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The Dutch Lung Cancer Audit-Radiotherapy (DLCA-R): real-world data on stage III non-small cell lung cancer patients treated with curative chemoradiation

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Abstract

Introduction: Chemoradiotherapy (CRT) is the standard of care in inoperable non-small cell lung cancer (NSCLC) patients, favoring concurrent (cCRT) over sequential CRT (seqCRT), with adjuvant immunotherapy in responders. Elderly and frail NSCLC patients have generally been excluded from trials in the past. In elderly patients however, the higher treatment related morbidity of cCRT, may outweigh the possible lower tumor control of seqCRT. For elderly patients with locally advanced NSCLC real-world data is essential to be able to balance treatment toxicity and treatment outcome. The aim of this study is to analyze acute toxicity and 3-month mortality of curative chemoradiation (CRT) in patients with stage III NSCLC and to analyze whether cCRT for elderly stage III NSCLC patients is safe.

Methods: The Dutch Lung Cancer Audit-Radiotherapy (DLCA-R) is a national lung cancer audit that started in 2013 for patients treated with curative intent radiotherapy. All Dutch patients treated for stage III NSCLC between 2015 and 2018 with seqCRT or cCRT for (primary or recurrent) stage III lung cancer are included in this population-based study. Information was collected on patient, tumor- and treatment characteristics and the incidence and severity of acute non-hematological toxicity (CTCAE-4 version 4.03) and mortality within three months after the end of radiotherapy. To evaluate the association between prognostic factors and outcome (acute toxicity and mortality within 3 months), an univariable and multivariable analysis was performed. The definition of cCRT was:radiotherapy started within 30 days after the start of chemotherapy.

Results: Out of all 20 Dutch departments of radiation oncology, 19 centers participated in the registry. A total of 2942 NSCLC stage III patients were treated with CRT. Of these 67.2% (n= 1977) were treated with cCRT (median age 66 years) and 32.8% (n=965) were treated with seqCRT (median age 69 years). Good performance status (WHO 0-1) was scored in 88.6% for patients treated with cCRT and in 71.0% in the patients treated with seqCRT. Acute non-hematological 3-month toxicity (CTCAE grade ≥3 or radiation pneumonitis grade ≥2) was scored in 21.9% of the patients treated with cCRT and in 17.7% of the patients treated with seqCRT. The univariable analysis for acute toxicity showed significantly increased toxicity for cCRT (p=0.008), WHO ≥2 (p=0.006), and TNM IIIC (p=0.031). The multivariable analysis for acute toxicity was significant for cCRT (p=0.015), WHO ≥2 (p=0.001) and TNM IIIC (p=0.016). The univariable analysis for 3-month mortality showed significance for seqCRT (p=0.025), WHO ≥2

(p<0.001), higher cumulative radiotherapy dose (p<0.001), higher gross tumor volume (GTV)total (p=0.020) and male patients (p<0.001). None of these variables reached significance in the multivariable analysis for 3-month mortality.

Conclusions: In this national lung cancer audit of inoperable NSCLC patients, 3-month toxicity was significantly higher in patients treated with cCRT (21.9% versus 17.7% for seqCRT) higher TNM stage IIIC, and poor performance (WHO≥2) patients.The 3-months mortality was not significantly different for tested parameters. Age was not a risk factor for acute toxicity, nor 3 months mortality.

Keywords: non-small cell lung cancer; elderly; chemoradiation; national audit; toxicity; mortality

1. Introduction

Based on randomized trials, chemoradiotherapy (CRT) is superior to radiotherapy alone in patients with stage III non-small cell lung cancer (NSCLC). Therefore, CRT is the standard of care, favoring concurrent (cCRT) over sequential (seqCRT) (1). The Dutch Lung Cancer Audit-Radiotherapy (DLCA-R) started in 2013 for lung cancer patients irradiated with curative intent. Real-world data has become extremely important to compare treatment toxicity and treatment outcome, especially in the elderly patients. According to the Dutch national guidelines, cCRT is the preferred treatment for inoperable stage III NSCLC. As trials often excluded elderly patients in the past, there is scarce evidence regarding the optimal treatment in the elderly with stage III NSCLC (2). For inoperable stage III NSCLC patients, a large treatment variation was observed between and within the Netherlands and Belgium in an observational population-based study (3). SeqCRT was significantly more frequently prescribed than cCRT to elderly patients and to patients with a high N-stage. Treatment decisions for elderly patients with NSCLC should however not be made on the basis of age alone. Comorbidity, weight loss and performance score are generally integrated in the tumor board treatment decision for elderly patients with stage III NSCLC. The aim of this study is to compare treatment toxicity and short-term survival of all NSCLC patients treated with cCRT and seqCRT in the Netherlands.

2. Methods

2.1.Study design

The nationwide Dutch Lung Surgery Audit (DLSA) started in 2012 to monitor the quality of lung operations in The Netherlands (4). The audit has been extended with a radiation oncology as well as a thoracic oncology registry. The Dutch Lung Cancer Audit for Radiotherapy (DLCA-R) collects information on all lung cancer patients receiving thoracic radiation with curative intent in the Netherlands since 2013.The parties that provide the data are the data managers of the hospitals. The treating physicians, physician assistants or specialized nurses score the toxicity. The central data collection is done by a trusted third party: Medical Research Data Management (MRDM). The collected data are analyzed by the Dutch Institute for Clinical Auditing (DICA) and benchmarked indicator results on the quality of care processes and patient outcomes are provided back to the hospitals in secured web-based dashboards.

Patients receiving curative radiotherapy for primary or recurrent stage I-III non-small cell lung cancer are included in this population-based study. From 2013 until 2018 a total of 14.426 patients were treated and registered in 19 out of the 20 radiation oncology departments in the Netherlands.

2.2. Patient selection

All registered patients who had curative chemoradiation for stage III A, B and C with pathologically proven or suspicion of NSCLC between January 1st, 2015 and December 31st, 2018, were evaluated. No ethical approval was required for this analysis under the Dutch law because all patient data is anonymized by MRDM. The analysis performed was approved by the scientific committee of the DLCA-R.

2.3. Definitions

Curative radiotherapy was defined in case a cumulative dose of 50 Gy or more was planned. cCRT was defined in case the irradiation started within 30 days after the start of the chemotherapy treatment. Non-hematologic toxicity and 3-months mortality were scored within three months after the last day of radiotherapy. Age was used as a continuous variable. Mortality and acute toxicity were measured as a dichotomous outcome. Toxicity was scored according to CTCAE-4 version 4.03 in case of non-hematological toxicity grade ≥3 or radiation pneumonitis grade ≥2 (5). TNM-7 was used in the database in 2015 and 2016. Since the

introduction of the TNM-8 as of January 1st, 2017, the audit used the new staging system. It is important to realize that in the TNM-7 stage III C NSCLC did not yet exist. The Gross Tumor Volume (GTV) tumor and GTV total (tumor and lymph nodes) were analyzed in cubic centimeters (cc) for cCRT and seqCRT patients.

2.4. Outcomes

All participating centers collected information on patient, tumor and treatment characteristics, and the incidence of mortality and severity of acute toxicity within three months after the end of radiotherapy treatment. From 2017 onwards each institute decided to fill in a more detailed or less detailed information sheet (bare minimum) of their patients treated. We analyzed stage III NSCLC patients treated from 2015 until 2018 with cCRT and seqCRT.

2.5. Statistical analysis

To evaluate the association between prognostic factors and outcome parameters (acute toxicity and 3-months mortality) an univariable and multivariable analysis was performed using the logistic regression method to obtain Odds Ratio's (OR) and 95% confidence intervals. We performed backward stepwise (conditional) analysis to find the optimal model based on the Log likelihood test. P-values ≤0.05 were considered statistically significant. Statistical analysis was performed with Statistical Package IBM SPSS Statistics (version 28.0.1.1(15)), R version 3.6.3 (2020-02-29) and R studio version 1.1.456.

3. Results

3.1. Baseline characteristics

Between 2015 and 2018, 2942 patients were treated by curative chemoradiation for stage III NSCLC and registered in the DLCA-R.

In Table 1, the baseline characteristics of all patients (n=2942) are shown. A total of 1977 patients (67.2%) were treated with cCRT with a median age of 66 years. A total of 965 (32.8%) were treated with seqCRT with a median age of 69 years. In the cCRT group 58.2% was male, comparable to 57.9% in the seqCRT group. Good performance status (WHO 0-1) was reported in 88.6% of the patients who had cCRT and 71.0% of the patients who had seqCRT. The NSCLC was pathologically proven in 98.3% of the cCRT group, compared to 96.5% of the seqCRT group. The primary tumor volumes were available for 271 patients in both groups. The median volume of the GTV (gross tumor volume) was 84 cc in the cCRT group and 50.5 cc in the seqCRT group. The median volume of the GTV total (primary tumor and lymph nodes) was 109.5 cc in the cCRT group and 75 cc in the seqCRT group. The cumulative radiotherapy dose was not given as planned in 3.6% of the cCRT group and in 1.9% of the seqCRT group. Different fractionation schemes were given for cCRT and seqCRT. The most common fractionation schemes for cCRT were 33 x 2 Gy (31%), 24 x 2.75 Gy (22%) and 30 x 2 Gy (13%). The following fractionation schemes were used frequently in sequential chemoradiation: 24 x 2,75 Gy (26%), 25 x 2,4 Gy (18%) and 33 x 2 Gy (13%).

3.2. Toxicity

Table 2 shows acute 3-month toxicity (grade ≥3) in 21.9% of the patients treated with cCRT and in 17.7% of the patients treated with seqCRT. In Table 3, the univariable analysis for acute toxicity showed significance for cCRT (p=0.008) (OR 0.78, CI 0.65-0.94), WHO PS ≥2 (p=0.006) (OR 1.56, CI: 1.13-2.14), and TNM stage IIIC (p=0.031) (OR 1.50, CI 1.04-2.16). The multivariable analysis for acute toxicity showed significance for cCRT (p=0.015) (OR 0.7, CI 0.62-0.95), WHO≥2 (p=0.001) (OR 1.73, CI 1.25-2.41) and TNM stage IIIC (p=0.016) (OR 1.59, CI 1.09-2,31). No influence of age was observed (p=0.331) for acute toxicity.

3.3. Mortality

Three-months mortality was scored in 3.6% of the patients treated with cCRT and in 7.0% of the patients treated with seqCRT (Table 2). In Table 4, the univariable analysis for 3-month mortality showed significance for seqCRT (p=0.025) (OR 1.22, CI 1.03-1.45) WHO ≥2 (p<0.001)

(OR 3.87, CI 2.28-6.58), higher cumulative dosis (p<0.001) (OR 0.92, CI 0.88-0.95) higher GTV total (p=0.020) (OR 1.00CI 1.00-1.01) and male patients (p<0.001) (OR 0.43, CI 0.29-0.64). In the multivariable analysis for 3-month mortality these variables were not significant anymore.

4. **Discussion**

Our study shows higher risk of 3-month toxicity in patients treated with concurrent chemoradiotherapy in real world, with worse performance status and higher TNM stage. Higher age did not increase the risk on 3 month toxicity or 3 month mortality.

In a recent Belgium nationwide analysis, 34% of all the patients with stage III NSCLC disease received chemoradiation, and 17% of those patients with stage IIIA disease had surgery (6). Moderate variability between centres was observed. It is hard to do a comparison with our data from the DLCA-R. We analysed the patients with inoperable stage III NSCLC treated with cCRT or seqCRT. In our results age did not increase the risk on 3-month toxicity nor 3-month mortality. cCRT should therefore not be dispensed on the basis of age alone (7).

In a large meta-analysis for NSCLC patients treated with cCRT based on individual patient data, risk factors for symptomatic pneumonitis were examined. Elderly patients receiving cCRT with carboplatin-paclitaxel were at greatest risk of lung toxicity (pneumonitis up to 77% in ages 61-70) (8). Unfortunately we have no information on the type of chemotherapy administered in our study. Almost all patients were treated before adjuvant durvalumab became standard of care, so it is important to know if toxicity increased after the introduction of adjuvant durvalumab. This will be subject of future DLCA-R analysis. The consensus based Dutch guideline for stage III NSCLC concludes that older NSCLC patients do not necessarily show a higher incidence of toxicity after chemoradiotherapy.This is supported by our data.

In a Japanese trial, 200 patients older than 70 years, with unresectable stage III NSCLC were randomly assigned to cCRT or radiotherapy alone showed increased hematological toxicity (grade 3 and 4) in older patients (>70 years) by the addition of carboplatin to radiotherapy (6). The DLCA-R does not register hematologic toxicity. It is Important to note is that a significantly prolonged survival was seen in the cCRT arm (9). In our study, we only can make conclusions on the 3-month mortality, because follow up after 3 months is not scored. Most patients are followed by the thoracic oncologists in the Netherlands. Driessen et al studied patient

characteristics predictive for tolerance and survival of chemoradiation in daily clinical practice. In a cohort of 216 patients they found that although relatively fit elderly were assigned to cCRT, treatment tolerance was worse especially for those with severe comorbidity when treated with cCRT and seqCRT with a Odds Ratio (OR) 6.2 (95%CI 1.6-24) and OR 6.4 (95%CI 1.8-22), respectively (10). Atagi et al. concluded in a randomized, controlled, phase 3 trial, that for a select group of elderly patients with locally advanced NSCLC, combination chemoradiotherapy provides a clinically significant benefit over radiotherapy alone (9)(2).

Three months mortality was scored in 3.6% of the patients treated with cCRT and in 7.0% of the patients treated with seqCRT. We did however not register the cause of death. In the Belgian lung cancer registry, the proportion of patients with stage III NSCLC who died within 60 days after end of primary (chemo)RT with curative intent was higher: 9.3% (6). Miller et al found that sequential chemotherapy and radiation was superior to concurrent chemoradiation in the elderly (≥ 70 years old) (11). They reported that sequential chemoradiation compared to concurrent chemoradiation, was associated with a 9% reduction in the risk of death in the elderly patients. We did not observe a significant difference in 3 months mortality in the elderly between patients treated with cCRT versus seqCRT. A possible explanation could be that for our elderly patients in the tumor board meeting a strict selection was applied for cCRT. .

This Dutch audit on lung cancer treatment provides the health professional with real-world data for patients stage III NSCLC treated with CRT. Very often elderly patients were excluded from trials studying chemoradiation. It is extremely important to analyze real world data of patients treated with curative chemoradiation in daily practice in the Netherlands. This study may help to gain insight in patient selection: in case of bad performance patients should be informed about some increased toxicity with cCRT, which could be a factor to consider seqCRT. For elderly patients in a good WHO PS, cCRT should however certainly be the primary choice of treatment.

Our study has several limitations. The DLCA-R does not register hematologic toxicity, cause of death, late toxicity or chemotherapy regimen administered. In the future, details of chemotherapy regimen and adjuvant immunotherapy will become transparent because the registrations aim to be connected on a patient level.
Another limitation is that scoring of co-morbidity and tumor volumes is not mandatory for the participating institutions that fill in the 'bare minimum' patient data. This resulted in a lot of missing GTV data. Nevertheless, due to the relatively large numbers, GTV was included in our

analysis and a higher GTV total was a significant factor in the univariable analysis for 3 month mortality.

Furthermore, our data was scored by the treating physician, specialized nurse or physician assistant and entered in the registry by a data manager. Prior external data verification showed high levels of patient inclusion and good quality of the registered data (12).

Whether a stage III patient will be treated with cCRT or seqCRT remains a multidisciplinary tumor board decision. In the Netherlands 95% of all lung cancer patients are discussed in a specialized tumor board (13). Despite the limitations, this nation-wide study included large numbers of patients treated in real life, reflecting current daily practice.

In the near future we will repeat the analyses in more recent years and report the results after the nationwide introduction of adjuvant immunotherapy .

Conclusions

This national lung cancer audit provides real-world outcome data for stage III NSCLC patients treated between 2015 and 2018 with CRT. In conclusion, this study shows higher risk of 3-month toxicity in patients with concurrent chemoradiotherapy, worse performance status and higher TNM stage. Age did not increase the acute toxicity risk. The multivariable analysis for 3-month mortality did not show significant differences in the variables tested. The data supports earlier studies and current clinical practice that cCRT is the preferred treatment for the young and fit elderly. SeqCRT is advised in the elderly and frail patients (WHO PS ≥2) because of reduced toxicity. Future research should focus on predicting prognostic factors for curative chemoradiation in the era of adjuvant immunotherapy.

Table 1. Patient-, tumor- and treatment characteristics of patients with non-small cell lung carcinoma stage III who had concurrent chemoradiation (cCRT) or sequential chemoradiation (seqCRT) from 2015 through 2018.

Table 2. Summary of patient outcomes of concurrent chemoradiation (cCRT) and sequential chemoradiation (seqCRT) in patients with stage III lung cancer.

Table 3. Univariable and multivariable analysis of acute toxicity.

Table 4. Univariable and multivariable analysis of 3-month mortality.

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Table 1. Patient-, tumor- and treatment characteristics of patients with non-small cell lung carcinoma stage III who had concurrent chemoradiation (cCRT) or sequential chemoradiation (seqCRT) from 2015 through 2018.

	cCRT	seqCRT
Number of patients treated	1977 (67%)	965 (33%)
Variable		
Age (median [range], years)	66 [31-89]	69 [33-89]
Missing	3	1
Year		
2015	488 (24.7%)	197 (20.4%)
2016	420 (21.2%)	173 (17.9%)
2017	509 (25.7%)	257 (26.6%)
2018	560 (28.3%)	338 (35.0%)
Gender		
Male	1151 (58.2%)	559 (57.9%)
Female	826 (41.8%)	406 (42.1%)
WHO		
0	718 (36.3%)	183 (19.0%)
1	1034 (52.3%)	502 (52.0%)
≥2	113 (5.7%)	164 (17.0%)
Missing	112 (5.7%)	116 (12.0%)
Primary or recurrent tumor		
Primary	1914 (96.8%)	921 (95.4%)
Recurrent	57 (2.9%)	43 (4.5%)
Unknown	6 (0.3%)	1 (0.1%)

Tumor location		
Trachea	3 (1.7%)	1 (0.1%)
Right lung	1099 (55.6%)	464 (48.1%)
Left Lung	606 (30.7%)	254 (26.3%)
Mediastinum	36 (1.8%)	11 (1.1%)
Right and left bronchi	118 (6.0%)	46 (4.8%)
Unknown	115 (5.8%)	189 (19.6%)
Pathologically proven disease		
NSCLC (tissue diagnosis)	1944 (98.3%)	931 (96.5%)
Suspicion NSCLC	33 (1.7%)	34 (3.5%)
TNM stage		
Stage IIIA	1207 (61.1%)	516 (53.5%)
Stage IIIB	677 (34.2%)	374 (38.8%)
Stage IIIC	93 (4.7%)	75 (7.8%)
Type of chemoradiation		
Concurrent:cCRT	1977 (67%)	-
Sequential: SeqCRT	-	965 (33%)
GTV tumor median, range, cc	84 [0-1213]	50.50 [0-614]
Missing/unknown	1762	887
GTV total (tumor, lymph nodes) median, cc [range],	109.5 [7-1300]	75.0 [5-614]
Missing/unknown	1773	898
Cumulative RT dose median, Gy [range],	66.0 [50.0-83.6]	66.0 [50.0-93.3]
Missing/unknown	0	0
Cumulative RT dose as planned		

Yes	1820 (92.1%)	768 (79.6%)
No	72 (3.6%)	18 (1.9%)
Missing/unknown	85 (4.3%)	179 (18.5%)

GTV = gross tumor volume.

	cCRT	seqCRT
Number of patients treated	1977 (67%)	965 (33%)
Variable		
Acute toxicity		
<3 or none (radiation pneumonitis < grade 2)	1424 (72%)	704 (73.0%)
≥3	432 (21.9%)	171 (17.7%)
Missing/unknown	121 (6.1%)	90 (9.3%)
3-month mortality		
No	1851 (93.6%)	879 (91.0%)
Yes	72 (3.6%)	68 (7.0%)
Missing/unknown	54 (2.7%)	18 (1.0%)

Table 2. Summary of patient outcomes of concurrent chemoradiation (cCRT) and sequential chemoradiation (seqCRT) in patients with stage III lung cancer.

Table 3. Univariable and multivariable analysis of acute toxicity.

NSCLC patiënts treated with chemoradiation in the Netherlands between 2015-2018.

Univariable analysis of non-hematological acute toxicity

Variable		OR	95% CI		
			Low	High	p-value
Age		0.996	0.989	1.004	0.331
Gender	Male	1.0	-	-	-
	Female	1.011	0.842	1.214	0.905
WHO	0 (ref)	1.0	-	-	-
	1	1.130	0.916	1.393	0.254
	>=2	1.557	1.133	2.140	**0.006**
TNM	IIIA (ref)	1.0	-	-	-
	IIIB	1.100	0.907	1.333	0.332
	IIIC	1.497	1.039	2.158	**0.031**
Cum dose		0.982	0.960	1.005	0.133
GTV tumor		1.000	0.999	1.001	0.822
GTV total		1.001	0.999	1.003	0.157
Treatment	cCRT	1.0	-	-	**-**
	seqCRT	0.780	0.650	0.937	**0.008**

Multivariable analysis of non-hematological acute toxicity

Variable		OR	95% CI		
			Low	High	p-value
WHO	0 (ref)	1.0	-	-	-
	1	1.157	0.936	1.430	0.179
	>=2	1.733	1.245	2.412	**0.001**

TNM	IIIA (ref)	1.0	-	-	-
	IIIB	1.067	0.873	1.305	0.525
	IIIC	1.585	1.089	2.308	**0.016**
Treatment	cCRT	1.0	-	-	**-**
	seqCRT	0.765	0.617	0.950	**0.015**

Table 4. Univariable and multivariable analysis of 3-month mortality.

NSCLC patiënts treated with chemoradiation in the Netherlands between 2015-2018.

Univariable analysis of 3-month mortality

Variable		OR	95% CI		
			Low	High	p-value
Age		1.001	0.998	1.004	0.604
Gender	Male	1.0	-	-	
	Female	0.429	0.290	0.637	**<0.001**
WHO	0 (ref)	1.0	-	-	-
	1	1.469	0.939	2.297	0.092
	≥ 2	3.870	2.277	6.579	**<0.001**
TNM	IIIA (ref)	1.0	-	-	-
	IIIB	1.297	0.908	1.854	0.153
	IIIC	1.613	0.838	3.106	0.153
Cumulative dose		0.917	0.884	0.951	**<0.001**
GTV tumor		1.000	0.999	1.002	0.492
GTV total		1.003	1.000	1.006	**0.020**
Treatment	cCRT	1.0	-	-	**-**
	seqCRT	1.220	1.026	1.452	**0.025**

Multivariable analysis of 3-month mortality

Variable		OR	95% CI		
			low	high	p-value
Gender	Male	1.0	-	-	-
	Female	0.884	0.500	1.563	0.672

WHO	0 (ref)	1.0	-	-	-
	1	0.628	0.348	1.133	0.123
	≥ 2	1.158	0.404	3.314	0.785
Cumulative dose		1.018	0.942	1.102	0.648
GTV total		1.001	0.999	1.003	0.212
Treatment	cCRT	1.0	-	-	-
	seqCRT	0.855	0.436	1.676	0.648