Prediction of toxicity in concurrent chemoradiation for non-small cell lung cancer

Uijterlinde, W.I.

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Chapter 2

Prediction of acute toxicity grade ≥ 3 in patients with locally advanced non-small cell lung cancer receiving Intensity Modulated Radiotherapy and concurrent low dose cisplatin

W.I. Uijterlinde
J.S.A. Belderbos
C. Baas
E. van Werkhoven
J. Knegjens
P. Baas
A.A. Smit
C. Rikers
M.M. van den Heuvel

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Abstract

Purpose: Intensity Modulated Radiotherapy (IMRT) is increasingly used with concurrent chemotherapy but toxicity data are not well investigated. We correlated clinical and dosimetric parameters with acute toxicity grade ≥ 3 in patients with locally advanced non-small cell lung cancer treated with IMRT and concurrent low dose cisplatin.

Patients and Methods: We analyzed age, Performance Status (PS), co-morbidities, gross tumor volume (GTV) and the percentage of the oesophagus irradiated with 50 Gy (V50*oes*) in relation with acute toxicity. The mean lung dose (MLD) and pulmonary toxicity was described. Treatment consisted of 24 x 2, 5 Gy and daily cisplatin 6 mg/m^2. Patients with a MLD≥ 20Gy or a PS of > 2 were excluded from CCRT. Toxicity was prospectively scored using the Common Toxicity Criteria for adverse events version 3.0. The Charlson Co-morbidity Index (CCI) was applied for scoring comorbidites. Multivariable logistic regressions for toxicity and survival estimates (Kaplan-Meier) were used for evaluation.

Results: From 2008 to 2011, 188 patients received standard concurrent chemoradiation. In 35 % of the patients acute toxicity grade ≥ 3 was reported. Grade 5 toxicity was scored in 1%.of the patients V50*oes*) OR=1.33 per 10%, p=0.01) and PS ≥ 2) OR=3.45, p=0.07) were significantly correlated with acute toxicity ≥ grade 3. No differences in toxicity were observed between age groups < 70, ≥70 (p=0.26) and those with a CCI score < 5, ≥ 5 and acute severe toxicity (p=0.36). Grade ≥ 3 pulmonary toxicity was seen in 7%. The 1 and 2 years Overall Survival in stage III disease was 78 and 52% respectively. Patients with a poor PS or a high CCI score had similar survival outcomes.

Conclusion: Concurrent low dose cisplatin using IMRT is effective in a large cohort of consecutive patients with NSCLC and life threatening toxicity is rare (1%). PS ≥ 2 and V50*oes* are correlated with acute toxicity grade ≥ 3.

Introduction

Today, concurrent chemoradiation (CCRT) is the treatment of choice for locally advanced non-small cell lung cancer (NSCLC). However, this is achieved at the cost of increased toxicity (1-3). Studies have been published on the use of weekly combination and daily low dose chemotherapy as a radiotherapy sensitizing agent (3;4). In these studies, esophagitis was more frequently noted in both schedules, while haematological toxicity was only increased in the weekly regimen. In this study a daily low dose of cisplatin was used as a radio sensitizer.

The data available on concurrent chemotherapy with Intensity Modulated Radiotherapy (IMRT) showed a slightly increased incidence of esophagitis that was explained by the ability to irradiate larger tumor volumes due to the steep dose fall-off of IMRT . IMRT facilitates a more conformal dose distribution leading to increased organ sparing compared to 3D-conformal-radiotherapy (3DCRT). The use of IMRT can achieve RT dose escalation of 25%/ 30% compared to 3D conformal RT.

To date, no evidence-based clinical selection criteria for chemoradiation are available, other than TNM stage and normal tissue tolerance for irradiation. Patient selection is generally based on age, performance status (PS) and preexisting co-morbidities (2;10). More than half of the patients with NSCLC stage III are not offered concurrent regimens, mostly because inclusion is restricted to patients < 70 years, good PS and minor co-morbidities (11). Co-morbidities are especially observed in the elderly and in smokers; both groups with a high incidence of lung cancer (1,3). However, the relation between clinical parameters, toxicity and treatment outcome is uncertain (12). As a result, patients can be over – or under treated.

Since IMRT has been introduced as a new treatment(13), current data are insufficient to determine clinical advantage of IMRT versus 3D CRT. We therefore related toxicity and clinical variables in patients with locally advanced NSCLC treated with IMRT and daily low dose cisplatin.

Patients and Methods

All consecutive NSCLC patients referred for radical radiotherapy in 2008, 2009 and 2010 were registered and considered for this analysis. The standard work-up regarding the staging of disease consisted of FDG-PET /CT and MRI of the brain to exclude distant metastases This was according to the Dutch guideline for staging NSCLC (12). When indicated, non-invasive mediastinal staging was performed with Endo (bronchial) ultrasound E(B)US. During a multi-disciplinary meeting, all patients who were considered candidates for concurrent chemoradiation were discussed.

Concurrent chemoradiation

The chemotherapy regimen consisted of cisplatin 6 mg/m^2 (24 administrations 5 times per week). Cisplatin was administered as a bolus injection, 1 to 1, 5 hour prior to radiotherapy (2). All patients were treated with IMRT of 66 Gy in 24 fractions daily, 5 times a week. For all patients, breathing induced motion of the pulmonary tumor was evaluated using four-dimensional imaging, using respiration correlated CT A midventilation-scan (MidV-scan) was reconstructed in which the moving tumor is closest to its time-averaged mean position (14). The GTV and all pathological lymph nodes were delineated on the MidV-scan. All patients had a FDG-PET-scan < 6 weeks before treatment. Critical organs were delineated according to a written protocol: heart, spinal cord, lungs and esophagus (from cricoid to gastro-esophageal-junction). The planning-constraints used for the organs at risk were; MLD ≤20 Gy, spinal cord ≤50 Gy, total heart ≤40 Gy and $^2/_3$ of the heart ≤50 Gy and $^1/_3$ of the heart ≤66 Gy. For the esophagus the percentage of the esophagus irradiated with 35Gy (V35) was used as prediction for acute esophagus toxicity. An IMRT-treatment plan was made with seven equally spaced, 10 or 6 MV photon beams sparing the contra-lateral lung. The prescription-dose was specified at a representative point in the PTV.

The dose in homogeneity within the PTV was > 90% and < 115%. The equivalent dose in 2-Gy fractions corrected for overall treatment time (EQD_2) was used as a measure of the intensity of chest RT, delivered to the tumor using the formula: $EQD2 = (d+\alpha/\beta) / (2+ \alpha/\beta) \times D = (2{,}75+10)/ (2+10) \times 66 = 70.125$; d = fraction dose; D= total dose; $\alpha/\beta = 10$.

Data collection

The following clinical parameters were prospectively collected for all patients receiving CCRT: co-morbidities, performance status (PS), age, acute toxicity and treatment adherence. The dosimetric parameters included the total GTV in cm^3 (sum of primary tumor and involved lymph nodes)_the MLD and V50*oes*. The V50 was recently analyzed and found a significant predictor for grade ≥ 3 acute esophagus toxicity in IMRT and concurrent daily cisplatin (5). The clinical predictor used was the V35 < 65%, described by Belderbos et al. However, this parameter was predictive for grade ≥ 2 acute esophagus toxicity in the 3D conformal radiotherapy technique and was no longer significant when tested in IMRT (15). During the treatment, toxicity was scored using the Common Toxicity Criteria of adverse events version 3.0 (CTCAE) on a weekly basis and afterwards every month. Toxicity was divided into gastro-intestinal, renal, esophageal pulmonary, hematological and other non-hematological toxicities. With regard to response assessment a CT thorax was performed 4-6 weeks after treatment. Follow up assessment of disease control was performed at 3-monthly intervals according to our local practice. For completing the follow up data on survival and disease progression, hospital charts, digital radiology systems in the NKI-AVL and referring hospitals were examined and the Social Security Administration was consulted.

Co-morbidity was objectively scored using an adapted Charlson Co-morbidity Index (CCI). This CCI classifies co-morbid conditions that might alter the risk of mortality for the use in longitudinal studies. This weighted index takes into account the number and severity of co morbid diseases and for quality of life and prognostic factors in patients with NSCLC (2;16-18). CCI scores are adjusted for age ≥ 50 years and ranges from 0- 6. The scores were obtained as a continuous variable and the maximum score used was ≥ 6. For age dichotome variables were used < 70 years and ≥ 70 years as well as age grouped by decades. The PSindex by Zubrod was used to categorize patients according to their daily wellbeing. The 7th edition of the Tumor, Node, and Metastasis (TNM) staging by the International Association for the Study of Lung Cancer (IASLC) was applied.

Statistical analysis

Toxicity was grouped into CTCAE grade < 3 vs. ≥ 3. Age was considered continuous for modeling and testing and was grouped for reporting. Patient characteristics at baseline were compared between the two toxicity groups using Fisher's test, the Kruskal-Wallis test or the linear-by-linear association test for ordered factors (CCI, PS). P-Values less than 0.05 were considered significant. A multivariable logistic model for toxicity was fitted with age, PS, CCI, tumor volume, MLD and V50*oes*. The log transformation was used to normalize the distribution of GTV. Overall and progression free survival since start of treatment were estimated with the Kaplan-Meier method. Analyses were performed using SPSS version 18.0 and R version 2.15.0 with package 'coin'.

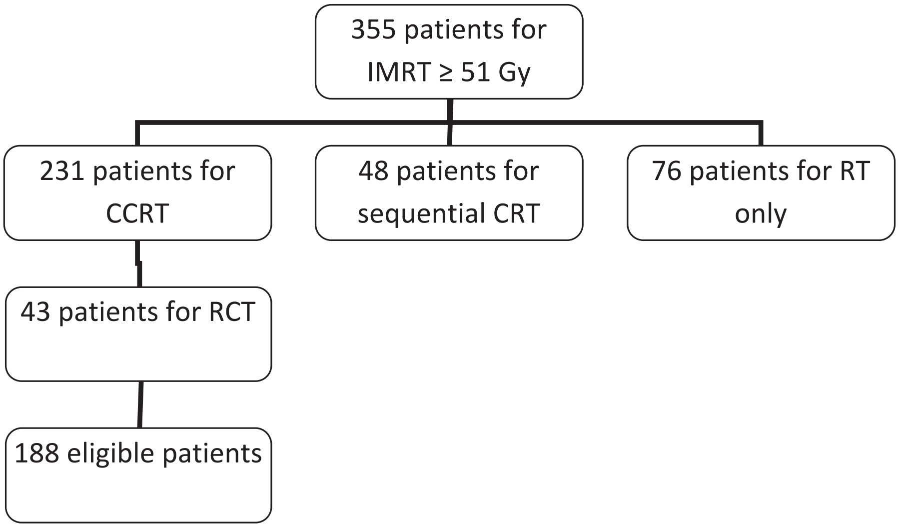
Results

From 2008 until 2010, a total of 355 patients with NSCLC were referred for radical radiotherapy. Two hundred and thirty-one patients received CCRT (66%), forty-eight patients received sequential chemotherapy and radiotherapy (12%) and 76 patients received a radical RT regimen (>51Gy total dose) only (21%). Of the CCRT group 43 patients (12%) were excluded from this analysis because they participated in lung clinical trials, leaving 188 patients for analysis (Figure 1). The main indication for a sequential treatment plan was a too large tumor volume within the thoracic cavity. In case the calculated MLD was > 20Gy our protocol dictates to first downsize the tumor using induction chemotherapy. Radiotherapy alone was only administered to the most fragile patients (Age ≥80, PS >2, severe co-morbidity) or those refusing chemotherapy.

The patient characteristics are summarized in Table 1. Briefly, the median age was 64 years, 61% were male. Twenty-nine percent of the patients was ≥ 70 and 80% had a PS of 0-1. Ten percent had stage I or II disease (10%) and were referred for CCRT because of poor pulmonary function or local recurrence after lobectomy. 64% had a CCI value of ≥4.

Discontinuation of the planned 24 chemotherapy administrations occurred in 31% of the patients due to renal and/or gastro intestinal toxicity. The mean number of cisplatin administrations was 21. .Three patients interrupted RT because of fever or for logistic reasons. One patient decided not to complete the planned radiotherapy (Table 1).

Figure 1. Eligibility



A total of 35 % of the patients experienced acute toxicity grade ≥ 3: 15% esophageal toxicity, 8% nausea and vomiting, 6% anorexia, 3% hematological toxicity, 2% weight loss and 1% nephrotoxicity (Table 2). The median MLD was 14.7 (2.9-21.8); grade ≥ 3 pulmonary toxicity was seen in 7% of the population and occurred 4 to 12 months after the start of treatment.

Table 1. Patient and Treatment characteristics (N=188)

	amount	**%**
Age		
Median (IQR)	64 (55–70)	
<70 years	134	71
^{3}70 years	54	29
Gender		
Male	115	61
Female	73	39
Race		
Caucasian	168	89
Afro American	8	5
Mediterranean	9	5
Oriental	3	1
Stage (7th edition)		
1& 2	19	10
3a	108	57
3b	60	32
4	1	1

	amount	**%**
Histology		
Adeno	40	22
Squamous	56	29
Mixed cell	19	11
NSCLC NOS	73	38
GTV (primary tumor and lymph nodes)	125 (76–217)	
median (IQR)	133	70
< 300cm^3	53	29
≥ 300cm^3	2	1
NA		
50 Gy *oes* (%)		
Median (IQR)	35 (22–47)	
NA	36	20
Mean lung dose (Gy)	15	96
Median (IQR)	12-18	4
NA		
Performance Status		
0	8	4
1	143	76
2	36	19
3	1	1
Charlson Index Value		
0&1	2	2
2	38	20
3	28	15
4	25	13
5	32	17
6	63	33
Acute toxicity (CTCAE 3.0)		
0	0	0
1	34	18
2	86	46
3	59	31
4	7	4
5	2	1
Toxicity CTC*AE 3.0*		
CTC< 3	120	64
CTC ≥3	68	36
Discontinuation of cisplatin		
Yes	57	30
No	131	70
Interruption of radiotherapy		
Yes	3	1
No	185	99
Discontinuation of radiotherapy		
Yes	1	1
No	187	99

	amount	%
Number of cisplatin		
administrations	16	9
1-10	31	17
11-20	141	75
21-24		

GTV: gross tumor volume; Gy: gray; IQR: inter quartile range; CTC: common toxicity criteria;

Table 2. Grade ≥ 3 acute toxicity in NSCLC patients treated with concurrent chemo radiotherapy

	N=188	%
Esophagus toxicity	30	15
Nausea & vomiting	15	8
Anorexia	10	6
Hematological toxicity	6	3
Weight loss	3	2
Nephrotoxicity	2	1
Pulmonary toxicity*	11	7

* Pulmonary toxicity was scored with a median follow up of 17 months

Grade 2 lung toxicity occurred in 17% of the population._Grade 5 toxicity was seen in 1%: two patients died within 3 weeks after treatment because of neutropenic sepsis and/or multi organ failure.

Age

Thirty-one of the 54 elderly patients (≥ 70 years) scored acute toxicity grade < 3 (57%), 23 of acute toxicity grade ≥ 3 (43%). In the group younger than 70 years, 89 of the 134 patients scored acute toxicity grade < 3 (66%) and 54 acute toxicity grade ≥ 3 (34%); (p=0.38) **(**Table 3). In a multivariable model, the risk of toxicity grade ≥ 3 increased with age (p=0.15, OR 1.31; CI 95%: 0.91-1.88) (Table 4)**.**

Charlson Comorbidity Index

There were 63 patients with a CCI of 6 (34%), which was the highest co-morbidity score observed. A grade 3 or higher acute toxicity was observed in 17 out of 64 patients (27%) who had a CCI score of 6, while 47 out of 63 patients (73%) experienced a grade 0-2 toxicity.

In patients with a CCI score of 4 -6, 43% had acute toxicity grade ≥ 3; 73% had a grade 0-1. In patients with a CCI score 0-3, 38% suffered from grade ≥ 3 toxicity; 62% of grade 0-1 (p= 0.15) (Table 3).

Performance Status

There were 151 patients (80%) with a PS 0-1, of whom 48 (32%) experienced acute toxicity grade ≥ 3. Of the 37 patients (20%) with a PS of 2-3, 20 (54%) experienced toxicity grade ≥ 3 (p=0.01) (Table 3). In the multivariate logistic model PS ≥ 2 was found to be significantly associated with toxicity (p=0.01; OR 3.45; CI 95%: 1.41-8.44) (Table 5).

V50oes

V50*oes* was significantly associated with all acute toxicity ≥ grade 3 in the univariate analysis (p=0.01 ’), When toxicity was selected and grouped in < grade 3 and ≥ grade 3 leaving out esophagitis, V50*oes* was no longer significant (p = 0.12) (Table 5). When fitted in a multivariable logistic model for all toxicity ≥ grade 3 correlating parameters, V50*oes* remained a significant predictor (p=0.01, OR 1.33 per 10 percentage points; CI 95%: 1.07-1.65) (Table 4).

Table 3. Toxicities grouped by grade and correlated with age, co morbidity, performance status, V50, tumor volume and weight loss in patients treated with concurrent chemo radiotherapy (n=188).

Table 3. Toxicities grouped by grade and correlated with age, co morbidity, performance status, V50, tumor volume and weight loss in patients treated with concurrent chemo radiotherapy (n=188)

Total		CTC< 3 120 (64%)	%	CTC≥3 68 (36%)	%	Total 188 (100%)	*P* value
Age							0.38
	median	63		66		64	
	IQR	56–70		55–72		55–70	
Age (grouped)							
·	32-69	89	66	54	34	134	
·	70-87	31	57	23	43	54	
Age 2							
·	32-50	8	50	3	50	16	
·	50-60	44	73	13	27	60	
·	60-69	37	67	11	33	55	
·	69-75	14	48	8	52	29	
·	75-87	17	61	8	39	28	
Charlson Index value							
·	0-2	24	60	16	40	40	0.15
·	3	18	64	10	36	28	
·	4	10	40	15	60	25	
·	5	22	69	10	31	32	
·	6	46	73	17	27	63	

Total	CTC< 3 120 (64%)	%	CTC≥3 68 (36%)	%	Total 188 (100%)	*P* value
Comorbidities						
• Aids	2	2	0	0		
• COPD Gold ≥ 3	45	38	28	23		
• Cardial	6	5	7	6		
• CHF	1	1	1	1		
• Dementia	0	0	1	1		
• Hemiplegia	1	1	0	0		
• MI	3	3	2	3		
• PVD	8	7	11	16		
• DM	14	12	4	6		
• Liver	1	1	0	0		
• Renal	1	1	1	1		
• Metastatic	85	71	52	76		
disease	6	5	7	6		
• Other	8	7	3	4		
Malignancy						
• Ulcer						
Performance Status						
• 0-1	103	68	48	32	151	0.01
• 2-3	17	46	20	54	37	
50Gy *oes*						
Sample size	96		56		152	
Median Volume (%)	33		41		35	0.004
IQR	19– 44		27–53		24– 46	
Gross tumor Volume						
(cm^3)	118		68		186	0.21
• Sample size	119		141		125	
• Median	74–215		92–222		76–217	
• IQR						

NA= not available / missing data; IQR= interquantile range; CHF= congestive heart failure; MI= myocardial infarct; PVD= peripheral vascular disease; DM= diabetes mellitus.

Table 4. Multivariable logistic model for all toxicity ≥ grade 3 correlating age, PS, GTV and V50oes and co morbidities

	Odds ratio	95% CI	P
Age Group per 10 years	1.31	0.91–1.88	0.15
Performance status (≥2 vs <2)	3.45	1.41–8.44	0.01
Charlson Index value (≥ 5 vs < 5)	0.59	0.29–1.22	0.15
V50 per 10 percentage points	1.33	1.07–1.65	0.01
Log Gross Tumor Volume per IQR (IQR=1.07)	1.06	0.64–1.76	0.82

V50:volume of the esophagus receiving 50 Gy; IQR: inter quartile range

Table 5. Selected toxicities grouped in grade < 3 and ≥ 3 CTC

Total		CTC< 3 122 (74%)	%	CTC≥3 43 (26%)	%	Total 165	*P* value
Age							0.73
	median	64		63			
	IQR	56–70		54–72			
Age 1							
·	32-69	87	75	29	25	116	
·	70-87	35	71	14	29	49	
Age 2							
·	32-50	10	77	3	23	13	
·	50-60	39	75	13	25	52	
·	60-69	37	77	11	23	48	
·	69-75	20	71	8	29	28	
·	75-87	16	67	8	33	24	
Charlson Index value							
·	0-2	25	76	8	24	33	0.67
·	3	18	75	6	25	24	
·	4	11	55	9	45	20	
·	5	22	73	8	27	30	
·	6	46	79	12	21	58	
Performance Status							
·	0-1	99	77	30	23	129	0.03
·	2-3	23	64	13	36	36	
50Gy *oes*							
Sample size		101		34		135	
Median (%)		36		40		35	0.12
IQR		23–46		26– 56		22–55	
Gross tmor volume (cm^3)							
·	Sample size	120		43		163	0.59
·	Median	119		135		125	
·	IQR	74–200		79–225		76–217	

NA: not available / missing data. Selected toxicities: nausea, vomiting, anorexia, weight loss, nephrotoxicity, anemia, neutropenia and trombopenia. Dysphagia and esophagitis are excluded.

Progression Free survival and Overall Survival

The median follow up was 17 months. The median progression free survival (PFS) in stage 3 was 18.1 months. The estimated 1-year and 2-year overall survival (OS) probability in stage 3 was, respectively, 78% (95% CI: 0.71-85) and 48% (95% CI 0.38-0.62) (Fig 2a and b). For stage 1 and 2 disease the 1- and 2-year OS was 84% and 69% respectively. The 2 year OS in 37 patients with PS ≥ 2 was 54% (CI 95 CI %: 33- 88). The ninety-five patients with a CCI index of 6 had a 2 year OS of 55% (CI 95%: 44-69).

Figure 2a. Overall survival

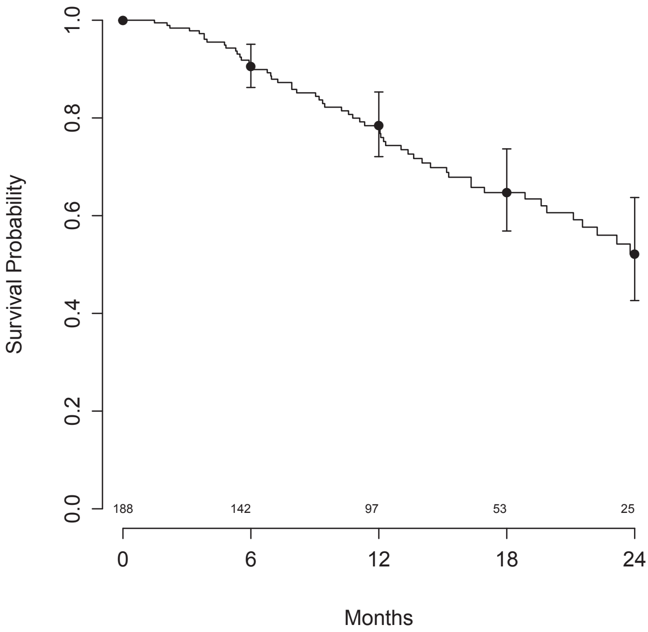
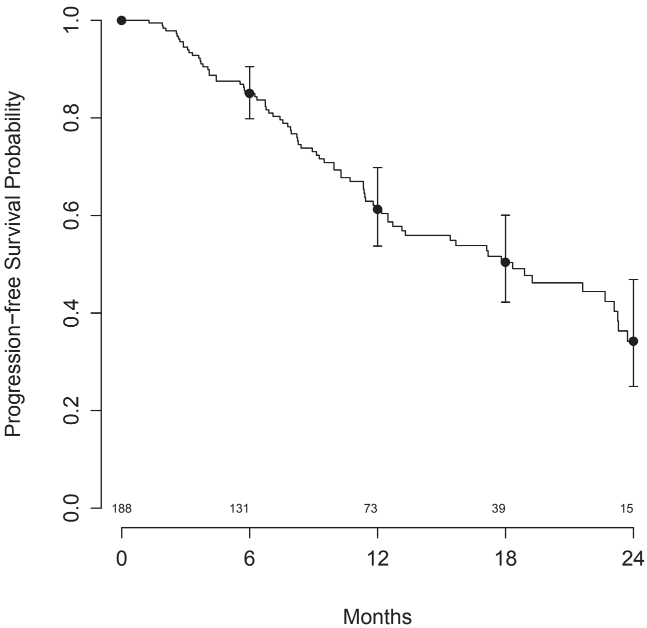


Figure 2b. Progression free survival



Discussion

There are no validated clinical parameters for the selection of patients for concurrent chemoradiation with IMRT and elderly or patients with co-morbidity are often refrained from CCRT because of fear for acute toxicity (19). However, in our study, we found no evidence for increased acute toxicity in older patients or patients with severe co-morbidity while the efficacy of the treatment remained satisfactory. Because IMRT has the benefit of further increasing the dose that can safely be prescribed in lung cancer patients, we believe this information is of vital importance in the selection of patients. (8;20). PS ≥ 2 was found to predict acute toxicity although there was no difference in overall survival in this group compared to patients with a PS of 0-1. In 3D conformal radiotherapy, the V35*oes* was used as a predictor for acute esophageal toxicity. In our analysis, *V50oes* was not a significant predictor for grade ≤ 3 toxicity other than esophagus toxicity. This result is supported by Kwint *et al* (5).

The description of clinical and dosimetric selection criteria for CCRT is important because the previous reported studies on CCRT have been performed in highly selected patients. Eligible patients were often younger than 70 years and a PS of 0-1. However, in the meta-analysis of Auperin et al. comparing sequential and concurrent chemoradiation, the benefit of CCRT was also present in patients over 75 years of age suggesting that by liberating the selection criteria we might increase the overall efficacy of treatment (2).

One could argue that low dose daily cisplatin is not the standard treatment in most countries. However, our patient group treated with this regimen showed promising survival data (2;4). Also, our toxicity data on IMRT with daily low dose cisplatin was acceptable. Based on these results, consensus was reached on the use of this regimen.

The presented data suggests that IMRT does not cause additional toxicity compared to 3D CRT because the results are in accordance with previous data on single agent cisplatin CCRT and other regimens (1;2; 4; 5;14;21.).

Despite the fairly high incidence of acute grade 3 toxicities there were hardly any fatal toxicities observed (1%). A recent Cochrane meta-analysis on CCRT reported a fatal toxicity rate in 4% . This difference might be explained by the exclusion of patients with a poor PS and a MLD > 20 and the favorable hematological toxicity of single-agent daily-dose cisplatin. Commonly used concurrent regimens such as cisplatin/etoposide or carboplatin/paclitaxel are more hematotoxic. Rosenman et al. found febrile neutropenia in 41% of the patients resulting in discontinuation of treatment and hospitalization (22-26).

In our study, the overall survival was superior to former phase II and III trials analyzing the same concurrent chemoradiation regimen (2) and other CCRT regimens (2). The difference in survival outcome in this study versus the EORTC phase I-II trial by Uiterhoeve (27) might partially be explained by the current staging procedures that have become routine daily practice since 2008. In the older trials, FDG-PET and MRI of the brain were not yet implemented and this certainly has an impact on selecting patients (28;29). Innovations in the irradiation techniques, such as the use of image-guided IMRT, might also have contributed to these results (30).

There are some limitations in this study. For survival analysis, we realize that the follow up of 17 months is rather short. Also, we realize that although toxicity scoring was performed thoroughly, outcomes can be liable due to interpretation differences.

Conclusions

CCRT with daily dose cisplatin and IMRT is well tolerated in a large cohort of patients with a MLD≤ 20 and a PS ≤2. It was tolerated as well in elderly patients with extensive co-morbidities but only provided they have an adequate performance status (PS<2). Because most patients are excluded from CCRT because of high(er) age or comorbidities, this information is relevant for multi-disciplinary team discussions. In patients with a PS ≥ 2- the incidence and severity of acute toxicity was higher but this did not translate in a worse survival rate.

In clinical practice, these results are of importance in the selection of patients with locally advanced NSCLC because better selected patients can be enrolled and those might benefit from this treatment. Also, our results can be used as a tool for decision making in multi-disciplinary meetings.

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