung surgeons (OR 1.6, CI 1.3–1.9). Also, regional differences in the use of chemoradiation were revealed, but they seemed larger between individual hospitals, independent of their region, volume of NSCLC patients, teaching status or radiotherapy facilities (Fig. 3).

Table 3
Multivariate analysis for the odds of resection for stage I and II NSCLC in the Netherlands during 2001–2006.

	OR	95%CI	*p*-value
Age (years)			
<60	Ref		
60–74	0.40	0.35–0.46	**<0.001**
≥75	0.09	0.08–0.11	**<0.001**
Gender			
Male	Ref		
Female	1.00	0.90–1.12	0.896
Year of diagnosis			
2001	Ref		
2002	1.20	1.01–1.39	**0.030**
2003	1.53	1.31–1.78	**<0.001**
2004	1.53	1.32–1.78	**<0.001**
2005	2.04	1.75–2.37	**<0.001**
2006	1.99	1.71–2.31	**<0.001**
T-stage			
T 1	Ref		
T 2	0.48	0.43–0.54	**<0.001**
T 3	0.21	0.18–0.25	**<0.001**
Hospital volume			
<50	Ref		
50–100	1.40	1.17–1.68	**<0.001**
>100	1.69	1.40–2.04	**<0.001**
Teaching status (chest physician)			
Non-teaching hospitals	Ref		
Teaching hospitals	0.91	0.80–1.05	0.212
Academic hospitals	1.02	0.74–1.42	0.741
Teaching status (lung-/thoracic surgery)			
Non-teaching hospitals	Ref		
Teaching hospitals (incl. academic hospitals)	1.58	1.28–1.94	**<0.001**
Radiotherapy facilities			
No	Ref		
Yes	0.92	0.77–1.05	0.304
Region			
I	0.94	0.82–1.12	0.452
II	1.52	1.23–1.76	**<0.001**
III	0.82	0.69–1.01	**0.045**
IV	Ref		
V	0.95	0.81–1.14	0.634
VI	0.97	0.85–1.17	0.729
VII	1.08	0.92–1.25	0.324
VIII	1.46	1.24–1.82	**<0.001**
IX	1.02	0.83–1.23	0.794

Hospital characteristics based on hospital of diagnosis.

Patients younger than 75 years diagnosed with stage IIIa in an academic hospital (26%), teaching hospital (26%) or in radiotherapy centre (22%) had a resection of their tumour-more often than patients in non teaching (15%) or hospitals without radiation facilities (16%). Resection rates in stage IIIa declined slightly during the study period (not significant), while combined treatment of stage IIIa disease with chemoradiation increased, from 24% in 2001–43% in 2006 ($p = 0.001$). A multivariate analysis revealed marked regional differences in the percentage of patients having surgery for their stage IIIa NSCLC, varying between 9 and 25% (Table 4).

Stage IV

The percentage of patients with stage IV NSCLC at primary diagnosis gradually increased during the study period from 38% in 2001–44% in 2006. The use of chemotherapy in the primary treatment of stage IV patients younger than 75 years also increased in this period, from 31% to 50% ($p = 0.001$), but approximately 40% of stage IV patients received no active treatment. Hospital differences in the palliative use of chemotherapy in stage IV NSCLC were not a part of the current study.

Survival

Patients who underwent a resection for stage I or II disease had a significantly higher survival than patients without a resection (Fig. 4). Adjusted for age, gender, T-stage and year of diagnosis, overall survival of stage I and II patients was significantly higher in hospitals with a higher resection rate and significantly lower in hospitals whose resection rate was lower than the group of hospitals within the 95% control limits of the funnel plot of Fig. 2 (HR 0.88, 95%CI 0.83–0.93 and HR 1.15, 95% CI 1.07–1.24, respectively). Though, no differences were found in overall survival for patients who underwent resection in the hospitals with high and with low resection ratios.

Discussion

The introduction of a national evidence-based guideline in 2004, appears to have had several effects on staging and patterns of care for NSCLC patients in our country. Especially the routine use of PET-scanning in the workup of patients for curative therapy led to an increased number of patients with stage IV at diagnosis. In addition, recommendations on the use of chemoradiation for stage III patients led to an increased utilization of radiotherapy combined with chemotherapy, concurrent or sequentially. Nevertheless this study reveals marked variation in treatment patterns and outcome of patients with NSCLC in our country. Not only are these differences influenced by patient or tumour characteristics, also the hospital of diagnosis seems to affect the treatment given. On the level of the individual hospital resection rates

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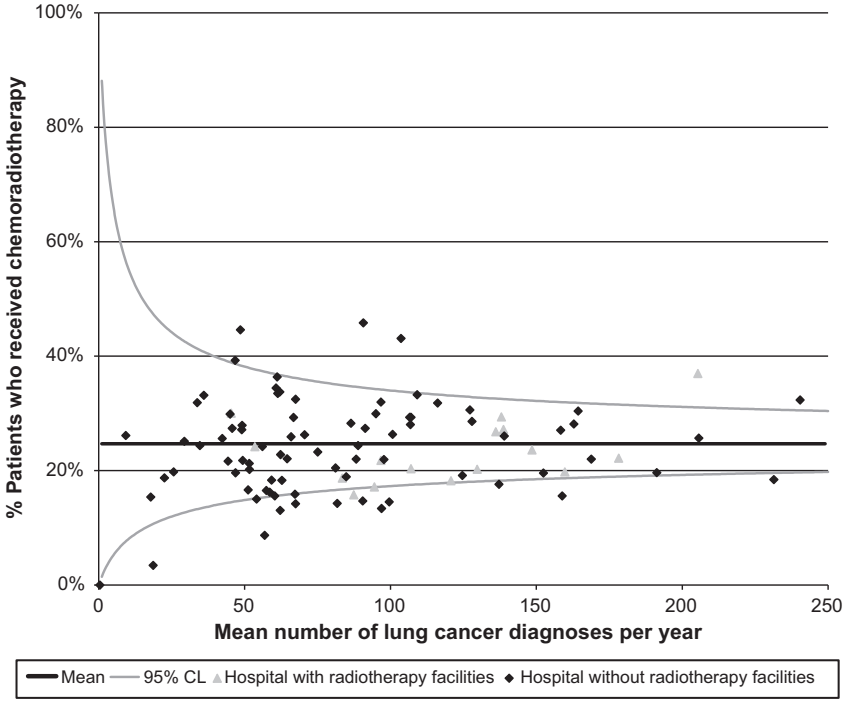

Figure 3. Percentage of stage III patients who received chemoradiation according to mean number of lung cancer diagnoses per year.

in stage I/II patients varied between 54 and 97 percent. The administration of potentially curative chemoradiation in stage III patients varied from less than 10 to more than 40 percent. These differences were only sporadically explained by structural differences between hospitals, like their teaching status or the availability of radiotherapy facilities. Nevertheless, the variation in optimal treatment rates identified in this study could mean that there's room for further improvement in the treatment of NSCLC patients in our country, possibly leading to actual survival benefits.

Inequality in the treatment of NSCLC has been addressed in many publications. Several patient factors are associated with lower odds of undergoing a potentially curative treatment for lung cancer. Higher age is the most important factor, but in studies from the United States as well as Europe gender, comorbidity, race, socio-economic status, region or country of origin have also proven to be predictive.[17–22] These inequalities are not only due to decreased access to care, but also differences in physicians' treatment choices and differences in guideline implementation and adherence are believed to be of influence. While active treatment of NSCLC patients appeared to be strongly associated with better survival, studies from Yorkshire and the Southeast of England[15,16] demonstrated wide regional variations in the use of active treatments like surgery and radiotherapy.[23,24] In one of these studies the use of any active treatment in NSCLC patients, independent of stage, ranged from 15% in one area to 42% in another. Despite corrections for case-mix the reasons behind this variation stayed unclear, but if the first hospital visited was a radiotherapy centre, patients were more likely to receive any active treatment.

In the present study, we analyzed the treatment compliance according to the Dutch evidence-based guidelines, not only at the regional level, but also on the level of the individual hospital. For early stage NSCLC (stage I and II) surgical resection by (bi)lobectomy or pneumonectomy is treatment of choice and for advanced stage NSCLC (stage III) a combined treatment with radiotherapy and chemotherapy (sequentially or concurrent) is the advised treatment.

After adequate staging, the best chances for survival in early stage NSCLC are obtained by surgical resection. Despite, our study showed marked differences in resection rates between individual hospitals and regions. Patients who were diagnosed in a (specialized) centre, with a training status for thoracic surgery, seem to have higher chances for resection. These results confirm the findings of a regional study from the Netherlands showing that patients diagnosed with stage I or II disease at specialized centres or higher volume hospitals are more likely to receive surgical therapy. These differences were seen in all age groups and led to a better survival of patients diagnosed in specialized centres than those that initially went to a community hospital.[25] Our study confirms these observations, but we cannot exclude that selective referral of patients with a good performance status has taken place before their NSCLC was diagnosed. Moreover, variation was most prominent on the individual hospital level, with resection rates for early stage NSCLC varying between 55 and 100%. Also among teaching hospitals and

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Table 4
Multivariate analysis for the odds of receiving combined modality therapy for stage III NSCLC

	OR	95% CI	*p*-value
Age (years)			
<60	Ref		
60–74	0.63	0.58–0.70	**<0.001**
≥75	0.16	0.14–0.18	**<0.001**
Gender			
Male	Ref		
Female	0.92	0.84–1.02	0.101
Year of diagnosis			
2001	Ref		
2002	1.21	1.03–1.42	**0.019**
2003	1.53	1.31–1.79	**<0.001**
2004	1.54	1.32–1.79	**<0.001**
2005	2.03	1.74–2.36	**<0.001**
2006	1.99	1.71–2.31	**<0.001**
T-stage			
T 1	Ref		
T 2	1.03	0.87–1.22	0.732
T 3	1.00	0.81–1.22	0.967
T 4	0.87	0.74–1.03	0.107
N-stage			
N 0	Ref		
N 1	0.56	0.42–0.75	**<0.001**
N 2	1.77	1.54–2.04	**<0.001**
N 3	1.64	1.40–1.93	**<0.001**
Hospital volume			
<50	Ref		
50–100	0.77	0.66–0.91	**0.002**
>100	0.89	0.76–1.05	**0.169**
Teaching status (chest physician)			
Non-teaching hospitals	Ref		
Teaching hospitals	0.90	0.79–1.03	0.128
Academic hospitals	0.64	0.48–0.86	**0.003**
Teaching status (lung-/thoracic surgery)			
Non-teaching hospitals	Ref		
Teaching hospitals (incl. academic hospitals)	1.59	1.29–1.96	**<0.001**
Radiotherapy facilities			
No	Ref		
Yes	0.93	0.79–1.09	0.345
Region			
I	0.96	0.82–1.12	0.589
II	1.54	1.29–1.84	**<0.001**
III	0.84	0.69–1.02	0.081
IV	Ref		
V	0.97	0.82–1.16	0.755
VI	1.00	0.85–1.17	0.978
VII	1.12	0.96–1.31	0.145
VIII	1.49	1.23–1.81	**<0.001**
IX	1.04	0.86–1.27	0.678

Hospital characteristics based on hospital of diagnosis.

specialized centres a wide range of variation was exhibited, between 64 and 89% and 75 and 93% respectively. Considering the results of our study, the choice for a teaching hospital or specialized hospital does not guarantee better care and guideline compliance.

In literature many reports have shown that resection rates and surgical outcome of patients with early stage NSCLC can be improved by treatment in experienced and specialized multidisciplinary teams.[2,3,26,27] The combination of heightened awareness, more adequate staging, improved surgical skill and postoperative care might lead to better outcome. In this context, the inverse relationship between procedural volume and mortality has been studied extensively.[24,28] In our study half of the resections for early stage NSCLC were performed in low volume hospitals with an annual volume less than 20. Mortality hardly differed between low- and high volume hospitals, but ranged from 1% in the younger (<60 years) to 8% in the oldest group (>75 years). Opposite to our findings in high volume hospitals, a lower mortality rate was found in the specialized centres (1%). This is remarkable, considering the higher resection rates we found in elderly patients diagnosed with stage I and II NSCLC in the same centres. Patient selection for operative treatment as well as peri-operative management of the older patient could thus be better in specialized centres. Future 'in depth' studies could reveal the aspects of these care processes (best practices) that lead to these better outcomes and can be used to improve the care for older NSCLC patients in the whole field.

In contrast with the plethora of studies investigating the differences in surgical outcome, only a few studies have investigated institutional differences for non-surgical treatments. In stage III patients with a favourable performance status, a potentially curative treatment by a combination of radio- and chemotherapy is recommended. In our study the use of this chemoradiation increased for stage IIIa as well as for stage IIIb patients. Nevertheless, our study showed a wide variation in the use of chemoradiation between regions and individual hospitals (Fig. 3), without a clear explanation based on their (infra)structural characteristics. For example, the use of chemoradiation was not different between hospitals with or without radiotherapy facilities. With the data available in the NCR, we can only suggest that differences in experience with the complex radiotherapy techniques and the nontrivial toxicity encountered in patients undergoing these treatments, is causing hospital variation in the use of chemoradiation.

Our study has several limitations. First, only a limited set of (infra)structural characteristics of hospitals was available. For example, during the study period PET-scanning was introduced gradually for the staging of NSCLC in the Netherlands from 2000 on.[14] Improved clinical staging in hospitals using PET-scans could have influenced outcome for different stages of the disease. The addition of PET to conventional workup can improve staging and prevents unnecessary surgery in one out of five patients with suspected non-small-cell lung cancer.[13] Though, in our study only a minor shift from early to advanced stages NSCLC was detected (Fig. 1a), the differential introduction of PET-scanning in the Netherlands can be a confounding factor for the survival analyses performed.

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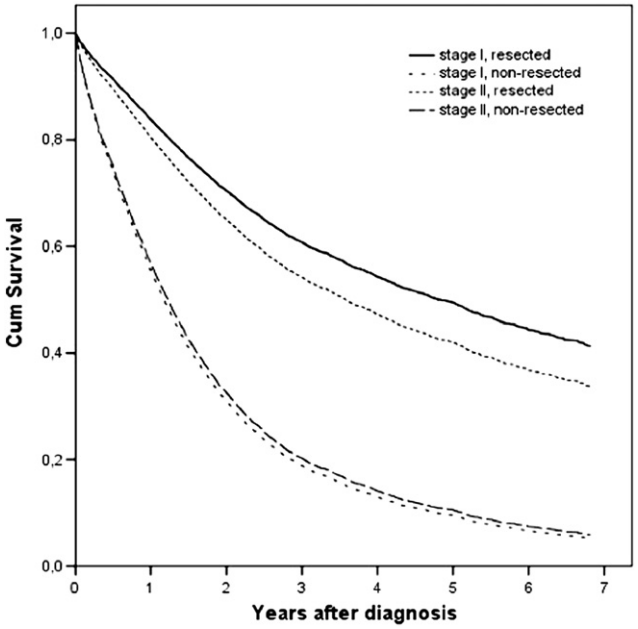

Figure 4. Survival of stage I and II NSCLC patients with or without surgical resection.

Furthermore, data on comorbidities and performance status of patients diagnosed with NSCLC were not available in the NCR. Lung cancer is predominantly a disease of the elderly. Physician treatment decisions can be guided by a patients' age and general medical condition, in all stages of the disease.[29,30] On the other hand, in the Dutch setting there are no indications that patient groups of individual hospitals are truly different. Nevertheless, remarkable variation in resection rates (stage I–II) and the use of combined modality treatment (stage III) was shown. These differences are relevant, because they led to differences in survival, as was shown for stage I–II patients diagnosed in groups of hospitals with low- and high resection rates.

In conclusion, treatment patterns and outcome of NSCLC patients vary by region and the hospital their cancer is diagnosed in. Though, resection rates are higher in hospitals training thoracic surgeons, variation between individual hospitals is much more distinct. Hospital characteristics like a high diagnostic volume, teaching status or availability of radiotherapy facilities proved no guarantee for optimal treatment compliance. Therefore, initiatives to improve quality of care for NSCLC patients should focus on actual differences in treatment patterns and outcome between hospitals, instead of using hospital characteristics as proxies for high quality of care. In addition, 'in depth' prospective documentation studies or medical audits could reveal high leverage processes of care that lead to the better outcomes. This information creates the opportunity to optimize treatment of NSCLC patients and move the medical field forward.

Conflict of interest statement

The authors hereby declare that there are no conflicts of interest that could inappropriately influence this manuscript with the title: 'Variation in treatment and outcome in patients with Non-small cell lung cancer by region, hospital type and volume in the Netherlands'.

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References

1. Chowdhury MM. A systematic review of the impact of volume of surgery and specialization on patient outcome; 2007.
2. Dransfield MT, Lock BJ, Garver Jr RI. Improving the lung cancer resection rate in the US department of veterans affairs health system. *Clin Lung Cancer* 2006;**7**(4):268–72.
3. Laroche C, Wells F, Coulden R, et al. Improving surgical resection rate in lung cancer. *Thorax* 1998;**53**(6):445–9.
4. Potosky AL, Saxman S, Wallace RB, Lynch CF. Population variations in the initial treatment of non-small-cell lung cancer. *J Clin Oncol* 2004;**22**(16):3261–8.
5. Walsh GL, Winn RJ. Baseline institutional compliance with NCCN guidelines: non-small-cell lung cancer. *Oncology (Williston Park)* 1997;**11**(11A):161–70.
6. IKC-net. IKC-net. 15-1-2010.
7. Karim-Kos HE, Janssen-Heijnen ML, van Iersel CA, van der Meer RM, de VE, Coebergh JW. The beginning of the end of the lung cancer epidemic in Dutch women? *Int J Cancer* 2008;**123**(6):1472–5.
8. Visser O, Coebergh JWW, Dijck van JAAM, Siesling S. *Incidence of cancer in the Netherlands 1998*. Utrecht: Vereniging van Integrale Kankercentra; 2002.
9. Fritz A, Percy C, Jack A, et al, editorss. *International classification of diseases for oncology.* 3rd ed. Geneva: WHO; 2000.
10. Wittekind C, Greene FL, Hutter RVP, Klimpfinger M, Sobin LH, editors. *TNM atlas*. Berlin: Springer-Verlag; 2004.
11. Schouten LJ, Jager JJ, van den Brandt PA. Quality of cancer registry data: a comparison of data provided by clinicians with those of registration personnel. *Br J Cancer* 1993;**68**(5):974–7.
12. Schouten LJ, Hoppener P, van den Brandt PA, Knottnerus JA, Jager JJ. Completeness of cancer registration in Limburg, the Netherlands. *Int J Epidemiol* 1993;**22**(3):369–76.
13. van Tinteren H, Hoekstra OS, Smit EF, et al. Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial. *Lancet* 2002;**359**(9315):1388–93.
14. ZonMw Doelmatigheidsonderzoek. PET gepast gebruik(t), ZonMw; 2007.
15. Kwaliteitsinstituut voor de gezondheidszorg CBO. Richtlijn Niet-kleincellig longcarcinoom: stadiering en behandeling, Van Zuiden Communications; 2004.
16. Agresti A, Coul BA. Approximate is better than "Exact" for interval estimation of binomial proportions. *Amer Statistician* 1998;**52**(2):119–26.
17. Cerfolio RJ, Bryant AS, Scott E, et al. Women with pathologic stage I, II, and III non-small cell lung cancer have better survival than men. *Chest* 2006;**130**(6):1796–802.

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18. Damhuis RA, Schutte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. *Eur Respir J* 1996;**9**(1):7–10.
19. Esnaola NF, Gebregziabher M, Knott K, et al. Underuse of surgical resection for localized, non-small cell lung cancer among Whites and African Americans in South Carolina. *Ann Thorac Surg* 2008;**86**(1): 220–6.
20. Jack RH, Gulliford MC, Ferguson J, Moller H. Geographical inequalities in lung cancer management and survival in South East England: evidence of variation in access to oncology services? *Br J Cancer* 2003;**88**(7):1025–31.
21. Jazieh AR, Kyasa MJ, Sethuraman G, Howington J. Disparities in surgical resection of early-stage non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2002;**123**(6):1173–6.
22. Lathan CS, Neville BA, Earle CC. The effect of race on invasive staging and surgery in non-small-cell lung cancer. *J Clin Oncol* 2006;**24** (3):413–8.
23. Cartman ML, Hatfield AC, Muers MF, Peake MD, Haward RA, Forman D. Lung cancer: district active treatment rates affect survival. *J Epidemiol Community Health* 2002;**56**(6):424–9.
24. Goodney PP, Lucas FL, Stukel TA, Birkmeyer JD. Surgeon Specialty and operative mortality with lung resection. *Ann Surg* 2005;**241**(1): 179–84.
25. Li WW, Visser O, Ubbink DT, Klomp HM, Kloek JJ, de Mol BA. The influence of provider characteristics on resection rates and survival in patients with localized non-small cell lung cancer. *Lung Cancer* 2008; **60**(3):441–51.
26. Bach PB, Cramer LD, Schrag D, Downey RJ, Gelfand SE, Begg CB. The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001;**345**(3):181–8.
27. Martin-Ucar AE, Waller DA, Atkins JL, Swinson D, O'Byrne KJ, Peake MD. The beneficial effects of specialist thoracic surgery on the resection rate for non-small-cell lung cancer. *Lung Cancer* 2004; **46**(2):227–32.
28. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;**346**(15): 1128–37.
29. Janssen-Heijnen ML, Smulders S, Lemmens VE, Smeenk FW, van Geffen HJ, Coebergh JW. Effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer. *Thorax* 2004;**59**(7):602–7.
30. Vulto AJ, Lemmens VE, Louwman MW, et al. Influence of age and comorbidity on receiving radiotherapy as part of primary treatment for cancer in South Netherlands, 1995 to 2002. *Cancer* 2006;**106**(12): 2734–42.

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