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Trends and variations in treatment of stage I–III non-small cell lung cancer from 2008 to 2018: A nationwide population-based study from the Netherlands

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ABSTRACT

Introduction: This Dutch population-based study describes nationwide treatment patterns and its variations for stage I-III non-small cell lung cancer (NSCLC).

Materials and methods: Patients diagnosed with clinical stage I-III NSCLC in the period 2008–2018 were selected from the Netherlands Cancer Registry. Treatment trends were studied over time and age groups. Use of radiotherapy versus surgery (stage I-II), and concurrent versus sequential chemoradiotherapy (stage III) were analyzed by logistic regression.

Results: In stage I, the rate of surgery decreased from 58 % (2008) to 40 % (2018) while radiotherapy use increased over time (from 31 % to 52 %), which mostly concerned stereotactic body radiotherapy (74 %). In stage II, 54 % of patients received surgery, and use of radiotherapy alone increased from 18 % to 25 %. The strongest factors favoring radiotherapy over surgery were WHO performance status (OR ≥ 2 vs 0: 23.39 (95% CI: 18.93−28.90)), increasing age (OR ≥ 80 vs <60 years: 14.52 (95% CI: 13.02−16.18)) and stage (OR stage II vs I: 0.61 (95% CI: 0.57−0.65)). In stage III, the combined use of chemotherapy and radiotherapy increased from 35 % (2008) to 39 % (2018). In all years, 23 % received concurrent chemoradiotherapy, 9 % sequential chemoradiotherapy, 23 % radiotherapy or chemotherapy alone, and 25 % best supportive care. The strongest factors favoring concurrent over sequential chemoradiotherapy were age (OR ≥ 80 vs <60 years: 0.14 (95% CI: 0.10−0.19)), WHO Performance status (OR ≥ 2 vs 0: 0.33 (95% CI: 0.24−0.47)) and region (OR east vs north: 0.39 (95% CI: 0.30−0.50)).

Conclusions: The use of radiotherapy became more prominent over time in stage I NSCLC. Combined use of chemotherapy and radiotherapy marginally increased in stage III: only one third of patients received chemoradiotherapy, mainly concurrently. Treatment variation seen between patient groups suggests tailored treatment decision, while variation between hospitals and regions indicate differences in clinical practice.

Abbreviations: NCR, Netherlands Cancer Registry; EoD, extent of disease; nos, not otherwise specified.

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1. Introduction

Non-small cell lung cancer (NSCLC) accounts for 80–85 % of the lung cancer diagnoses in Western countries [1,2]. Almost one quarter of patients present with stage I, one tenth with stage II and one fifth with stage III disease [3].

Surgery is seen as the preferred treatment modality for stage I-II NSCLC [4–9]. Radiotherapy in general and stereotactic body radiotherapy (SBRT) specifically, however, are alternative curative treatment options for stage I [10,11] and the latter was widely implemented between 2003 and 2008 [12–16]. Around 2010, SBRT was included in international guidelines as an alternative treatment option for inoperable patients with peripheral tumors, but not for those who are considered operable [4–9]. On the other hand, several authors have reported an increasing use of SBRT in early-stage NSCLC, both in operable patients instead of surgery [17] and in patients who previously would have received best supportive care alone [12,15,18].

In patients with unresectable stage III disease, chemoradiotherapy (CRT) has been the standard treatment for more than twenty years [19]. Concurrent CRT (cCRT) is recommended over sequential CRT (sCRT) in international guidelines [7–9], as it decreases locoregional progression and improves overall survival [20]. The recently approved adjuvant treatment with durvalumab further improves outcomes in stage III [21] but is only given to patients with no progression after CRT [9,22]. Although evidence and international guidelines favor cCRT, variation in the use of CRT is seen between and within countries [23–26].

The patterns of care for patients with NSCLC in the Netherlands have been described for earlier years in previous studies [27,28], but a recent elaborative overview also addressing SBRT and detailed CRT options is lacking. Insights into recent patterns of care indicate whether clinical practice meets the treatment guidelines for NSCLC and is furthermore useful for the prediction and planning of future oncological care. This study describes treatment patterns for patients diagnosed with stage I-III NSCLC between 2008 and 2018 in the Netherlands. In addition, variables associated with the use of radiotherapy versus surgery in stage I and II disease, and cCRT versus sCRT in stage III disease were identified. Insights into factors associated with treatment decisions can help to identify patients who received (sub)optimal treatment.

2. Materials and methods

2.1. Patients

Patients diagnosed with clinical stage I-III NSCLC between 2008 and 2018 were selected from the Netherlands Cancer Registry (NCR). The NCR is a nationwide population-based registry containing information on patient, tumor, and the delivered first line treatment of all newly diagnosed cancer patients. Trained registrars extract these data from the Dutch hospitals' medical records. Patients with histologically or cytologically confirmed NSCLC and those with only a clinical diagnosis were included in this study. Patients became only clinically diagnosed in case of a strong suspicion of NSCLC for which treatment was given while histological and cytological confirmation was lacking. Patients who were diagnosed with NSCLC at autopsy, or who resided or received treatment abroad were excluded.

2.2. Definitions

Staging was based on the Tumor Node Metastases (TNM) classification edition 6 until 2009, edition 7 in the period 2010–2016, and edition 8 since 2017. Until 2012, 12 % of the patients lack TNM and only had Extent of Disease (EoD) available. In brief, EoD describes whether the disease is localized (EoD 2), regionally spread (EoD 3–5) or metastasized (EoD 6). We translated EoD into stages according to the TNM edition applicable for the year of diagnosis. EoD 3 and 4 can be translated into stage II or III, depending on the T- and N-stage. As this information was missing for these records, we randomly assigned stage II or stage III according to the ratio between these stages in 2012–2013 (1:2.7). Alternative approaches to translating EoD were investigated in sensitivity analyses (Supplementary Document 1).

SBRT is a high precision radiotherapy technique that delivers large doses to the tumor in a few fractions. Radiotherapy as part of CRT was always conventionally fractionated. cCRT was defined as chemotherapy and radiotherapy starting within 30 days from each other [23], irrespective of the order. If the end date of therapy was available, radiotherapy starting or stopping during chemotherapy, and chemotherapy starting or stopping during radiotherapy were also considered concurrent, irrespective of the time between the start of both treatment modalities. sCRT was defined as chemotherapy and radiotherapy starting between 30 and 90 days from each other if no part of cCRT. If either chemo- or radiotherapy started with an interval time longer than 90 days and both were not part of CRT, they were classified as distinct treatments. The registration of start and end of therapy was most complete in recent years. In case chemo- or radiotherapy had a missing start date, the treatment was classified as chemotherapy and radiotherapy not otherwise specified (nos).

We divided the Netherlands into five regions, each including at least 3 radiotherapy institutes and 11 hospitals of which $\geq$1 university hospital. Driving time to a radiotherapy facility was defined as one way travelling time by car and calculated using the postal code of the nearest radiotherapy facility and the patient's home address. Driving time was clustered by 15 min, with a top cluster containing $\geq$45 min driving time.

Hospitals were classified as university or non-university hospitals, where the single cancer specific hospital in the Netherlands was included as university hospital. In addition, the mean annual number of surgeries for NSCLC performed per hospital was calculated and categorized. Since 2012, surgical care for lung cancer in the Netherlands is concentrated in hospitals that perform $\geq$20 lung cancer resections per year [29]. If a hospital did not perform any surgery for NSCLC in a subset of the years, it was classified in the no surgery-category in these years, and in the applicable category in the other years.

Between 2008 and 2018, half of the radiotherapy institutes provided radiotherapy with curative intent to an annual average of 147 patients or more with stage I-III NSCLC. These institutes were categorized as high volume. The other half of the institutes provided radiotherapy to an annual average of less than 147 patients and were categorized as low volume. Furthermore, radiotherapy institutes were divided by in-house and independent. In-house radiotherapy was defined as a radiotherapy department embedded in the organization of a hospital diagnosing lung cancer, while independent radiotherapy includes radiotherapy institutes not embedded in the organization of a diagnosing hospital.

Comorbidities as registered in the hospitals' medical records were available until 2015 for patients in the southern part of the Netherlands (~15 % of the Dutch population, an overview of all comorbidities registered is available in Supplementary Table 1). WHO performance status and reasons for best supportive care were registered nationwide since 2015. WHO performance status, also called ECOG or Zubrod score, is a scale for fitness ranging from experiencing no restrictions in daily activities (score 0) to being completely bedridden (score 4) [30].

2.3. Analyses

Patient and disease characteristics as well as the frequency of the various types of treatment modalities were stratified according to stage. Trends in the applied treatment modalities over time and for age groups including five years were presented in graphs, also stratified for stage. Age groups with less than 30 patients were not shown. For some regions in the earlier years, SBRT might be recorded as conventional radiotherapy in the NCR. Therefore, we decided not to present SBRT in the graphs. As the chemotherapy and radiotherapy nos-cohort potentially could include patients treated with CRT, its percentage was added to the lines of cCRT and sCRT and depicted in a dotted format. This was done to

estimate the highest possible rate of both cCRT and sCRT.

Logistic regression analyses were performed to identify variables associated with the use of radiotherapy versus surgery in patients with stage I and II, whereby patients receiving both modalities were excluded. As stage II included a limited number of patients and treatment options were comparable to stage I, we combined both stages. To identify variables associated with the use of cCRT versus sCRT in patients with stage III, logistic regression analyses were also used. In these analyses we excluded 2008–2012, as combined modality treatment could then not always be classified due to the missing start and end dates of therapy. Since comorbidities and WHO performance status were only available for subsets of patients, analyses on comorbidities included only those diagnosed in the southern part of the Netherlands until 2015 and analyses on performance status included only those diagnosed in 2015−2018. Analyses were adjusted for all factors that were statistically significant in crude analyses, except for the number of comorbidities and the performance status. Furthermore, all Dutch university hospitals have in-house radiotherapy and frequently perform surgeries for NSCLC, hence the analyses on university versus non-university hospitals were not adjusted for these variables. Ninety-five percent confidence intervals (95% CI) resulting from the analyses reflect probable estimates for the odds radios (OR) using a p-value of 0.05 as critical level.

All analyses were performed using the SAS statistical software, version 9.4, SAS Institute Inc., Cary, NC, USA.

Table 1
Characteristics of patients diagnosed with non-small cell lung cancer in the Netherlands between 2008 and 2018, stratified for clinical stage.

	Stage I		Stage II		Stage III	
	N = 25,405		N = 9272		N = 26,905	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Male	14,371	(56.6)	5875	(63.4)	16,905	(62.8)
Age at diagnosis, years						
<60	4017	(15.8)	1462	(15.8)	5226	(19.4)
60–69	8144	(32.1)	2801	(30.2)	8408	(31.3)
70–74	4981	(19.6)	1753	(18.9)	4619	(17.2)
75–79	4464	(17.6)	1619	(17.5)	4198	(15.6)
≥80	3799	(15.0)	1637	(17.7)	4454	(16.6)
Median (p25, p75)	70.0	(63.0−77.0)	71.0	(63.0−77.0)	69.0	(62.0−77.0)
Period of diagnosis						
2008–2010	6055	(23.8)	1586	(17.1)	7576	(28.2)
2011–2014	8521	(33.5)	3437	(37.1)	9517	(35.4)
2015–2018	10,829	(42.6)	4249	(45.8)	9812	(36.5)
Region in the Netherlands						
North	2704	(10.6)	1091	(11.8)	3410	(12.7)
East	4281	(16.9)	1674	(18.1)	4550	(16.9)
South	5983	(23.6)	2260	(24.4)	6674	(24.8)
South west	5909	(23.3)	2051	(22.1)	6067	(22.5)
North west	6528	(25.7)	2196	(23.7)	6204	(23.1)
Morphology						
Squamous cell carcinoma	6297	(24.8)	3771	(40.7)	9721	(36.1)
Adenocarcinoma	10,088	(39.7)	3243	(35.0)	9257	(34.4)
Large cell carcinoma	1660	(6.5)	853	(9.2)	5114	(19.0)
Clinical diagnosis only	7093	(27.9)	1241	(13.4)	2650	(9.8)
Other	267	(1.1)	164	(1.8)	163	(0.6)
Primary therapy						
RT alone	10,162	(40.0)	1872	(20.2)	3083	(11.5)
Surgery alone	10,283	(40.5)	2716	(29.3)	1036	(3.9)
Chemotherapy alone	199	(0.8)	190	(2.0)	3051	(11.3)
Concurrent CRT	181	(0.7)	464	(5.0)	6228	(23.1)
Sequential CRT	54	(0.2)	159	(1.7)	2391	(8.9)
RT and chemotherapy (distinct therapies)	79	(0.3)	84	(0.9)	1226	(4.6)
RT and chemotherapy, dates unknown	30	(0.1)	68	(0.7)	901	(3.3)
Surgery and chemotherapy	1578	(6.2)	1627	(17.5)	856	(3.2)
Surgery and RT	220	(0.9)	216	(2.3)	152	(0.6)
Surgery and RT and chemotherapy (distinct therapies / CRT)	201	(0.8)	424	(4.6)	791	(2.9)
Other/unknown therapy	34	(0.1)	30	(0.3)	365	(1.4)
Best supportive care	2384	(9.4)	1422	(15.3)	6825	(25.4)
Received any RT	10,927	(43.0)	3287	(35.5)	14,772	(54.9)
Received SBRT	8082	(74.0)	719	(21.9)	313	(2.1)
Comorbidities at diagnosis being assessed[A]	3965	(15.6)	1377	(14.9)	3989	(14.8)
≥1 comorbidity at diagnosis	3514	(88.6)	1125	(81.7)	3207	(80.4)
Median number of comorbidities (p25, p75)	2.0	(1.0−3.0)	2.0	(1.0−3.0)	2.0	(1.0−3.0)
Most frequent comorbidities						
Chronic pulmonary disease	1639	(41.3)	477	(34.6)	1317	(33.0)
Hypertension	1300	(32.8)	425	(30.9)	1216	(30.5)
Previous malignancy	1224	(30.9)	270	(19.6)	622	(15.6)
WHO performance status at diagnosis being assessed[B]	6886	(27.1)	2806	(30.3)	6507	(24.2)
0	3036	(44.1)	1223	(43.6)	2430	(37.3)
1	2643	(38.4)	1115	(39.7)	2619	(40.2)
2	936	(13.6)	325	(11.6)	895	(13.8)
3	247	(3.6)	126	(4.5)	482	(7.4)
4	24	(0.3)	17	(0.6)	81	(1.2)

RT: radiotherapy; CRT chemoradiotherapy; SBRT stereotactic body radiotherapy; p25: 25th percentile; p75: 75th percentile.
[A] Comorbidities were mainly registered until 2015 and principally for patients in the southern part of the Netherlands.
[B] WHO performance scores are registered since 2015.

3. Results

Between 2008 and 2018 a total of 119,789 NSCLC cases were registered, including 61,621 (51 %) with clinical stage I-III of whom 39 were excluded from our study because of treatment abroad. The annual number of diagnoses with clinical stage I-III increased from 4992 in 2008 to 6580 in 2018 (Supplementary Fig. 1). The proportion of stage I remained similar between 2008 (22 %) and 2018 (23 %), while for stage II the proportion increased from 4 % to 9 %. For stage III the proportion decreased from 28 % to 21 %.

3.1. Patient characteristics

Fifty-seven percent of the patients with stage I were male, compared to 63 % in stage II and III (Table 1). Age distribution and region of residence were comparable across the stages. Of the patients with registered comorbidities, those with stage I more often had ≥1 comorbidity. Chronic pulmonary disease was the most common comorbidity, followed by hypertension and previous malignancies. WHO performance status was available for 26 % of patients and those with stage III had the worst performance status. Information on histological type was lacking in 28 % of stage I, 13 % of stage II and 10 % of stage III patients. These patients were registered as having only a clinical diagnosis of NSCLC.

3.2. Trends in treatment over time

In patients with stage I, the percentage receiving radiotherapy increased from 31 % in 2008 to 52 % in 2018, whereas the use of surgery decreased (from 58 % to 40 %) (Fig. 1A). Since 2015, more patients received radiotherapy than surgery: 52 % and 41 %, respectively, in 2015−2018. SBRT was given to 74 % of patients with stage I who received radiotherapy. In patients with stage II, surgery remained the most delivered therapy in all years: 54 % was operated on in the total study period (Fig. 1B). Use of radiotherapy alone in these patients increased from 18 % in 2008 to 25 % in 2018, while best supportive care decreased. Twenty-two percent of the irradiated patients with stage II received SBRT. In patients with stage III, the use of combined chemotherapy and radiotherapy increased from 35 % in 2008 to 39 % in 2018 (Fig. 1C). In the total study period, 23 % of patients received cCRT and 9 % sCRT. Eleven percent of the patients with stage III received surgery with or without (neo)adjuvant therapy, 23 % radiotherapy or chemotherapy alone, and 25 % best supportive care. For all stages, refusal of curative-intent treatment by the patient or family was the main reason for best supportive care.

3.3. Trends in treatment according to age

In stage I and II, higher age was associated with less surgery, more radiotherapy, and more best supportive care (Fig. 2A and B). Radiotherapy use was highest in patients aged 80–84 years. In stage III, higher age was associated with less cCRT and sCRT, more radiotherapy alone and more best supportive care (Fig. 2C).

3.4. Multivariable adjusted analyses: stage I and II

In multivariable analyses, patients with stage I had a higher probability of receiving radiotherapy instead of surgery than those with stage II (Table 2). In addition, female sex and increasing age were associated with increased probability of receiving radiotherapy. ORs ranged from 1.64 (95% CI: 1.52−1.77) in patients aged 60–69 years to 14.52 (95% CI: 13.02−16.18) in those aged ≥80 years, compared to age <60 years. Patients aged ≥70 years (reference: <70 years) had an OR of 3.12 (95% CI: 2.97–3.28) for radiotherapy versus surgery, which was 3.97 (95% CI: 3.75–4.19) in those aged ≥75 years (reference: <75 years). Being diagnosed in more recent years, having more comorbidities and a WHO performance status ≥1 were also associated with a higher probability of receiving radiotherapy.

The likelihood of receiving radiotherapy instead of surgery was lower for patients with a 15−44 min driving time to a radiotherapy facility, compared to patients with less than 15 min driving time. Regional differences in the choice of treatment were evidenced by ORs ranging from 0.85 (95% CI: 0.77−0.93) to 1.17 (95% CI: 1.07−1.28). Patients being diagnosed in a university hospital, in a hospital with no or low volume NSCLC surgery, or with in-house radiotherapy, were more likely to receive radiotherapy. For the latter, the association was the strongest (OR: 1.57, 95% CI: 1.46−1.69). The association of in-house radiotherapy with treatment remained fairly constant over time and differences between regions were present in the whole study period (Supplementary Table 2). Non-university hospitals, however, were only associated with less use of radiotherapy in 2015−2018.

3.5. Multivariable adjusted analyses: stage III

In patients diagnosed with stage III disease in the period 2013–2018, female sex (OR: 0.82, 95% CI: 0.72−0.94) and higher age were associated with a lower probability to be treated with cCRT instead of sCRT (Table 3). The OR for cCRT versus sCRT was 0.22 (95% CI: 0.16−0.29) in patients aged ≥70 versus <70 years and 0.25 (95% CI: 0.18−0.34) in those aged ≥75 versus <75 years. No association between the number of comorbidities and treatment was present. Patients with a WHO performance status ≥1 were less likely to receive cCRT than those with a performance status of 0.

The use of either cCRT or sCRT differed by region, with ORs ranging from 0.39 (95% CI: 0.30−0.50) to 0.62 (95% CI: 0.48−0.79). Furthermore, patients diagnosed in a non-university hospital had a lower probability of receiving cCRT than those diagnosed in a university hospital (OR: 0.65, 95% CI: 0.51−0.84). No association between driving time to a radiotherapy facility and the delivered CRT schedule could be found. The difference between university and non-university hospitals was comparable over time, while regional differences decreased over time (Supplementary Table 3).

4. Discussion

This nationwide study demonstrates an increased use of radiotherapy instead of surgery in patients with stage I NSCLC in the Netherlands over the past decade. In stage II, the rate of radiotherapy as sole therapy slightly increased over time, while the rate of best supportive care decreased. Use of combined chemotherapy and radiotherapy marginally increased in stage III. Only one third of these patients received CRT, about two thirds of whom concurrently. Treatment varied between patients, hospitals, and regions.

4.1. Stage I and II

The strong increasing trend in radiotherapy use in stage I disease differs from the trend reported earlier in the Netherlands. Between 1990 and 2009, a slight increase in radiotherapy use was seen in a nationwide study [28] and another study including four Dutch regions showed no change in the use of radiotherapy in stage I and II in 1997–2008 [27]. This might be explained by SBRT being not widely available at that time, however information on the percentage of patients receiving SBRT lacked in these studies. For the period 2008–2018, we showed in nationwide data that most irradiated patients with stage I received SBRT (74 %), which possibly is an underestimation as SBRT might be reported as conventional radiotherapy in the NCR in some regions in the earlier years.

The finding of increased use of radiotherapy instead of surgery is in line with treatment trends observed in early-stage NSCLC in the USA [17], and may reflect the consideration of SBRT being also a valuable alternative treatment option in operable patients or patients refusing

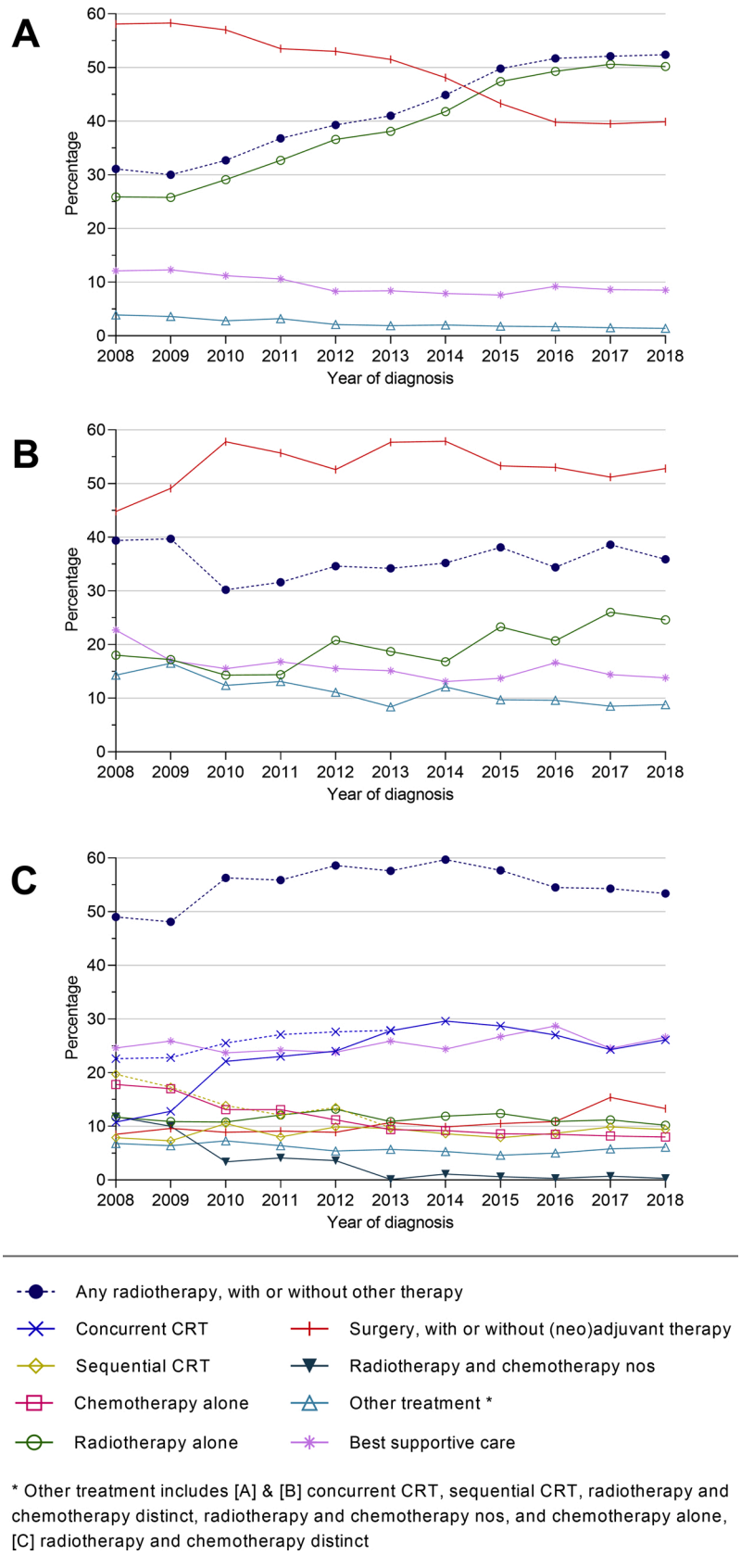

Fig. 1. Trends in primary treatment of non-small cell lung cancer in the Netherlands, presented over incidence years and stratified for [A] clinical stage I (N = 25,405), [B] clinical stage II (N = 9272), [C] clinical stage III (N = 26,905).

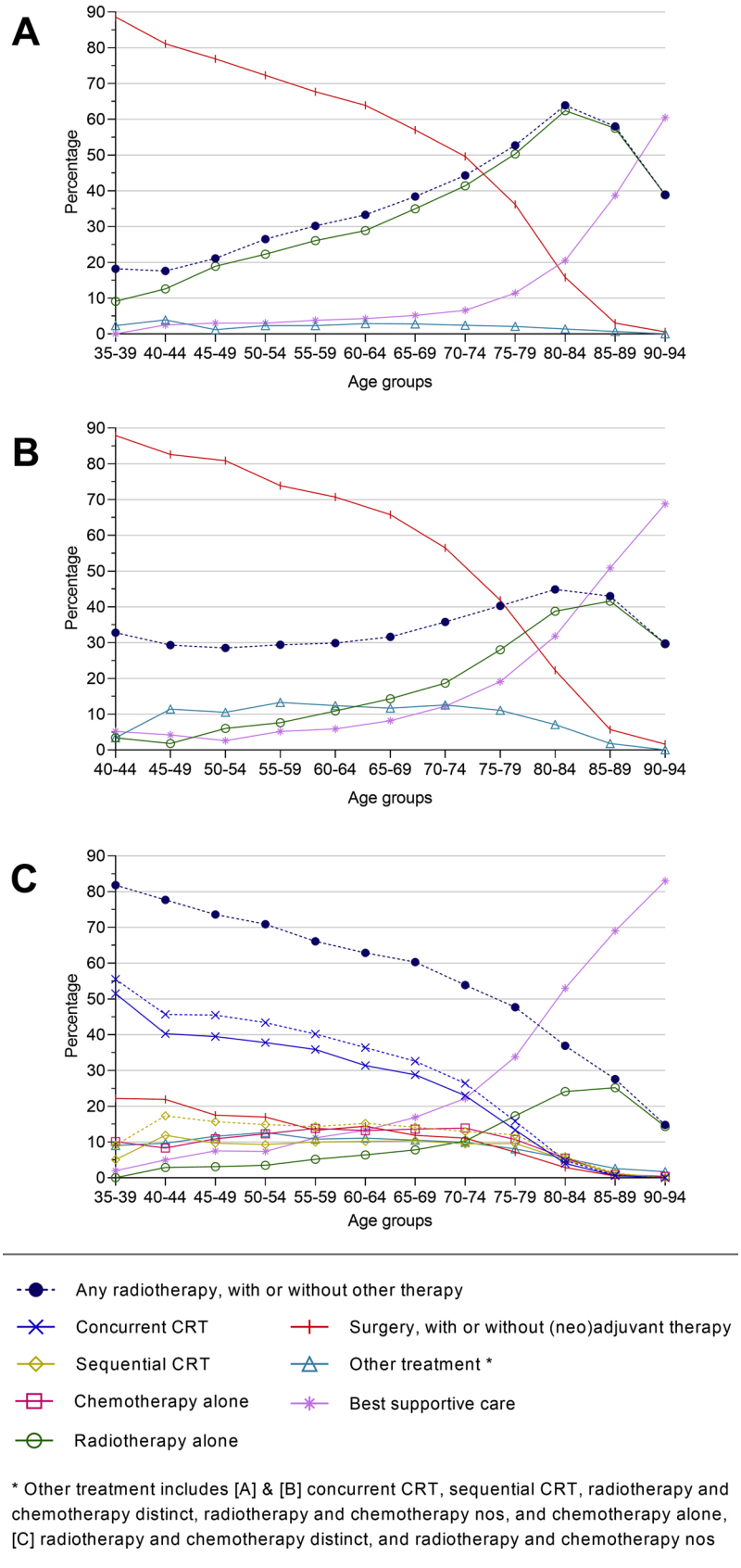

Fig. 2. Trends in primary treatment of non-small cell lung cancer in the Netherlands, presented according to 5-year age groups and stratified for [A] clinical stage I (N = 25,367), [B] clinical stage II (N = 9234), [C] clinical stage III (N = 26,852).

Table 2
Odds ratios (OR) of receiving radiotherapy (RT) compared to surgery for patients diagnosed with clinical stage I-II non-small cell lung cancer in the Netherlands between 2008 and 2018.

	RT		Surgery		Crude		Adjusted[A]	
	N = 13,153		N = 16,204					
	n	*(%)*	*n*	*(%)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Stage								
I	10,506	(79.9)	11,861	(73.2)	Reference		Reference	
II	2647	(20.1)	4343	(26.8)	**0.69**	**(0.65−0.73)**	**0.61**	**(0.57−0.65)**
Sex								
Male	7770	(59.1)	9209	(56.8)	Reference		Reference	
Female	5383	(40.9)	6995	(43.2)	**0.91**	**(0.87−0.96)**	**1.08**	**(1.03−1.14)**
Age at diagnosis, years[B]								
<60	1213	(9.2)	3682	(22.7)	Reference		Reference	
60–69	3396	(25.8)	6368	(39.3)	**1.62**	**(1.50−1.75)**	**1.64**	**(1.52−1.77)**
70–74	2648	(20.1)	3278	(20.2)	**2.45**	**(2.26−2.66)**	**2.51**	**(2.31−2.73)**
75–79	2892	(22.0)	2182	(13.5)	**4.02**	**(3.69−4.38)**	**4.31**	**(3.94−4.71)**
≥80	3004	(22.8)	694	(4.3)	**13.14**	**(11.83−14.59)**	**14.52**	**(13.02−16.18)**
Period of diagnosis								
2008–2010	2172	(16.5)	4050	(25.0)	Reference		Reference	
2011–2014	4215	(32.0)	5898	(36.4)	**1.33**	**(1.25−1.42)**	**1.36**	**(1.27−1.46)**
2015–2018	6766	(51.4)	6256	(38.6)	**2.02**	**(1.89−2.15)**	**2.09**	**(1.94−2.24)**
Region in the Netherlands								
North	1523	(11.6)	1734	(10.7)	Reference		Reference	
East	2067	(15.7)	2886	(17.8)	**0.82**	**(0.75−0.89)**	**0.88**	**(0.80−0.97)**
South	2783	(21.2)	4208	(26.0)	**0.75**	**(0.69−0.82)**	**0.85**	**(0.77−0.93)**
South west	3044	(23.1)	3536	(21.8)	0.98	(0.90−1.07)	0.92	(0.84−1.01)
North west	3736	(28.4)	3840	(23.7)	**1.11**	**(1.02−1.20)**	**1.17**	**(1.07−1.28)**
One way driving time for radiotherapy, minutes								
<15 min	5373	(40.8)	5984	(36.9)	Reference		Reference	
15–<30 min	6491	(49.3)	8288	(51.1)	**0.87**	**(0.83−0.92)**	**0.91**	**(0.86−0.96)**
30–<45 min	1178	(9.0)	1781	(11.0)	**0.74**	**(0.68−0.80)**	**0.86**	**(0.78−0.95)**
≥45 min	111	(0.8)	151	(0.9)	0.82	(0.64−1.05)	1.06	(0.80−1.39)
Median (p25, p75)	17.0	(10.0−23.0)	18.0	(11.0−24.0)	**0.99**[C]	**(0.99−0.99)**	1.00[C]	(0.99−1.00)
Type of institute of diagnosis								
University	1702	(12.9)	1892	(11.7)	Reference		Reference	
Non-university	11,450	(87.1)	14,307	(88.3)	**0.89**	**(0.83−0.95)**	**0.85**	**(0.79−0.92)**
In-house radiotherapy in the institute of diagnosis								
No	9550	(72.6)	12,655	(78.1)	Reference		Reference	
Yes	3602	(27.4)	3544	(21.9)	**1.35**	**(1.28−1.42)**	**1.57**	**(1.46−1.69)**
The average annual number of surgeries for NSCLC in the institute of diagnosis								
≥20	9598	(73.0)	12,361	(76.3)	Reference		Reference	
10–<20	484	(3.7)	794	(4.9)	**0.79**	**(0.70−0.88)**	1.04	(0.92−1.19)
1–<10	379	(2.9)	501	(3.1)	0.97	(0.85−1.12)	**1.26**	**(1.08−1.47)**
No surgery	2691	(20.5)	2543	(15.7)	**1.36**	**(1.28−1.45)**	**1.41**	**(1.32−1.52)**
Number of comorbidities[D]								
0	135	(7.3)	476	(18.1)	Reference		Reference	
1	451	(24.2)	821	(31.2)	**1.94**	**(1.55−2.42)**	**1.93**	**(1.52−2.45)**
2	517	(27.8)	665	(25.3)	**2.74**	**(2.19−3.43)**	**2.47**	**(1.94−3.15)**
≥3	757	(40.7)	669	(25.4)	**3.99**	**(3.21−4.96)**	**3.41**	**(2.69−4.33)**
Median (p25, p75)	2.0	(1.0−3.0)	2.0	(1.0−3.0)	**1.39**[C]	**(1.33−1.46)**	**1.34**[C]	**(1.27−1.40)**
WHO performance status[E]								
0	1165	(26.3)	2773	(66.3)	Reference		Reference	
1	2080	(46.9)	1291	(30.9)	**3.83**	**(3.48−4.23)**	**3.79**	**(3.40−4.21)**
≥2	1192	(26.9)	118	(2.8)	**24.04**	**(19.66−29.40)**	**23.39**	**(18.93−28.90)**

RT: radiotherapy; OR: odds ratio; CI: confidence interval; p25: 25th percentile; p75: 75th percentile; values in bold are statistically significant.

[A] The analyses were corrected for clinical stage, sex, age at diagnosis, period of diagnosis, region, one way driving time for radiotherapy, type of institute of diagnosis, whether the institute of diagnosis had in-house radiotherapy, and the average annual number of surgeries for NSCLC in the institute of diagnosis. The analyses on the type of institute of diagnosis is not corrected for in-house radiotherapy and the average annual number of surgeries for NSCLC. WHO performance status and comorbidities were only included in the multivariable models on these variables.

[B] Crude and adjusted ORs are 3.03 (95% CI: 2.89–3.18) and 3.12 (95% CI: 2.97–3.28), respectively, for patients aged ≥70 years compared to those aged <70 years, and 3.76 (95% CI: 3.57–3.97) and 3.97 (95% CI: 3.75–4.19), respectively, for patients aged ≥75 years compared to those aged <75 years.

[C] Variable included as continuous factor, with value 0 as reference.

[D] Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands.

[E] Analyses in a subset of patients diagnosed since 2015.

surgery. Although the guidelines for the treatment of NSCLC only recommend SBRT in inoperable patients [7–9], a pooled analysis of clinical trials suggested equipoise for overall survival between SBRT and surgery in operable patients [10]. Observational studies, however, showed a better overall survival after surgery [16,31–34], although these studies may be subject to unmeasured and consequently unadjusted selection bias, as a result of patient selection or physician preferences for surgery or SBRT [35,36].

Studies from the Netherlands and Australia comparing the periods before and after the clinical introduction of SBRT, showed a shift from palliative radiotherapy/best supportive care to curative radiotherapy [12,15,18]. Our study included the period after the implementation of

Table 3
Odds ratios (OR) of receiving concurrent chemoradiotherapy (CRT) compared to sequential CRT for patients diagnosed with clinical stage III non-small cell lung cancer between 2013 and 2018.

	Concurrent CRT		Sequential CRT		Crude		Adjusted[A]	
	N = 3968		N = 1319					
	n	*(%)*	*n*	*(%)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Sex								
Male	2318	(58.4)	757	(57.4)	Reference		Reference	
Female	1650	(41.6)	562	(42.6)	0.96	(0.85–1.09)	**0.82**	**(0.72–0.94)**
Age at diagnosis, years[B]								
<60	1181	(29.8)	232	1181	Reference		Reference	
60–69	1608	(40.5)	489	1608	**0.65**	**(0.54–0.77)**	**0.64**	**(0.54–0.76)**
70–74	727	(18.3)	253	727	**0.56**	**(0.46–0.69)**	**0.56**	**(0.46–0.69)**
75–79	372	(9.4)	232	372	**0.31**	**(0.25–0.39)**	**0.30**	**(0.24–0.37)**
≥80	80	(2.0)	113	80	**0.14**	**(0.10–0.19)**	**0.14**	**(0.10–0.19)**
Period of diagnosis								
2013–2015	2051	(51.7)	624	(47.3)	Reference		Reference	
2016–2018	1917	(48.3)	695	(52.7)	**0.84**	**(0.74–0.95)**	**0.87**	**(0.77–0.99)**
Region in the Netherlands								
North	618	(15.6)	115	(8.7)	Reference		Reference	
East	550	(13.9)	254	(19.3)	**0.40**	**(0.31–0.52)**	**0.39**	**(0.30–0.50)**
South	1019	(25.7)	303	(23.0)	**0.63**	**(0.49–0.79)**	**0.62**	**(0.48–0.79)**
South west	811	(20.4)	314	(23.8)	**0.48**	**(0.38–0.61)**	**0.44**	**(0.35–0.56)**
North west	970	(24.4)	333	(25.2)	**0.54**	**(0.43–0.69)**	**0.50**	**(0.40–0.64)**
One way driving time for radiotherapy, minutes								
<15 min	1575	(39.7)	520	(39.4)	Reference		Reference	
15–<30 min	2056	(51.8)	665	(50.4)	1.02	(0.89–1.17)	1.02	(0.89–1.17)
30–<45 min	318	(8.0)	122	(9.2)	0.86	(0.68–1.08)	0.85	(0.67–1.09)
≥45 min	19	(0.5)	12	(0.9)	0.52	(0.25–1.08)	0.54	(0.25–1.17)
Median (p25, p75)	17.0	(11.0–23.0)	17.0	(11.0–23.0)	1.00	(0.99–1.00)	1.00	(0.99–1.00)
Type of institute of diagnosis								
University	405	(10.2)	87	(6.6)	Reference		Reference	
Non-university	3563	(89.8)	1232	(93.4)	**0.62**	**(0.49–0.79)**	**0.65**	**(0.51–0.84)**
Radiotherapy institute volume of NSCLC treatments								
Low volume	1213	(30.6)	370	(28.1)	Reference		Reference	
High volume	2751	(69.4)	949	(71.9)	0.88	(0.77–1.01)	0.87	(0.75–1.01)
Number of comorbidities[D]								
0	124	(24.3)	27	(19.1)	Reference		Reference	
1	158	(31.0)	47	(33.3)	0.73	(0.43–1.24)	0.82	(0.47–1.42)
2	116	(22.7)	32	(22.7)	0.79	(0.45–1.40)	0.88	(0.48–1.60)
≥3	112	(22.0)	35	(24.8)	0.70	(0.40–1.22)	0.85	(0.46–1.56)
Median (p25, p75)	1.0	(1.0–2.0)	1.0	(1.0–2.0)	0.90[C]	(0.78–1.04)	0.94[C]	(0.80–1.09)
WHO performance status[E]								
0	1012	(51.5)	236	(34.9)	Reference		Reference	
1	849	(43.2)	358	(53.0)	**0.55**	**(0.46–0.67)**	**0.62**	**(0.51–0.75)**
≥2	103	(5.2)	82	(12.1)	**0.29**	**(0.21–0.40)**	**0.33**	**(0.24–0.47)**

CRT: chemoradiotherapy; OR: odds ratio; CI: confidence interval; p25: 25th percentile; p75: 75th percentile; values in bold are statistically significant.

[A] The analyses were corrected for age at diagnosis, period of diagnosis, region, and type of institute of diagnosis. WHO performance status and comorbidities were only included in the multivariable models on these variables.

[B] Crude and adjusted ORs are 0.51 (95% CI: 0.45–0.58) and 0.22 (95% CI: 0.16–0.29), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.36 (95% CI: 0.31–0.42) and 0.25 (95% CI: 0.18–0.34), respectively, for patients aged ≥75 years compared to those aged <75 years.

[C] Variable included as continuous factor, with value 0 as reference.

[D] Analyses in a subset of patients diagnosed until 2015 in the southern part of the Netherlands.

[E] Analyses in a subset of patients diagnosed since 2015.

SBRT in the Netherlands (2005–2007 [12,15]) and demonstrated that the decreasing trend of best supportive care slightly continued in stage I. In stage II, a change in treatment from best supportive care to the use of radiotherapy was demonstrated. However, this shift depends on the translation from EoD to TNM (Supplementary Document 1). Furthermore, the use of different editions of TNM affected our results in patients with stage II, as tumors sized 5–7 cm (T2bN0) were considered stage I in edition 6 and stage II in edition 7. Tumors of 5 cm or larger are not ideal candidates for SBRT [7–9], hence patients with these tumors probably received surgery, which may explain the 9 % increase in surgery in stage II between 2009 and 2010. Most other changes in TNM editions are within stages and therefore do not significantly affect our results.

A recently published Dutch study showed that patients were more frequently selected for radiotherapy instead of surgery when they were older and had a lower clinical T stage [37]. In addition, the current study found that female sex, comorbidities, and a WHO performance status ≥1 were patient characteristics associated with increased likelihood of receiving radiotherapy compared to surgery. Also in studies from other countries patients were less likely to receive surgery with a WHO performance status ≥1 [24,34], comorbidities [17,24], or at higher age [17, 24], suggesting uniform tailoring of treatment to these patients. Males and females, however, had equal probability of receiving surgery compared to no-surgery [24] or radiotherapy [17,34] in these studies. Reasons for treatment differences between sexes in the Netherlands remain unknown.

Although the Netherlands is a small country and the distance to health care facilities is relatively short, we demonstrated differences between regions and clusters of driving time in the choice of treatment. Regional differences in the use of radiotherapy were previously reported for the period 1997–2008 in the Netherlands [27]. Increased travel time was associated with less surgery in England, although 10-min clusters of driving time were not associated with radiotherapy use [38]. We showed

that a 15−44 min driving time to a radiotherapy facility was associated with less radiotherapy and more surgery compared to less than 15 min driving time. The probability of receiving radiotherapy in patients with ≥45 min driving time, however, did not differ from those in the <15 min-cluster. This may be explained by the opportunity of patients with considerable travel time to stay near the hospital during the treatment period [39,40].

We demonstrated a higher probability of radiotherapy use in patients diagnosed in a university hospital, in hospitals with in-house radiotherapy or with no or less than 10 surgeries for NSCLC per year. These observations suggest that treatment decisions in the Netherlands rely upon expertise available in the hospital where NSCLC is initially diagnosed. Contrary to our findings, the use of radiotherapy or surgery did not differ between university and non-university hospitals in the USA. Treatment decision in the USA, however, was associated with health care insurance status [17], which is irrelevant in the Netherlands as all residents have a compulsory basic health care insurance package covering both surgery and radiotherapy [41].

4.2. Stage III

The benefit of combined treatment with chemotherapy and radiotherapy in patients with unresectable stage III NSCLC became apparent more than 20 years ago [19]. As a consequence, the combined use of chemotherapy and radiotherapy in patients with stage III in the Netherlands strongly increased in 1990−2009. Information on CRT schedules then applied are unavailable [28]. The current study shows that the increase in the combined use of chemotherapy and radiotherapy slightly continued between 2008 and 2018. However, only one third of the patients received CRT, most (72 %) concurrently. Other patients with stage III received radiotherapy (12 %) or chemotherapy (11 %) alone, surgery (11 %) or best supportive care (25 %). Comorbidities, performance status, tumor size and patient's decision are indicated to be the prime reasons for non-radical intent treatment in stage III in one Dutch regional cancer care network [42]. The rates of CRT in Belgium and South Korea are comparable to our results [23,24,26]. However, sCRT was more frequently administered in Belgium [23] and half of the South Korean patients treated with CRT received trimodality treatment (including surgery) [26], which was given to only 3 % of all stage III patients in our study. In the USA, CRT is more frequently used and the proportion of definitive CRT given concurrently is almost 85 % [25].

Previously, it was reported that female and older patients were more likely to receive sCRT instead of cCRT than male and younger patients in the Netherlands [23], which was also shown in the current study for the years 2013−2018. Reasons behind the treatment difference in males and females should be explored in future research. In the USA and Belgium, CRT use diminished with increasing age [24,25], but no association between age and treatment schedule was observed [23,25]. Patients with a WHO performance status of 0 or 1 are considered eligible for cCRT [43], and no tailoring of CRT treatment is expected for performance status 1 compared to 0. However, in this study, patients with a WHO performance status 1 were less likely to receive chemoradiation concurrently. In Belgium, though, no difference in CRT schedule was found between patients with a performance status of 0 and 1 [24].

We furthermore showed heterogeneity in the application of cCRT in clinical practice in the Netherlands, which may be unwarranted. A higher probability of treatment with cCRT was demonstrated in the northern part of the Netherlands, which is considered rural compared to other regions. No associations were found between driving time and cCRT versus sCRT. In the USA, metropolitan regions did not differ from non-metropolitan regions in the probability of receiving CRT instead of radiotherapy alone, while increased distance to a care facility was modestly associated with a higher probability of CRT use [25]. Patients in the current study were more likely to receive cCRT instead of sCRT when they were diagnosed in a university hospital. In Belgium and the USA, however, the type of hospital of diagnosis did not affect the probability of receiving CRT [24,25].

4.3. Considerations

This study provides insights into variation of treatment between patients, hospitals and regions, indicating which patients received (sub) optimal treatment. Part of the treatment variation seen between patient groups suggests tailored treatment decision, although not all variation may be based on outcomes or shared decision making. Moreover, the variation reported between hospitals and regions indicate differences in clinical practice. Our findings were discussed in the Dutch Association of Radiation Oncology's division of lung cancer and all radiotherapy institutes were provided the opportunity to receive feedback on the distribution of treatment in the region of their institute. The distribution of treatment in regions of the other institutes were shown as benchmark, as well as the overall distribution in the Netherlands. In a future study, this variation may be related to survival and potentially patient reported outcomes to determine best practices.

Invasive procedures to obtain a histological or cytological confirmation may pose a significant risk of complications in fragile patients. Therefore, these procedures may be omitted in patients with clinical suspicion of NSCLC who are not fit enough to undergo these procedures [15,44]. In this study, 28 % of clinical stage I cases lack histological or cytological confirmation, most of whom received radiotherapy. Only 9 % lacked confirmation in a study in the USA [45]. Previously, the probability of malignancy was calculated to be 90 % in patients in the Netherlands with clinical stage I who received SBRT [46]. Therefore, it is unlikely that we included a substantial number of patients with benign disease.

Observational studies applied various age criteria for defining elderly [12,15,25,27,28,32,34]. When using the arbitrary age criterion ≥70 compared to ≥75 years, elderly with stage I or II had a different probability of receiving radiotherapy versus surgery, while the probability of receiving cCRT versus sCRT in elderly with stage III was comparable. However, we showed a gradual shift in treatment across ages instead of a strict age limit above which treatment choice differed, also in stage III. Our findings imply that instead of the calendar age the biological age is used as criterion for treatment selection, which is in line with guidelines on the treatment of NSCLC stating that treatment decision should reflect the fitness of individual patients rather than age [7,8].

Around 2012–2014, multiple radiotherapy facilities in the Netherlands opened satellite departments, resulting in a reduction of the mean driving time to a radiotherapy facility from 20.6 min in 2008 to 16.9 min in 2018. Due to the observational nature of our study, we cannot say if this development changed treatment patterns significantly.

4.4. Strengths and limitations

Comorbidities and WHO performance status were only available for a subset of patients, hampering detailed analyses. Another limitation is that we have only information on delivered but not on intended treatment. As a result of progression before starting radiation in intended sCRT, only chemotherapy may be delivered. Consequently, the number of sCRT treatments actually delivered is likely less than the number of intended sCRT treatments. Furthermore, reasons for non-compliance to the treatment guidelines are not registered, except for reasons for best supportive care. Another limitation was that stratification of stage IIIa and IIIb was impeded by the different TNM editions applicable in the study period, in which subgrouping of stage IIIa and IIIb changed and an additional category (IIIc) was introduced (TNM8). Finally, the use of adjuvant treatment with durvalumab after CRT in stage III disease could not be evaluated, as durvalumab was introduced only in 2018. Nevertheless, this population-based study provides a comprehensive overview of the developments and variations in treatment for stage I-III NSCLC in the Netherlands between 2008 and 2018.

4.5. Conclusions

This nationwide population-based study demonstrates patterns of care in stage I-III NSCLC in the Netherlands during the recent period 2008–2018. Radiotherapy is the predominant treatment modality in stage I since 2015, whereas surgery remained the most frequently applied therapy in stage II. The combined use of chemotherapy and radiotherapy only marginally increased in stage III. In 2018, only 26 % of patients with stage III received cCRT. In all stages, treatment varied between patient groups which suggests tailored treatment. Treatment variation between hospitals and regions indicate differences in clinical practices.

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Transparency document

The Transparency document associated with this article can be found in the online version.

CRediT authorship contribution statement

Jelle Evers: Methodology, Formal analysis, Writing - original draft, Visualization, Project administration. **Katrien de Jaeger:** Conceptualization, Methodology, Validation, Writing - review & editing. **Lizza E.L. Hendriks:** Conceptualization, Methodology, Validation, Writing - review & editing. **Maurice van der Sangen:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Chris Terhaard:** Methodology, Writing - review & editing. **Sabine Siesling:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Dirk De Ruysscher:** Conceptualization, Methodology, Validation, Writing - review & editing. **Henk Struikmans:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition. **Mieke J. Aarts:** Conceptualization, Methodology, Validation, Formal analysis, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

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Appendix A. Supplementary data

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