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Trends and variations in the treatment of stage I-III small cell lung cancer from 2008 to 2019: A nationwide population-based study from the Netherlands

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ABSTRACT

Objectives: Recent treatment patterns for small cell lung cancer (SCLC) in the Netherlands were unknown. This nationwide population-based study describes trends and variations in the treatment of stage I-III SCLC in the Netherlands over the period 2008–2019.

Materials and methods: Patients were selected from the population-based Netherlands Cancer Registry. Treatments were studied stratified for clinical stage. In stage II-III, factors associated with the use of concurrent (cCRT) versus sequential chemoradiation (sCRT) and accelerated versus conventionally fractionated radiotherapy in the context of cCRT were identified.

Results: In stage I (N = 535), 29% of the patients underwent surgery in 2008–2009 which increased to 44% in 2018–2019. Combined use of chemotherapy and radiotherapy decreased in stage I from 47% to 15%, remained constant (64%) in stage II (N = 472), and increased from 57% (2008) to 70% (2019) in stage III (N = 5,571). Use of cCRT versus sCRT in stage II-III increased over time (odds ratio (OR) $_{2008\text{-}2011\ vs\ 2016\text{-}2019}$: 0.53 (95%-confidence interval (95%CI): 0.41–0.69)) and was strongly associated with lower age, WHO performance status 0, and diagnosis in a hospital with in-house radiotherapy. Forty-six percent of patients with stage III received cCRT in 2019. Until 2012, concurrent radiotherapy was mainly conventionally fractionated, thereafter a hyperfractionated accelerated scheme was administered more frequently (57%). Accelerated radiotherapy was strongly associated with geographic region ($OR_{south\ vs\ north}$: 4.13 (95%CI: 3.00–5.70)), WHO performance ($OR_{1\ vs\ 0}$: 0.50 (95%CI: 0.35–0.71)), and radiotherapy facilities treating $\geq$ 16 vs < 16 SCLC patients annually (OR: 3.01 (95%CI: 2.38–3.79)).

Conclusions: The use of surgery increased in stage I. In stages II and III, the use of cCRT versus sCRT increased over time, and since 2012 most radiotherapy in cCRT was accelerated. Treatment regimens and radiotherapy fractionation schemes varied between patient groups, regions and hospitals. Possible unwarranted treatment variation should be countered.

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1. Introduction

Small cell lung cancer (SCLC) accounts for approximately 12% of all lung cancer diagnoses worldwide and is often (~70%) metastasized at first presentation [1]. Almost all patients without distant metastases are diagnosed with locoregionally advanced disease [2]. Historically, SCLC was classified either as limited (disease confined to one hemithorax and regional lymph nodes that can be encompassed in the same radiation portal as the primary tumor) or extensive disease (the remainder). Limited disease roughly translates into the potentially curable TNM stages I-III, whereas extensive disease translates into stage IV [3].

Chemoradiation (CRT) is the cornerstone of treatment with curative intent for non-metastatic SCLC since the 1980s [4,5]. However, for very early stages (T1-2N0), surgical resection and stereotactic body radiotherapy (SBRT), both followed by adjuvant chemotherapy, are considered valid treatment strategies [6–8]. For advanced non-metastatic disease stages, concurrent CRT (cCRT) is the standard of care. Sequential CRT (sCRT) is used in unfit patients [6–8]. In 1999, a randomized phase III-trial showed that an accelerated twice-daily radiotherapy fractionation scheme was more effective than the conventional once-daily scheme [9]. However, concerns about its toxicity and logistic issues have challenged the adaptation of the twice-daily scheme [10,11]. In patients in good clinical condition who have no progressive disease after CRT, prophylactic cranial irradiation (PCI) is recommended [12]. Nevertheless, PCI results in a significant neurocognitive decline [13] and did become controversial as in stage IV disease, when compared to only MRI follow-up of the brain, survival was not superior after PCI and MRI follow-up, despite a reduced incidence of brain metastases [14].

Patterns of care for PCI in the Netherlands have previously been described [15]. This study describes further recent trends in treatment strategies for stage I-III SCLC in the Netherlands (2008–2019), which remained unclear. Furthermore, variables associated with the use of cCRT versus sCRT and accelerated versus conventionally fractionated radiotherapy in the context of cCRT were identified. These data provide insights into the variations in curative treatment regimens applied in SCLC from 2008 until 2019.

2. Materials and methods

2.1. Study population

Patients diagnosed with clinical stage I-III SCLC in 2008–2019 were selected from the nationwide Netherlands Cancer Registry (NCR), which contains information on patient, disease, and the primary treatment given [16]. Trained data managers extracted these data from hospitals' medical records. TNM editions 6 (2008–2009), 7 (2010–2016), and 8 (2017–2019) were used. Patients diagnosed at autopsy, or who resided or received treatment abroad were excluded.

2.2. Definitions

Combined use of radiotherapy and chemotherapy was classified as cCRT, sCRT or distinct therapies (Supplementary Fig. 1). Concurrent treatment was defined as either chemotherapy or radiotherapy starting during the other treatment modality, or the modalities starting ≤ 30 days from each other. Sequential treatment was defined as chemotherapy and radiotherapy staring 31-≤90 days apart. If the interval between the start of chemotherapy and radiotherapy was longer than 90 days, the modalities were classified as distinct treatments. In case of a missing starting date, treatments were classified as chemotherapy and radiotherapy not otherwise specified (nos). Both PCI and SBRT combined with chemotherapy were classified as distinct therapies. Radiotherapy in the context of cCRT was considered accelerated when the interval between the start and end of a full course of radiotherapy was 15–28 days. A radiotherapy course <15 days or exceeding 28 days was considered terminated prematurely and conventionally fractionated, respectively.

We divided the Netherlands into five geographic regions, each including ≥3 radiotherapy facilities and ≥11 hospitals, including ≥1 university hospital. Clustered travelling times to a radiotherapy facility, defined as a one-way trip by car, were: <15, 15–<30 or ≥30 min. Radiotherapy facilities' volume was dichotomized: half of the facilities provided radiotherapy to a mean of <16 patients with stage I-III SCLC annually, the other half to a mean of ≥16 patients. Furthermore, radiotherapy facilities were divided by in-house (embedded in the organization of a diagnosing hospital) and independent (other facilities).

Data on comorbidities at diagnosis as registered in medical records were available only until 2015 for patients in the southern part of the Netherlands (covering ~ 15% of the Netherlands) [17]. WHO performance status, also referred to as ECOG or Zubrod scale [18], and reasons for best supportive care (BSC) were registered for all patients since 2015.

2.3. Analyses

Patient and disease characteristics, the frequency of applied combined treatment modalities, and trends in treatment over time as well as for separate age groups were all stratified for clinical stage. Because of the limited number of patients with stage I and II, trends in these stages were not statistically tested and the graphs on these stages present moving averages over three subsequent years and age groups. For stage III disease the trends in treatment over time were tested using a univariable linear regression analyses. As patients within the chemotherapy and radiotherapy nos-cohort potentially received CRT, this percentage was added to the lines of both cCRT and sCRT and depicted in a dotted format to represent an estimate of their highest possible rates.

In patients with stage II and III disease, logistic regression analyses were performed to identify variables associated with the use of cCRT versus sCRT and accelerated versus conventionally fractionated cCRT. As stage II included a limited number of patients and because the received treatments were largely comparable to those of stage III, both stages were combined. In stage I, the treatment applied differs, but the small number of patients hampered further investigation in treatment variation. For each association investigated, a set of variables for adjustment were selected. Variables were included in the adjustment set if including the variable in multivariable analyses changed one of the odds ratios (OR) of the association investigated with at least 10% compared to the ORs resulting from the univariable analyses. The number of comorbidities and WHO performance status were never included in the adjustment sets, as these variables were only limited available. The analyses on university versus non-university hospitals were furthermore never adjusted for in-house radiotherapy, as this is considered a basic component of university hospitals. Ninety-five percent confidence intervals (95%CI) reflect probable estimates for the OR using a p-value of 0.05 as critical level.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, USA).

3. Results

3.1. Patient characteristics

A total of 20,678 patients were diagnosed with SCLC in 2008–2019. The proportion of stage IV disease increased from 64% in 2008 to 70% in 2019, while the proportion of stage III disease decreased from 32% to 24%. The proportions of stage I (3%) and stage II disease (1–3%) remained constant. This study includes 6,578 (32%) patients diagnosed with clinical stage I-III disease. One patient was excluded from our study because of treatment abroad.

Almost half of the patients were male and the median ages at diagnosis in stage I, II and III disease were 70, 69 and 67 years, respectively (Table 1). In patients for whom comorbidities were assessed, 80–88% had at least one comorbidity, of which hypertension was most prevalent.

Table 1
Characteristics of patients in the Netherlands diagnosed with small cell lung cancer in 2008–2019, stratified for clinical stage.

	Stage I		Stage II		Stage III	
	N = 535		N = 472		N = 5,571	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*
Male	278	(52.0)	237	(50.2)	2,643	(47.4)
Age at diagnosis, years						
<60	75	(14.0)	79	(16.7)	1,212	(21.8)
60–<70	185	(34.6)	174	(36.9)	2,088	(37.5)
70–<75	111	(20.7)	98	(20.8)	962	(17.3)
75–<80	89	(16.6)	78	(16.5)	781	(14.0)
≥80	75	(14.0)	43	(9.1)	528	(9.5)
Median (p25, p75)	70.0	(63.0, 77.0)	69.0	(61.0, 75.0)	67.0	(61.0, 74.0)
Period of diagnosis						
2008–2011	180	(33.6)	144	(30.5)	2,006	(36.0)
2012–2015	177	(33.1)	149	(31.6)	1,881	(33.8)
2016–2019	178	(33.3)	179	(37.9)	1,684	(30.2)
Region						
North	53	(9.9)	61	(12.9)	760	(13.6)
East	99	(18.5)	84	(17.8)	997	(17.9)
South	135	(25.2)	141	(29.9)	1,406	(25.2)
South west	116	(21.7)	70	(14.8)	1,175	(21.1)
North west	132	(24.7)	116	(24.6)	1,233	(22.1)
Comorbidities at diagnosis being assessed [A]	85	(15.9)	74	(15.7)	835	(15.0)
≥1 comorbidity at diagnosis	68	(80.0)	65	(87.8)	671	(80.4)
Median number of comorbidities (p25, p75)	2.0	(1.0, 3.0)	2.0	(1.0, 3.0)	1.0	(1.0, 3.0)
Most frequent comorbidities						
Hypertension	21	(24.7)	25	(33.8)	282	(33.8)
Chronic pulmonary disease	32	(37.6)	29	(39.2)	256	(30.7)
Diabetes mellitus	14	(16.5)	9	(12.2)	141	(16.9)
WHO performance status at diagnosis available [B]	152	(28.4)	161	(34.1)	1,523	(27.3)
0	68	(44.7)	54	(33.5)	491	(32.2)
1	58	(38.2)	75	(46.6)	695	(45.6)
2	21	(13.8)	24	(14.9)	240	(15.8)
3	5	(3.3)	7	(4.3)	77	(5.1)
4	0	(0.0)	1	(0.6)	20	(1.3)
Primary therapy						
Concurrent CRT	94	(17.6)	200	(42.4)	2,165	(38.9)
Sequential CRT	12	(2.2)	16	(3.4)	421	(7.6)
RT and chemotherapy - distinct therapies	40	(7.5)	56	(11.9)	770	(13.8)
RT and chemotherapy - nos	23	(4.3)	11	(2.3)	223	(4.0)
RT alone	92	(17.2)	26	(5.5)	109	(2.0)
RT alone	36	(6.7)	35	(7.4)	1,065	(19.1)
Surgery (+/- chemotherapy, +/- RT)	189	(35.3)	85	(18.0)	41	(0.7)
BSC / other therapy / unknown therapy [C]	49	(9.2)	43	(9.1)	777	(13.9)
Received any RT (excl. PCI)	269	(50.3)	328	(69.5)	3,703	(66.5)
Received SBRT	82	(30.5)	13	(4.0)	15	(0.4)
Received PCI	168	(31.4)	243	(51.5)	2,774	(49.8)

CRT: chemoradiation; RT: radiotherapy; BSC: best supportive care; SBRT: stereotactic body radiotherapy; PCI: prophylactic cranial irradiation; p25: 25th percentile; p75: 75th percentile.

A Comorbidities were registered until 2015 for patients in the southern part of the Netherlands.

B WHO performance status is registered since 2015 and missing for 34.9% of the patients diagnosed in 2015-2019.

C 13 patients (all with clinical stage III) received other/unknown therapy.

Seventeen percent of stage I patients had a WHO performance status ≥ 2, whereas these figures were 20% and 22% for stage II and III cases, respectively. Surgery was the treatment mostly applied in stage I (received by 35%), followed by cCRT (18%) and radiotherapy alone (17%). In stage II and III, cCRT was most often applied (42% and 39%, respectively), followed by surgery in stage II (18%) and chemotherapy alone in stage III (19%). Nine percent of patients with stage I and II disease received BSC, which was 14% of those with stage III disease. Refusal of curative-intent treatment by the patient was the main reason.

3.2. Trends in treatment

In stage I, the percentage of patients treated with both chemotherapy and radiotherapy decreased from 47% in 2008–2009 to 15% in 2018–2019, while the use of surgery increased from 29% to 44% (Fig. 1). Seventy-one percent of these patients received adjuvant chemotherapy. Fifty-six percent of those undergoing surgery in 2008–2013 had no prior pathology confirmation, which decreased to 39% in 2014–2019. The percentage of patients receiving radiotherapy alone increased from 8% in 2008–2009 to 22% in 2018–2019, of whom 75% received SBRT. Only 16% of patients receiving SBRT had also chemotherapy administered.

In stage II, the rate of combined use of chemotherapy and radiotherapy remained constant over time (64%) (Fig. 2). In 2008–2009, some combined use could not be classified due to a missing start date. Since 2010, 44% of the patients received cCRT, 3% sCRT and 12% chemotherapy and radiotherapy as distinct therapies. The proportion of concurrently treated patients receiving accelerated radiotherapy increased from 24% (2009–2011) to 65% (2018–2019). Only a subset of stage II patients underwent surgery (18%) or received SBRT (4%).

In stage III, the percentage of patients receiving both chemotherapy and radiotherapy increased from 57% in 2008 to 70% in 2019 ($p < 0.001$) (Fig. 3). Four percent of patients had treatment classified as chemotherapy and radiotherapy nos, mainly in 2008–2009. The use of cCRT increased from 37% in 2010 to 46% in 2019 ($p < 0.001$), while use of sCRT (8%) and use of the modalities as distinct therapies remained constant in 2010–2019 (15%) ($p = 0.97$ and $p = 0.30$, respectively). Since 2012, most patients treated with cCRT received accelerated radiotherapy (57%). The use of chemotherapy alone decreased from 28% (2008) to 14% (2019) ($p < 0.001$).

In patients with stage I disease, 39% received PCI in 2008–2009, 46% in 2011–2013 and 13% in 2018–2019. These figures were 46–50%, 55–59% and 40–41% in patients with stage II and III disease, respectively.

In all stages, treatment shifted gradually across ages (Supplementary Fig. 2). Older patients received less often surgery, cCRT and PCI, and more often radiotherapy alone or BSC. In stage II and III, older patients also received more often chemotherapy without radiotherapy.

3.3. Concurrent and sequential chemoradiation

The variables strongest associated with cCRT versus sCRT in stage II-III were period of diagnosis (OR 2008-2011 vs 2016-2019: 0.53), age at diagnosis (OR ≥80 vs <60years: 0.13) and WHO performance status (OR ≥2 vs 0: 0.23) (Table 2). The likelihood of receiving cCRT instead of sCRT ranged by region: ORs were 0.52–1.72. Patients diagnosed in a university hospital or hospital with in-house radiotherapy had a higher probability of receiving cCRT. Also ≥30 min of travel time for radiotherapy compared to <15 min was associated with less cCRT.

In 2008–2019, 45% of the patients with stage II-III disease treated with cCRT received accelerated radiotherapy and 44% conventionally fractionated radiotherapy. For the remaining 11% the fractionation scheme could not be determined.

The variables strongest associated with accelerated versus conventionally fractionated radiotherapy were period of diagnosis (OR 2008-2011 vs 2016-2019: 0.21), region (OR south vs north: 4.13) and the

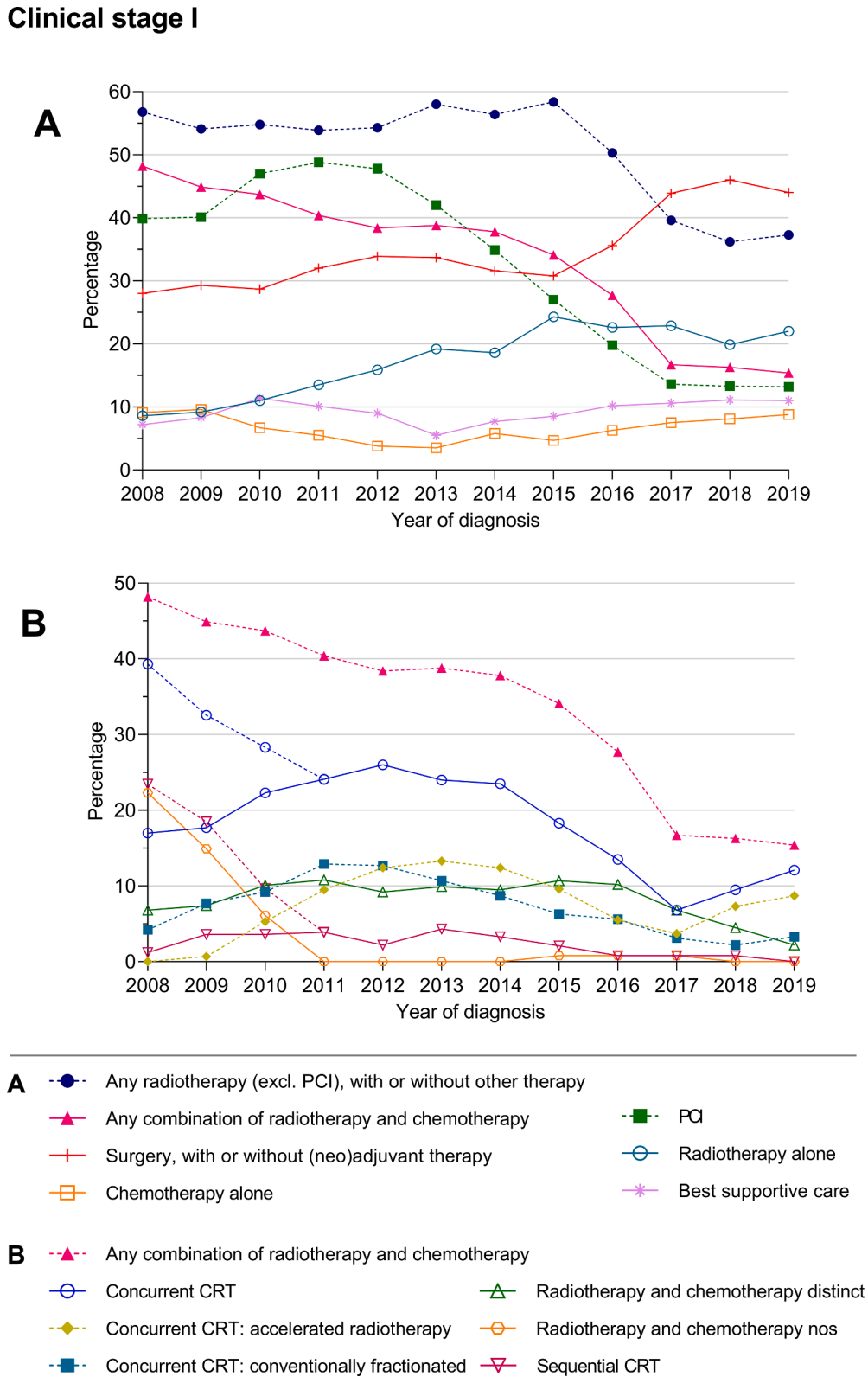

Fig. 1. Trends over the years of diagnosis for [A] all primary treatment applied (%) and [B] use of both chemotherapy and radiotherapy (%), in patients with clinical stage I small cell lung cancer in the Netherlands, N = 535 (moving averages over 3 subsequent years).

volume of SCLC patients in the radiotherapy facility (OR ≥16 vs <16 SCLC patients/year: 3.01) (Table 3). No differences between age groups were observed, except for those aged 75–79 years compared to <60 years (OR: 0.66). Both patients with ≥30 min of travel time for radiotherapy compared to <15 min and those with a WHO performance status of 1 compared to 0 were less likely to receive accelerated radiotherapy. Patients diagnosed in a hospital with in-house radiotherapy had a higher probability of receiving accelerated radiotherapy (OR: 1.42). Only 6% of these patients had chemotherapy administered somewhere else than their radiotherapy, compared to 93% of the patients diagnosed

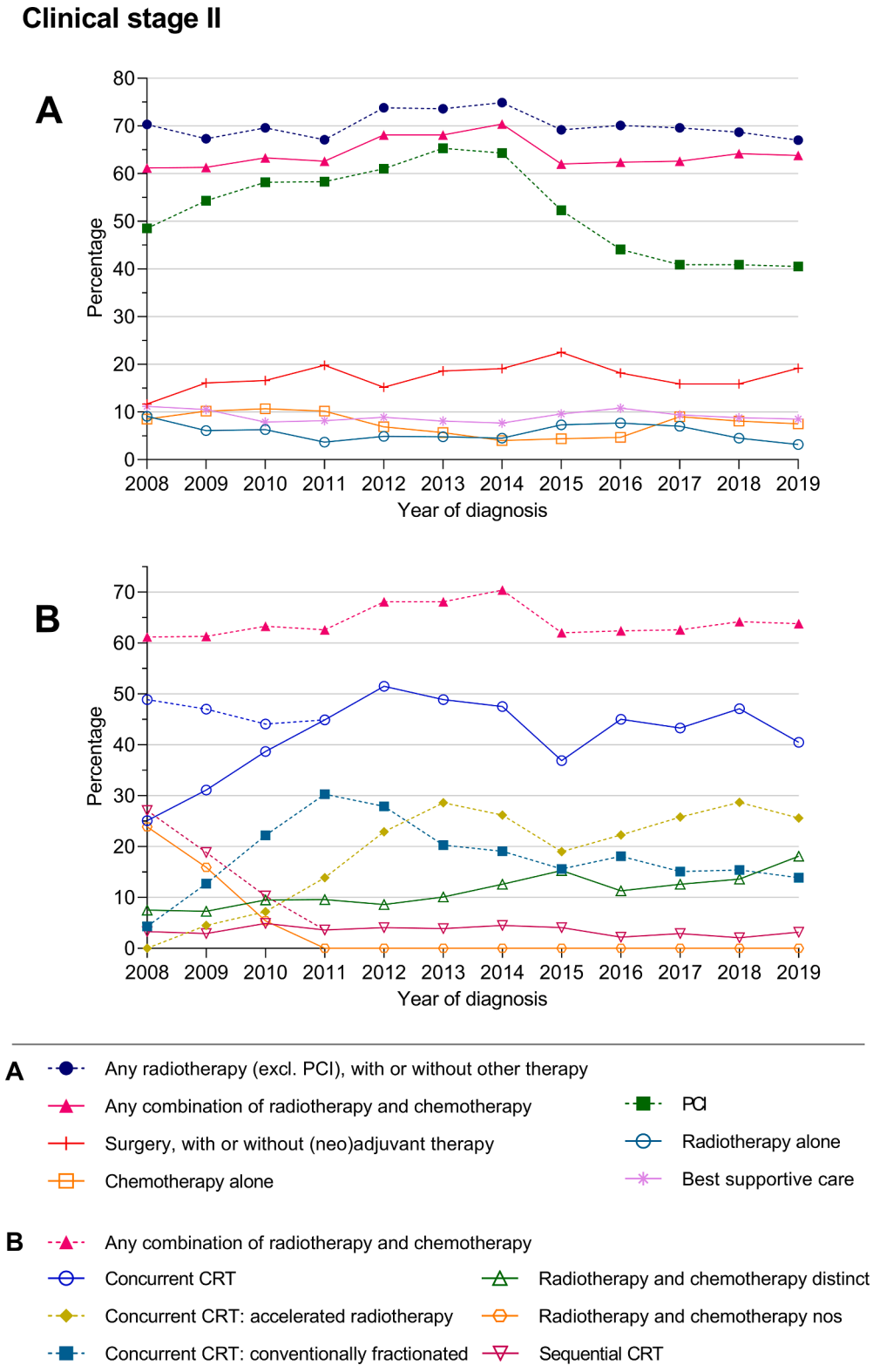

Fig. 2. Trends over the years of diagnosis for [A] all primary treatment applied (%) and [B] use of both chemotherapy and radiotherapy (%), in patients with clinical stage II small cell lung cancer in the Netherlands, N = 472 (moving averages over 3 subsequent years).

in a hospital without in-house radiotherapy.

In 2008–2009, not all combinations of chemotherapy and radiotherapy could be classified as CRT (cCRT/sCRT) or distinct therapies. Nevertheless, sensitivity analyses showed comparable estimates for the multivariable analyses when including only 2010–2019 (Supplementary Table 1 and 2).

4. Discussion

This study describes recent trends and variations in treatment strategies for stage I-III SCLC in the Netherlands. An increased use of surgery and decreased combined use of chemotherapy and radiotherapy was observed in stage I disease, while the combined use of chemotherapy

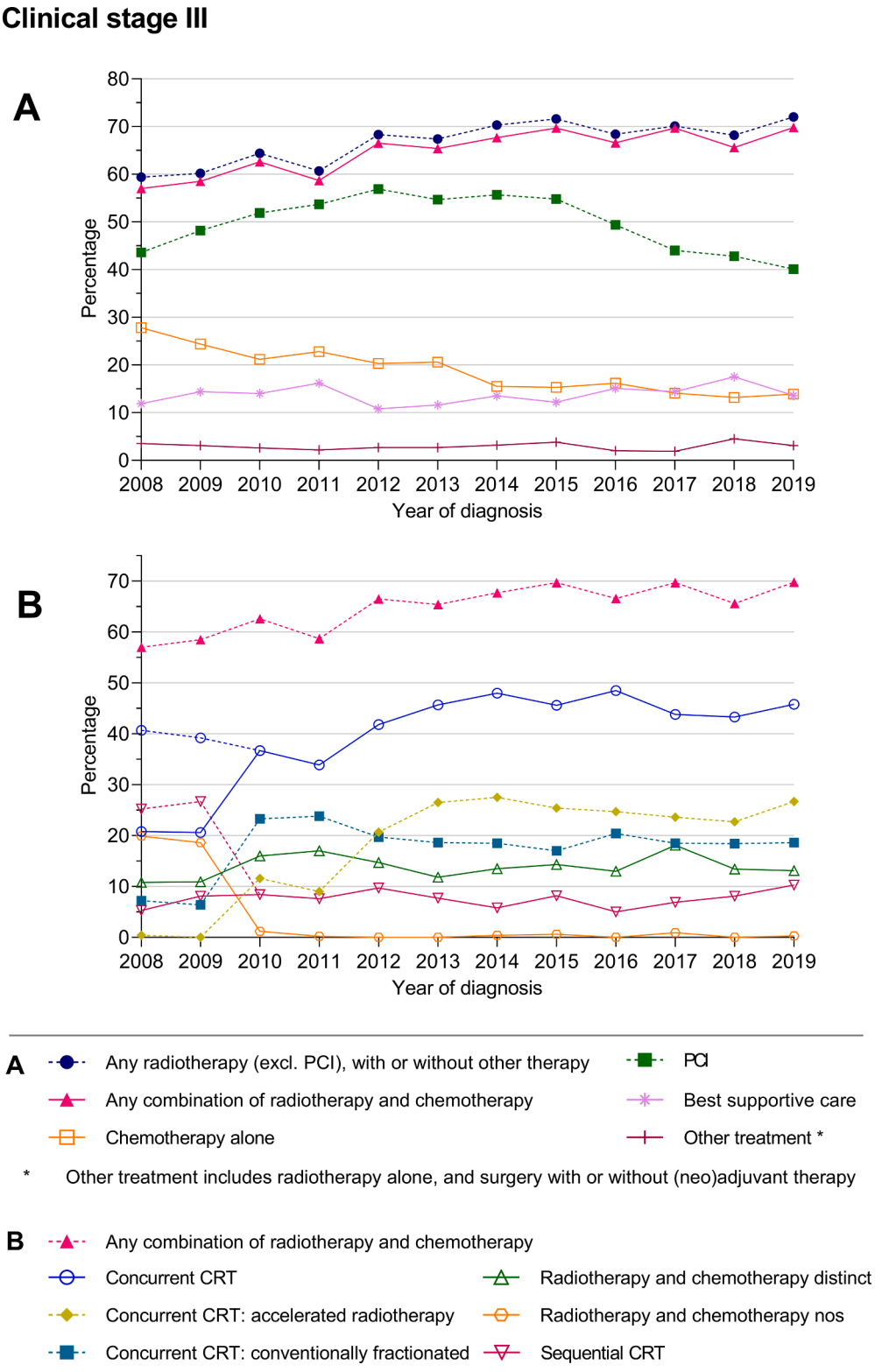

Fig. 3. Trends over the years of diagnosis for [A] all primary treatment applied (%) and [B] use of both chemotherapy and radiotherapy (%), in patients with clinical stage III small cell lung cancer in the Netherlands, N = 5571.

and radiotherapy remained stable in stage II and increased in stage III disease. Most patients with stage II-III disease received cCRT in a hyperfractionated accelerated scheme since 2012.

Similarly to our results, the use of surgery in stage I increased in the USA [19,20] from 14.9% (2004) to 28.5% (2013) [19]. This trend is in line with current treatment guidelines considering surgery with adjuvant chemotherapy as a treatment option in T1-2 N0-tumors [6–8], as relatively favorable survival outcomes were reported in cohorts and historical series [21–25]. In our study, an increasing percentage of patients with stage I disease had a pathology confirmation before surgery. This suggests that a decreasing number of patients had their surgery based on an initial non-small cell lung cancer (NSCLC) diagnosis, but no

Table 2
Odds ratios (OR) of receiving concurrent chemoradiation (CRT) compared to sequential CRT in patients diagnosed with small cell lung cancer clinical stage II-III in the Netherlands between 2008 and 2019

	Concurrent CRT		Sequential CRT		Crude		Adjusted [A]	
	N = 2,365		N = 437					
	n	(%)	n	(%)	OR	(95% CI)	OR	(95% CI)
Sex								
Male	1,084	(45.8)	203	(46.5)	Reference		Reference	
Female	1,281	(54.2)	234	(53.5)	1.03	(0.84–1.26)	0.90	(0.73–1.11)
Age at diagnosis, years [B]								
<60	713	(30.1)	93	(21.3)	Reference		Reference	
60—69	1,030	(43.6)	159	(36.4)	0.84	(0.64–1.11)	0.80	(0.60–1.05)
70–74	377	(15.9)	78	(17.8)	**0.63**	**(0.46–0.87)**	**0.58**	**(0.42–0.81)**
75–79	206	(8.7)	76	(17.4)	**0.35**	**(0.25–0.50)**	**0.30**	**(0.21–0.43)**
≥80	39	(1.6)	31	(7.1)	**0.16**	**(0.10–0.28)**	**0.13**	**(0.08–0.23)**
Period of diagnosis								
2008–2011	604	(25.5)	152	(34.8)	**0.62**	**(0.48–0.80)**	**0.53**	**(0.41–0.69)**
2012–2015	920	(38.9)	154	(35.2)	0.93	(0.72–1.20)	0.85	(0.66–1.10)
2016–2019	841	(35.6)	131	(30.0)	Reference		Reference	
Region								
North	344	(14.5)	53	(12.1)	Reference		Reference	
East	428	(18.1)	96	(22.0)	**0.69**	**(0.48–0.99)**	0.73	(0.51–1.06)
South	635	(26.8)	63	(14.4)	**1.55**	**(1.05–2.29)**	**1.72**	**(1.16–2.57)**
South west	408	(17.3)	118	(27.0)	**0.53**	**(0.37–0.76)**	**0.52**	**(0.37–0.75)**
North west	550	(23.3)	107	(24.5)	0.79	(0.55–1.13)	0.84	(0.59–1.21)
One-way travel time for radiotherapy, minutes								
<15 min	905	(38.3)	160	(36.6)	Reference		Reference	
15 - <30 min	1,203	(50.9)	211	(48.3)	1.01	(0.81–1.26)	1.01	(0.81–1.26)
≥30 min	257	(10.9)	66	(15.1)	**0.69**	**(0.50–0.95)**	**0.69**	**(0.50–0.95)**
Median (p25, p75)	18.0	(11.0, 24.0)	18.0	(11.0, 25.0)	0.99	(0.98–1.00)	0.99	(0.98–1.00)
Type of hospital of diagnosis								
University	236	(10.0)	29	(6.6)	Reference		Reference	
Non-university	2,129	(90.0)	408	(93.4)	**0.64**	**(0.43–0.96)**	**0.64**	**(0.43–0.96)**
In-house radiotherapy								
No	1,850	(78.2)	359	(82.2)	Reference		Reference	
Yes	515	(21.8)	78	(17.8)	1.28	(0.98–1.67)	**1.45**	**(1.06–1.98)**
Radiotherapy facility volume of SCLC treatments								
<16 patients annually	666	(28.2)	122	(28.0)	Reference		Reference	
≥16 patients annually	1,698	(71.8)	313	(72.0)	0.99	(0.79–1.25)	0.91	(0.69–1.18)
Number of comorbidities at diagnosis [D]								
0	60	(20.4)	8	(22.2)	Reference		C	C
1	110	(37.4)	9	(25.0)	1.63	(0.60–4.44)		
2	55	(18.7)	10	(27.8)	0.73	(0.27–1.99)		
≥3	69	(23.5)	9	(25.0)	1.02	(0.37–2.82)		
WHO performance status [E]								
0	350	(43.0)	33	(26.0)	Reference		Reference	
1	390	(47.9)	61	(48.0)	**0.60**	**(0.39–0.94)**	0.72	(0.45–1.14)
≥2	74	(9.1)	33	(26.0)	**0.21**	**(0.12–0.36)**	**0.23**	**(0.13–0.40)**

CRT: chemoradiation; CI: confidence interval; values in bold are statistically significant.
A The analyses on sex and period of diagnosis were corrected for age at diagnosis, the analysis on age at diagnosis was corrected for period of diagnosis and region, the analysis on region was corrected for radiotherapy facility volume of SCLC treatments, the analyses on travel time for radiotherapy and type of hospital of diagnosis were not corrected as none of the variables fullfeed the criteria for inclusion in the adjustment sets, the analysis on in-house radiotherapy was corrected for region and type of hospital of diagnosis, the analysis on radiotherapy facility volume of SCLC treatments was corrected for region and in-house radiotherapy, the analysis on WHO performance status was corrected for age at diagnosis and region.
B Crude and adjusted ORs are 0.49 (95% CI: 0.39-0.60) and 0.45 (95% CI: 0.36-0.56), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.36 (95% CI: 0.28-0.46) and 0.32 (95% CI: 0.24-0.41), respectively, for patients aged ≥75 years compared to those aged <75 years.
C No multivariable analyses were performed, considering the limited number of patients.
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.

data was available on whether the initial diagnosis upon (central) revision of pathology was NSCLC instead of SCLC. SBRT followed by chemotherapy may nowadays also be used [6], despite limited evidence [26]. In our study, one third of all irradiated patients with stage I disease received SBRT, mostly without adjuvant chemotherapy. The use of radiotherapy alone in stage I, increased over time. Reasons for not administering chemotherapy were not available. In the USA, half of the stage I patients receiving SBRT also had chemotherapy administered, 43% of whom prior to SBRT [19].

Our study demonstrates that combined use of chemotherapy and radiotherapy increased in stage III disease, which concerns the majority of patients included. Increased use of both modalities was already observed in the period 1997–2007 in the Netherlands, as well as in 2004–2011 in England [27,28]. Unfortunately, details on CRT variations lacked in these studies [27,28], and CRT could not be distinguished from chemotherapy followed by PCI [28]. We found that 39–42% of the patients with stage II-III disease received cCRT and 3–8% sCRT. Furthermore, the use of cCRT versus sCRT increased over time and varied between patient groups, hospitals, and geographic regions. Variation in SCLC treatment within a country was also demonstrated in England, where chemotherapy regimens and administration varied between hospital networks [29].

Until 2012, a minority of patients with stage II-III disease received cCRT in a hyperfractionated accelerated scheme. This corresponds with

Table 3
Odds ratios (OR) of receiving accelerated radiotherapy (RT) compared to conventionally fractionated RT as part of concurrent chemoradiation in patients diagnosed with small cell lung cancer clinical stage II-III in the Netherlands between 2008 and 2019

	Accelerated RT		Conventionally fractionated RT		Crude		Adjusted [A]	
	N = 1,069		N = 1,049					
	n	*(%)*	*n*	*(%)*	*OR*	*(95% CI)*	*OR*	*(95% CI)*
Sex								
Male	476	(44.5)	497	(47.4)	Reference		Reference	
Female	593	(55.5)	552	(52.6)	1.12	(0.95–1.33)	1.12	(0.95–1.33)
Age at diagnosis, years [B]								
<60	314	(29.4)	317	(30.2)	Reference		Reference	
60–69	482	(45.1)	450	(42.9)	1.08	(0.88–1.32)	1.01	(0.80–1.27)
70–74	168	(15.7)	167	(15.9)	1.02	(0.78–1.32)	0.90	(0.66–1.22)
75–79	89	(8.3)	100	(9.5)	0.90	(0.65–1.24)	**0.66**	**(0.45–0.96)**
≥80	16	(1.5)	15	(1.4)	1.08	(0.52–2.22)	0.63	(0.27–1.47)
Period of diagnosis								
2008–2011	107	(10.0)	324	(30.9)	**0.25**	**(0.19–0.32)**	**0.21**	**(0.16–0.28)**
2012–2015	504	(47.1)	379	(36.1)	1.00	(0.83–1.22)	0.96	(0.78–1.18)
2016–2019	458	(42.8)	346	(33.0)	Reference		Reference	
Region								
North	102	(9.5)	188	(17.9)	Reference		Reference	
East	195	(18.2)	185	(17.6)	**1.94**	**(1.42–2.66)**	**1.46**	**(1.05–2.03)**
South	447	(41.8)	138	(13.2)	**5.97**	**(4.39–8.12)**	**4.13**	**(3.00–5.70)**
South west	84	(7.9)	284	(27.1)	**0.55**	**(0.39–0.77)**	**0.59**	**(0.41–0.84)**
North west	241	(22.5)	254	(24.2)	**1.75**	**(1.30–2.36)**	1.37	(1.00–1.86)
One-way travel time for radiotherapy, minutes								
<15 min	428	(40.0)	400	(38.1)	Reference		Reference	
15 - <30 min	553	(51.7)	511	(48.7)	1.01	(0.84–1.21)	0.82	(0.67–1.00)
≥30 min	88	(8.2)	138	(13.2)	**0.60**	**(0.44–0.80)**	**0.63**	**(0.46–0.87)**
Median (p25, p75)	17.0	(11.0, 23.0)	18.0	(11.0, 25.0)	**0.98**	**(0.98–0.99)**	**0.98**	**(0.97–0.99)**
Type of hospital of diagnosis								
University	93	(8.7)	105	(10.0)	Reference		Reference	
Non-university	976	(91.3)	944	(90.0)	1.17	(0.87–1.56)	1.17	(0.87–1.56)
In-house radiotherapy								
No	900	(84.2)	780	(74.4)	Reference		Reference	
Yes	169	(15.8)	269	(25.6)	**0.54**	**(0.44–0.68)**	**1.42**	**(1.03–1.94)**
Radiotherapy facility volume of SCLC treatments								
<16 patients annually	142	(13.3)	439	(41.9)	Reference		Reference	
≥16 patients annually	927	(86.7)	609	(58.1)	**4.71**	**(3.80–5.84)**	**3.01**	**(2.38–3.79)**
Number of comorbidities at diagnosis [D]								
0	34	(17.9)	16	(22.9)	Reference		C	C
1	77	(40.5)	24	(34.3)	1.51	(0.71–3.20)		
2	38	(20.0)	10	(14.3)	1.79	(0.72–4.47)		
≥3	41	(21.6)	20	(28.6)	0.96	(0.43–2.15)		
WHO performance status [E]								
0	216	(47.6)	121	(37.0)	Reference		Reference	
1	201	(44.3)	177	(54.1)	**0.64**	**(0.47–0.86)**	**0.50**	**(0.35–0.71)**
≥2	37	(8.1)	29	(8.9)	0.71	(0.42–1.22)	0.54	(0.28–1.04)

RT: radiotherapy; CI: confidence interval; values in bold are statistically significant.
A The analyses on sex and type of hospital of diagnosis were not corrected as none of the variables fullfeed the criteria for inclusion in the adjustment sets, the analysis on age at diagnosis was corrected for period of diagnosis, region and radiotherapy facility volume of SCLC treatments, the analyses on period of diagnosis and radiotherapy facility volume of SCLC treatments were corrected for region, the analysis on region was corrected for radiotherapy facility volume of SCLC treatments, the analysis on travel time for radiotherapy was corrected for in-house radiotherapy and radiotherapy facility volume of SCLC treatments, the analysis on in-house radiotherapy was corrected for region, type of hospital of diagnosis and radiotherapy facility volume of SCLC treatments, the analysis for WHO performance status was corrected for region and radiotherapy facility volume of SCLC treatments.
B Crude and adjusted ORs are 0.93 (95% CI: 0.77-1.13) and 0.79 (95% CI: 0.63-1.0.99), respectively, for patients aged ≥70 years compared to those aged <70 years, and 0.88 (95% CI: 0.67-1.17) and 0.65 (95% CI: 0.48-0.92), respectively, for patients aged ≥75 years compared to those aged <75 years.
C No multivariable analyses were performed, considering the limited number of patients.
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.

the limited use of twice-daily cCRT reported for the USA until 2012, where only 11% of the patients with non-metastatic disease received twice-daily radiotherapy [30]. Limited use may reflect logistic challenges of a twice-daily regimen, concerns about its toxicity [10,11], or doubt about the reported benefit of the accelerated fractionation arm in the Turrisi-trial [9], as a relatively low dose was administered in the once-daily arm (45 Gy in 25 fractions). The more recent CONVERT-trial revealed no statistically significant difference in survival between twice-daily and once-daily radiotherapy with a higher total dose (66 Gy in 33 fractions) [31]. The toxicity rates were comparable between both arms and lower than in the Turrisi-trial. As the CONVERT-trial was powered to demonstrate superiority of once-daily radiotherapy and not equivalence, it should not be an argument to justify administering once- instead of twice-daily cCRT. The first trial results were presented in 2015 and most patients treated with cCRT in the Netherlands received accelerated radiotherapy since 2012. Reassuringly, we found no difference in the use of accelerated versus conventionally fractionated cCRT between 2012 and 2015 and 2016–2019 in multivariable analyses, suggesting that the trial results were not commonly used for falsely justifying once-daily cCRT in Dutch clinical practice.

Among patient-related factors, WHO performance status was most strongly associated with variation in fractionation schemes. In a recent European expert panel, fitness of patients was also identified as an important decision criterion for the choice of radiotherapy fractionation

[32]. Variation was furthermore present between regions and radiotherapy facilities, which corresponds with the finding of the expert panel on a lack of uniform treatment decision regarding fractionation schemes in radiotherapy facilities across Europe [32].

Although the benefit of PCI in limited stage SCLC was already demonstrated in 1999 [12], our study shows an increase in use of PCI during 2008–2012, which might reflect increased attention to PCI after publication of a randomized trial in 2007 showing its benefit in extensive disease [33]. Nevertheless, between 2012 and 2019, the use of PCI substantially decreased in stage I-III disease following concerns about neurocognitive decline [13] and its reported lack of survival benefit in stage IV disease when compared to only MRI follow-up of the brain [14]. This decreasing trend in the Netherlands has previously been described comprehensively [15].

Between 2008 and 2019, the proportion of diagnoses with stage III disease decreased while the proportion of stage IV disease increased. This shift probably reflects changes in staging by different TNM editions applicable in the study period: tumors with pleural effusion were classified T4 (in combination with N0: stage IIIB) in TNM6 (2008–2009) and M1 (stage IV) in TNM7-8. In patients with malignant pleural effusion, chemotherapy need to be considered instead of CRT [34], causing a relatively lower use of CRT in stage III in 2008–2009. Also, diagnostic procedures in clinical practice improved over time, like screening for brain metastases with a brain-MRI instead of CT-scan. This resulted in more accurate staging of the disease and as such stage migration [35], favoring the treatability of patients in the study population diagnosed in more recent years. A future study may look into treatment outcomes.

The variations in treatment patterns observed in the current study were addressed in the Dutch Association of Radiation Oncology's division of lung cancer, and radiotherapy facilities were provided the opportunity to receive feedback on treatments applied in their region compared to other regions. Variation in clinical practice may reflect the preferences of patients or physicians. Both twice-daily radiotherapy and cCRT may be logistically challenging, the latter in case chemotherapy and radiotherapy are provided by different institutes, which requires patients to visit both a hospital and a radiotherapy facility on certain treatment days. To investigate the consequences of treatment variation, a future study may relate the variation in clinical practice to treatment outcomes. This may also provide insight in unwarranted aspects of variation.

Our study may have misclassified conventionally fractionated radiotherapy as accelerated, in case treatment was terminated prematurely after 15–28 days. This differential misclassification probably affected frail and elderly patients who are at the highest risk of treatment associated toxicity [36] and therefore most likely to terminate treatment prematurely. Falsely classifying these patients as having received accelerated radiotherapy may consequently have biased the analyses on WHO performance status and age presented in Table 3.

Another limitation regards the limited availability of comorbidities and WHO performance status which hampered both adjusting analyses for these factors and performing multivariable analyses on comorbidities, resulting in residual confounding. As the comorbidities and WHO performance status were available only for subsets of patients diagnosed in a specific region and/or years, the analyses on these variables may not necessarily be generalizable to the total study population. Nevertheless, it is not expected that these subsets differ from other patients in the Netherlands diagnosed in the study period. Comorbidities may furthermore be underreported in the hospitals' medical records, causing non-differential misclassification. However, we assume that the comorbidities relevant for treatment decision are registered, hence the effect of this misclassification is expected to be limited.

A final limitation of our study concerns having information available only on the delivered but not on the intended treatment. As a consequence, we cannot report on treatment adjustments nor provide direct insights in the process of treatment decision. We present factors associated with the treatments given and it should be noted that another treatment may initially be decided on.

4.1. Conclusions

This nationwide population-based study demonstrates increased use of surgery in stage I SCLC in 2008–2019. Combined use of chemotherapy and radiotherapy decreased in stage I, remained constant in stage II and increased in stage III disease. In 2019, 46% of the patients with stage III disease received cCRT, the majority of whom with accelerated radiotherapy. We identified patient groups who were more likely to receive cCRT versus sCRT and showed variation between hospitals and geographical regions. Choice of fractionation schemes was associated with patients' fitness, radiotherapy facilities' volume for SCLC, and geographical regions. Treatment variations were fed back to the radiation oncologists of the nationwide division of lung cancer. A future study may relate the variation observed to treatment outcomes, to investigate the consequences of treatment variation. Possible unwarranted treatment variation should subsequently be countered.

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CRediT authorship contribution statement

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

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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