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Original article

Development of symptomatic brain metastases after chemoradiotherapy for stage III non-small cell lung cancer: Does the type of chemotherapy regimen matter?

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ABSTRACT

Objectives: Symptomatic brain metastases (BM) occur frequently after chemoradiotherapy (CRT) for stage III NSCLC. Aim of the current study was to determine whether the specific chemotherapy used in a CRT regimen influences BM development.
Materials and methods: Retrospective multicenter study including all consecutive stage III NSCLC who completed CRT. Primary endpoints: symptomatic BM development, whether this was the only site of first relapse. Differences between regimens were assessed with a logistic regression model including known BM risk factors and the specific chemotherapy: concurrent versus sequential (cCRT/sCRT), within cCRT: daily low dose cisplatin (LDC)-cyclic dose polychemotherapy; LDC-(non-)taxane cyclic dose; LDC–polychemotherapy subgroups of ≥50 patients.
Results: Between January 2006 and June 2014, 838 patients were eligible (737 cCRT, 101 sCRT). 18.2% developed symptomatic BM, 8.0% had BM as only site of first relapse. BM patients were significantly younger, female, had more advanced N-stage and had adenocarcinoma histology. In both cCRT and sCRT BM were found in 18% ($p = 0.904$). In cyclic dose cCRT ($N = 346$) and LDC ($N = 391$) BM were found in 18.8% and 17.9%, respectively ($p = 0.757$). In 7.2% and 8.7%, respectively, BM were the only site of first relapse ($p = 0.463$). The chemotherapy used (cCRT versus sCRT) had no influence on BM development, not for all brain relapses nor as only site of first relapse (OR 0.88 ($p = 0.669$), OR 0.93 ($p = 0.855$), respectively). LDC versus cyclic dose cCRT was not significantly different: neither for all brain relapses nor as only site of first relapse (OR 0.96 ($p = 0.819$), OR 1.21 ($p = 0.498$), respectively).

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Comparable results were found for LDC versus cyclic dose non-taxane ($N = 277$) and cyclic dose taxane regimens ($N = 69$) and for cCRT regimens with ≥50 patients (LDC versus cisplatin/etoposide ($N = 188$), cisplatin/vinorelbin ($N = 65$), weekly cisplatin/docetaxel ($N = 60$)).
Conclusion: approximately 18% developed symptomatic BM after stage III diagnosis, not dependent on type of chemotherapy regimen used within a CRT treatment.

1. Introduction

The standard treatment for most patients with stage III non-small cell lung cancer (NSCLC) is combined chemoradiation (CRT). Concurrent CRT (cCRT) results in a superior overall survival (OS) compared to sequential CRT (sCRT) [1]. As brain metastases frequently occur in locally advanced NSCLC it is routine practice to perform brain imaging during staging [2,3]. The brain is still a frequent site of relapse after CRT, as 13–15% of patients develop symptomatic brain metastases within the first year after NSCLC diagnosis [4,5]. Most brain relapses are diagnosed in this first year, but over 30% occur later [4,5]. Symptomatic brain metastases have a negative impact on quality of life (QoL) and are associated with a worse OS [6,7]. Known risk factors for brain metastases are adenocarcinoma histology and younger age [4,8]. Several chemotherapy regimens are used as part of CRT. In the European Society for Medical Oncology (ESMO) NSCLC guideline, two to four cycles of cyclic dosed platinum based doublet chemotherapy are recommended [3]. Platinum is usually combined with etoposide or vinorelbine [3]. An alternative schedule often used in the United States is weekly carboplatin/paclitaxel [9]. Other concurrent regimens are cyclic dose platinum/pemetrexed [10], weekly platinum/docetaxel [11] or daily low dose cisplatin [12].

To our knowledge, there are no phase III head-to-head comparisons of these regimens showing an improved OS with a specific regimen. A recent retrospective study ($N = 1842$) compared outcomes of stage III NSCLC patients treated with cisplatin/etoposide or carboplatin/paclitaxel concurrent with radiotherapy within the Veterans Health Administration and no significant OS differences were found [9].

The impact of the specific chemotherapy regimen used during CRT on the development of symptomatic brain metastases is still unclear. To answer the question whether there is any influence of the CRT chemotherapy regimen used on the development of these brain metastases, we performed a retrospective multicenter study in stage III NSCLC treated with CRT.

2. Materials and methods

2.1. Study subjects

Data of all consecutive stage III NSCLC patients from five Dutch teaching hospitals, treated with definitive CRT (with/without surgery) between January 1st 2006 and June 30th 2014 were retrospectively analyzed. Exclusion criteria were: diagnosis of another malignancy within two years of stage III NSCLC (except cervical cancer in situ, skin cancer, previously diagnosed NSCLC treated with curative intent); no ^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)-scan; no adequate brain imaging (*i.e.* no magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CE-CT)) during staging; no CRT completion (in order to exclude bias from suboptimal treatment); prophylactic cranial irradiation (PCI) treatment.

The following details were extracted from the medical records: age; gender; world health organization performance status (WHO PS); smoking status; date of pathology diagnosis; staging brain imaging modality; histology; molecular testing (yes/no, results); T- and N-stage; TNM stage; cCRT or sCRT; chemotherapy regimen; dose radiotherapy (Gy); treatment completion (*i.e.* all planned cycles chemotherapy (delay/dose reductions allowed) and radiotherapy completion); surgery post CRT; date progressive disease and first site of progression (brain only, extracranial only, both); date symptomatic brain metastases diagnosis, symptoms; whether regular brain imaging was performed during follow-up; date of death/last follow-up. CRT regimens were classified as daily low dose cisplatin and cyclic dose doublet chemotherapy. Within the cyclic dose doublet chemotherapy group, subgroups were made for taxane and non-taxane based regimens. Patients treated with sequential cyclic dose doublet chemotherapy followed by radiotherapy or cCRT were classified as "cyclic dose" regardless of the concurrent chemotherapy regimen used. Last date of follow-up was June 30th, 2015.

The ethics committee of the MUMC+ evaluated the protocol (METC 14-5-054) and stated that study approval was not mandatory according to the Dutch law "Medical Research (human subjects) Act" [13].

2.2. Statistical analysis

Statistical analysis was performed with SPSS (version 20; SPSS Inc., Chicago, IL). Patient characteristics were described for the total group and according to treatment regimen. Significant differences between regimens were assessed by X^2-test, Fisher's exact test, Mann-Whitney-U test or ANOVA when applicable. Primary endpoints were development of symptomatic brain metastases and whether the brain was the only site of first relapse, these were compared with the X^2-test. A binary logistic regression model for brain metastases development was constructed including covariates that are known risk factors for brain metastases (age, gender, histology, stage). Chemotherapy regimens (sCRT versus cCRT and in the cCRT group daily low dose cisplatin versus cyclic dose regimens) were added to this regression model. Also, subgroup analyses were performed in the cCRT subgroup for low dose cisplatin versus non-taxane and taxane based regimens respectively. For the cCRT subgroup, logistic regression analysis was also performed for low dose cisplatin versus subgroups of chemotherapy with ≥50 patients.

Progression free survival (PFS) was defined as time from stage III diagnosis till disease progression or death; OS was defined as the time from stage III diagnosis till death. Patients without event who were alive at last follow-up or who were lost-to-follow-up were censored at last date of follow-up. The Kaplan–Meier method was used to estimate distribution of survival. Log-rank test was used to test difference in survival between subgroups. P-values ≤ 0.05 for two-sided tests were considered statistically significant. Distribution of cumulative incidence of symptomatic brain metastases was estimated with the competing-risks regression method by Fine and Gray. For this analysis we used STATA (version 14.0; StataCorp LP, Texas) as this function is not available in SPSS. Patients without event who were alive at last follow-up or who were lost-to-follow-

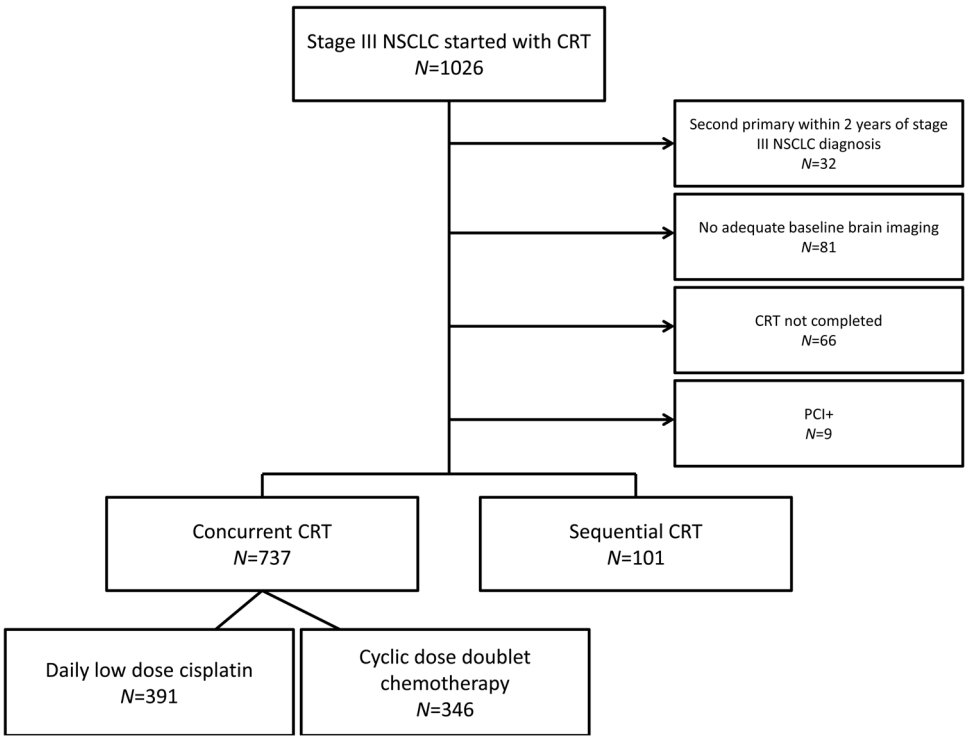

Fig. 1. consort diagram for study inclusion.

up were censored at last date of follow-up. Death without brain metastases was considered a competing event.

3. Results

3.1. Patient characteristics

Between January 1st 2006 and June 30th 2014, 1026 patients were treated with CRT. 188 patients were excluded for the following reasons: second primary ($N = 32$), no adequate baseline brain imaging ($N = 81$), CRT not completed ($N = 66$) or PCI ($N = 9$) (CONSORT diagram in Fig. 1).

Hence, 838 patients were eligible: 737 cCRT and 101 sCRT treated. Patient characteristics for all patients and cCRT/sCRT subgroups are shown in Table 1. Characteristics for the cCRT patients treated with cyclic dose doublet chemotherapy versus daily low dose cisplatin are depicted in Table 2 (chemotherapy regimens further specified in table S1). 87% of the sCRT treated patients received 3 cycles of cyclic doublet chemotherapy, the others received 4 cycles. In the cCRT group, 76.9% received 3 cycles of cyclic dose doublet chemotherapy (including an optional induction chemotherapy cycle), the others received 4 cycles except 2 patients who received 2 cycles.

3.2. Development of symptomatic brain metastases

153/838 patients (18%) were diagnosed with brain metastases in the follow-up, of which 143 (93%) were symptomatic. For the remaining 10, it was not clear whether they had symptoms or not. The percentage of symptomatic brain metastases diagnosis was not significantly different for sCRT and cCRT patients 18/101 (18%) versus 135/737 (18%, $p = 0.904$). Cumulative brain metastases incidence is shown in Fig. 2, no significant difference was found for sCRT versus cCRT treated patients (hazard ratio (HR) (95% CI) 0.93 (0.564-1.539), $p = 0.781$). In 7/101 (6.9%) and 59/737 (8.0%), respectively,

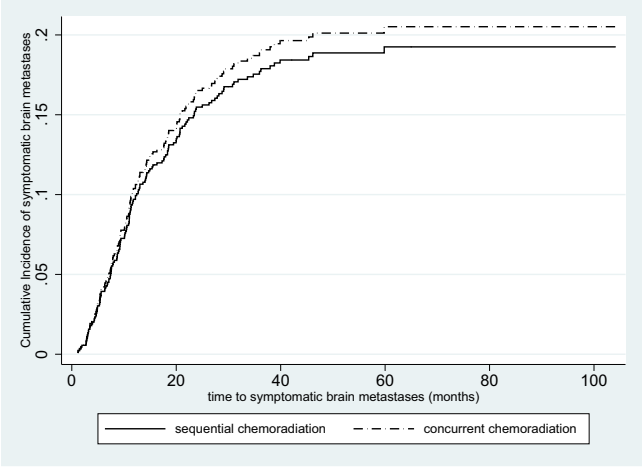

Fig. 2. cumulative incidence of brain metastases for patients treated with concurrent or sequential chemoradiotherapy.

the brain was the only site of first relapse, this was not significantly different ($p = 0.707$). As compared to patients not developing symptomatic brain metastases, those with metastases were significantly younger (mean age 59 versus 63 years, $p < 0.001$), had female gender (44% versus 34%, $p = 0.018$), had adenocarcinoma histology (57% versus 35%, $p < 0.001$) and had a more advanced N-stage (93% versus 86%, $p = 0.018$) (Table 3).

Within the cCRT subgroup, no significant differences were observed between cyclic dose doublet chemotherapy ($N = 346$) and daily low dose cisplatin ($N = 391$). 65/346 (18.8%) and 70/391 (17.9%) patients were diagnosed with symptomatic brain metastases, respectively ($p = 0.757$). In 25/346 (7.2%) cyclic dose doublet chemotherapy and 34/391 (8.7%) daily low dose cisplatin patients respectively, the brain was the only site of first relapse ($p = 0.463$).

Table 1
patient characteristics for all eligible patients.

Patient characteristic	Total group *N* = 838	cCRT group *N* = 737	sCRT group *N* = 101
Mean age ± SD	62 ± 10	62 ± 10	66 ± 11
(range)	30–84	(30–84)	(34–83)
Male *N* (%)	535 (64)	468 (64)	67 (66)
WHO PS *N* (%)			
0–1	779 (93)	691 (94)	88 (87)
2	34 (4)	23 (3)	11 (11)
Missing	25 (3)	23 (3)	2 (2)
Smoking status *N* (%)			
Current	239 (29)	201 (27)	38 (38)
Former	344 (41)	291 (40)	53 (52)
Never	8 (1)	6 (1)	2 (2)
Unknown	247 (29)	239 (32)	8 (8)
Histology *N* (%)			
Adenocarcinoma	324 (39)	283 (38)	41 (41)
Squamous cell carcinoma	281 (33)	237 (32)	44 (44)
Other/NOS	233 (28)	217 (29)	16 (16)
Brain imaging initial diagnosis *N* (%)			
MRI	720 (86)	635 (86)	85 (84)
CE-CT	118 (14)	102 (14)	16 (16)
Stage *N* (%)			
IIIA	494 (59)	441 (60)	53 (52)
IIIB	344 (41)	296 (40)	48 (48)
T-stage *N* (%)			
T0-2	412 (49)	358 (49)	54 (54)
T3-4	426 (51)	379 (51)	47 (47)
N-stage *N* (%)			
N0-1	109 (13)	101 (14)	8 (8)
N2-3	729 (87)	636 (86)	93 (92)
CRT chemo used *N* (%)			
Cyclic dose		339 (46)	101 (100)
Low dose cisplatin		398 (54)	0 (0)
Radiotherapy (Gy)			
Mean ± SD	65.4 ± 3.4	65.5 ± 3.2	64.6 ± 4.8
Range	45–89.3	45–89.3	45–79.2
Surgery as part of multimodality treatment *N* (%)			
Yes	93 (11)	92 (13)	1 (1)
Type induction/sequential			
Platinum/Gemcitabine		133 (18)	67 (66)
Platinum/Paclitaxel		8 (1)	2 (2)
Platinum/Pemetrexed		41 (6)	23 (23)
Platinum/Etoposide		41 (6)	0 (0)
Cisplatinum/Vinorelbine		3 (0.4)	1 (1)
Unknown		0 (0)	7 (7)
None		508 (69)	0 (0)
Dose reduction *N* (%)			
Yes	45 (5)	36 (5)	9 (9)

Abbreviations: N: number; cCRT: concurrent chemoradiation; sCRT: sequential chemoradiation; SD: standard deviation; WHO PS: world health organization performance status; NOS: not otherwise specified; MRI: magnetic resonance imaging; CE-CT: contrast enhanced computed tomography; T: tumor; N: node; CRT: chemoradiation; Gy: gray.

3.3. Predictors for symptomatic brain metastases development

In the total group (*N* = 838), a lower risk of developing symptomatic brain metastases was seen in older patients (age as continuous variable, odds ratio (OR) (95% CI) 0.97 (0.95–0.99), $p = 0.002$) and squamous carcinoma histology (OR 0.24 (0.14–0.42), $p = 0.001$). The chemotherapy regimen used (cCRT versus sCRT) did not influence the brain metastases risk (OR 0.88 (0.50–1.57), $p = 0.669$). Comparable results were found for the brain as the only site of first relapse: OR of 0.97 (0.94–0.99, $p = 0.006$) for increasing age, OR 0.26 (0.11–0.61, $p = 0.002$) for squamous versus adenocarcinoma histology, OR 0.93 (0.40–2.14, p = 0.855) for cCRT versus sCRT (Table 4).

In the cCRT group (*N* = 737), a lower risk of developing symptomatic brain metastases was found for older patients (OR 0.98 (0.96–0.99), $p = 0.037$) and for squamous versus adenocarcinoma histology (OR 0.19 (0.10–0.36), $p < 0.001$). For the brain as the only site of first relapse, older patients (OR 0.97 (0.94–1.00), $p = 0.034$) and patients with squamous histology (OR 0.25 (0.10–0.64), $p = 0.004$) had a lower risk. In none of these subgroup analyses, chemotherapy regimen (daily low dose cisplatin versus cyclic dose doublet chemotherapy) had an impact on symptomatic brain metastases development (Table 4). Comparable results were found for daily low dose cisplatin (*N* = 391) versus cyclic dose non-taxane (*N* = 277) and cyclic dose taxane based regimens (*N* = 69). There was also no significant difference in brain metastases develop-

Table 2
patient characteristics for patients treated with concurrent chemo-radiation.

Patient characteristic	cyclic dose doublet chemotherapy *N* = 346	Daily low dose cisplatin *N* = 391	*p*-value
Mean age ± SD	62 ± 10	62 ± 10	0.746
(range)	31–84	30–83	
Male *N* (%)	223 (65)	245 (63)	0.646
WHO PS *N* (%)[a]			0.463
0–1	324 (93)	367 (93)	
2	9 (3)	14 (4)	
Smoking status *N* (%)[a]			0.035
Current	125 (37)	76 (49)	
Former	213 (62)	78 (50)	
Never	4 (1)	2 (1)	
Histology *N* (%)			0.036
Adenocarcinoma	146 (42)	137 (35)	
Squamous cell carcinoma	113 (33)	124 (32)	
Other/NOS	87 (25)	130 (33)	
EGFR mutation *N* (%)[a]			0.439
Yes	2 (2)	3 (4)	
No	101 (98)	75 (96)	
KRAS mutation *N* (%)[a]			0.472
Yes	38 (35)	26 (31)	
No	69 (65)	59 (69)	
ALK rearrangement *N* (%)[a]			0.919
Yes	3 (12)	4 (13)	
No	22 (88)	27 (87)	
Brain imaging initial diagnosis *N* (%)			0.083
MRI	290 (84)	345 (88)	
CE-CT	56 (16)	46 (12)	
Stage *N* (%)			0.226
IIIA	199 (58)	242 (62)	
IIIB	147 (42)	149 (38)	
T-stage *N* (%)			0.941
T0-2	169 (49)	189 (48)	
T3-4	177 (51)	202 (52)	
N-stage *N* (%)			
N0-1	45 (13)	56 (14)	0.604
N2-3	301 (87)	335 (86)	
Type concurrent chemotherapy *N* (%)			N/A
Cisplatin/etoposide	188 (54)	–	
Carboplatin/etoposide	22 (6)	–	
Cisplatin/vinorelbin ± cetuximab	65 (19)	–	
Carboplatin/vinorelbin	4 (1)	–	
Cisplatin/pemetrexed	6 (2)	–	
Weekly platinum/docetaxel (± induction cyclic dose chemotherapy)	61 (18)	–	
Cisplatin low dose daily	–	391 (100)	
Radiotherapy (Gy) Mean (±SD)	65 (±5)	66 (±1)	<0.001
Range	45–89	52–68	
Surgery after cCRT *N* (%)			0.686
Yes	45 (13)	47 (12)	
Dose reduction *N* (%)			
Yes	36 (10)	0 (0)	<0.001
Routine brain imaging in follow-up *N* (%)			
Yes	0 (0)	0 (0)	–

Abbreviations: N: number; SD: standard deviation; WHO PS: world health organization performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral antigen; ALK: anaplastic lymphoma kinase; MRI: magnetic resonance imaging; CE-CT: contrast enhanced computed tomography; T: tumor; N: node; CRT: chemoradiation; Gy: gray; cCRT: concurrent chemoradiation.

[a] computed only for patients with known variables.

ment for the subgroups of cCRT regimens with ≥50 patients: daily low dose cisplatin (*N* = 391) versus cisplatin/etoposide (*N* = 188), cisplatin/vinorelbine ± cetuximab (*N* = 65), weekly cisplatin/docetaxel (*N* = 60) respectively (tables S2 and S3).

3.4. Progression free survival and overall survival

The median follow-up (95% CI) for patients being alive was 45.1 (42.3–47.8) months. PFS (95% CI) was 16.7 (14.1–19.4) months for cCRT and 13.3 (10.9–15.7) months for sCRT (hazard ratio (HR) 0.82 (0.64–1.06, $p = 0.122$). The OS was 24.5 (21.9–27.2) and 16.8 (13.7–19.8) months, respectively (HR 0.76 (0.59–0.98), $p = 0.034$). One-year survival was 70% and 66%, respectively ($p = 0.451$). For daily low dose cisplatin cCRT, PFS was 15.1 (11.0–19.3) months compared to 17.2 (14.0–20.3) months for cyclic dose cCRT (HR 1.11 (0.92–1.33), $p = 0.270$). OS was 23.7 (19.9–27.5) months for daily low dose cisplatin cCRT and 25.5 (21.9–29.0) months for cyclic

Table 3
patient characteristics for patients developing symptomatic brain metastases, compared to those without symptomatic brain metastases.

Patient characteristic	Brain metastases $N = 153$	No brain metastases $N = 685$	p-value
Mean age ± SD	59 ± 9	63 ± 10	<0.001
(range)	36–80	30–84	
Male *N* (%)	85 (56)	450 (66)	0.018
WHO PS *N* (%)[a]			
0–1	141 (98)	638 (95)	0.165
2	3 (2)	31 (5)	
Smoking status *N* (%)[a]			
Current	51 (46)	188 (39)	0.400
Former	59 (53)	285 (59)	
Never	1 (1)	7 (1)	
Histology *N* (%)			
Adenocarcinoma	87 (57)	237 (35)	<0.001
Squamous cell carcinoma	19 (12)	262 (38)	
Other/NOS	47 (31)	186 (27)	
EGFR mutation *N* (%)[a]			
Yes	3 (5)	3 (2)	0.357
No	57 (95)	146 (98)	
KRAS mutation *N* (%)[a]			
Yes	28 (40)	47 (31)	0.173
No	42 (60)	106 (69)	
ALK rearrangement *N* (%)[a]			
Yes	2 (10)	5 (12)	0.825
No	18 (90)	37 (88)	
Brain imaging initial diagnosis *N* (%)			
MRI	130 (85)	590 (86)	0.708
CE-CT	23 (15)	95 (14)	
Stage *N* (%)			
IIIA	86 (56)	408 (60)	0.446
IIIB	67 (44)	277 (40)	
T-stage *N* (%)			
T0-2	78 (51)	334 (49)	0.619
T3-4	75 (49)	351 (51)	
N-stage *N* (%)			
N0-1	11 (7)	98 (14)	0.018
N2-3	142 (93)	587 (86)	
Radiotherapy (Gy)			
Mean ± SD	65 ± 3	65 ± 4	0.875
Range	45–79	45–89	
Surgery after cCRT N (%)			
Yes	20 (13)	73 (11)	0.390
Dose reduction N (%)			
Yes	5 (3)	40 (6)	0.319

Abbreviation;: N: number; SD: standard deviation; WHO PS: world health organization performance status; NOS: not otherwise specified; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma viral antigen; ALK: anaplastic lymphoma kinase; MRI: magnetic resonance imaging; CE-CT: contrast enhanced computed tomography; T: tumor; N: node; CRT: chemoradiation; Gy: gray; cCRT: concurrent chemoradiation.

[a] computed only for patients with known data.

dose cCRT, respectively (HR 1.08 (0.90–1.30, $p = 0.397$). One-year survival was 68% and 73%, respectively ($p = 0.116$).

4. Discussion

The brain is a frequent site of symptomatic relapse after CRT and this has a negative impact on QoL and OS [4–7]. In this retrospective multicenter study the type of chemotherapy did not have an impact on the incidence of symptomatic brain metastases in stage III NSCLC patients treated with CRT. Also, no significant differences were found for sCRT versus cCRT treated patients. Although brain metastases before treatment start were excluded by brain MRI/CT and all patients were ^{18}FDG-PET-CT staged, still 18% of patients were diagnosed with symptomatic brain metastases, and for almost half of them the brain was the only site of first relapse. As demonstrated in previous studies, adenocarcinoma histology and younger age were significant predictors for brain metastases development [4,8].

An explanation for our findings is that subclinical brain metastases are already present at staging and that the type of chemotherapy regimens does not differ in the effect to eradicate these tumor deposits. This is likely due to the fact that these chemotherapies have almost no penetration through an intact blood-brain barrier and/or are substrates for brain efflux pumps [14]. In general, chemotherapy added to local radical treatment improves OS, as was found in a recent meta-analysis (HR 0.88 ($p = 0.0009$), 4% increase in 5-year survival) [15]. Impact on brain metastases development was not evaluated. To evaluate whether the lack of impact of the chemotherapy regimen on symptomatic brain metastases was specific to the brain we performed the same analyses for extracranial relapses. No significant differences were found for sCRT versus cCRT treated patients. Also, no differences

Table 4
Multivariate logistic regression analysis for symptomatic brain metastases development.

All chemoradiation patients ($N = 838$)		
Brain relapse pattern	OR (95% CI)	p-value
All brain relapses		
Gender (female vs male)	1.05 (0.72–1.53)	0.807
Age (continuous, older vs younger)	0.97 (0.95–0.99)	**0.002**
T-stage (T3-4 vs T0-2)	1.19 (0.81–1.74)	0.375
N-stage (N2-3 vs N0-1)	1.80 (0.89–3.64)	0.102
Treatment regimen (concurrent vs sequential)	0.88 (0.50–1.57)	0.669
Histology (squamous vs adenocarcinoma)	0.24 (0.14–0.42)	**<0.001**
Histology (NOS vs adenocarcinoma)	0.75 (0.50–1.14)	0.174
Brain as the only site of first relapse		
Gender (female vs male)	1.15 (0.68–1.95)	0.613
Age (continuous, older vs younger)	0.97 (0.94–0.99)	**0.006**
T-stage (T3-4 vs T0-2)	1.24 (0.71–2.14)	0.449
N-stage (N2-3 vs N0-1)	0.93 (0.40–2.18)	0.866
Treatment regimen (concurrent vs sequential)	0.93 (0.40–2.14)	0.855
Histology (squamous vs adenocarcinoma)	0.26 (0.11–0.61)	**0.002**
Histology (NOS vs adenocarcinoma)	0.99 (0.56–1.75)	0.981
Only concurrent chemoradiation patients ($N = 737$)		
Brain relapse pattern	OR (95% CI)	p-value
All brain relapses		
Gender (female vs male)	1.01 (0.67–1.51)	0.974
Age (continuous, older vs younger)	0.98 (0.96–0.99)	**0.037**
T-stage (T3-4 vs T0-2)	1.18 (0.78–1.77)	0.431
N-stage (N2-3 vs N0-1)	1.88 (0.90–3.93)	0.095
Treatment regimen (low dose cisplatin vs cyclic dose)	0.96 (0.65–1.41)	0.819
Histology (squamous vs adenocarcinoma)	0.19 (0.10–0.36)	**<0.001**
Histology (NOS vs adenocarcinoma)	0.73 (0.47–1.12)	0.153
Brain as the only site of first relapse		
Gender (female vs male)	1.21 (0.69–2.12)	0.497
Age (continuous, older vs younger)	0.97 (0.94–1.00)	**0.034**
T-stage (T3-4 vs T0-2)	1.25 (0.70–2.24)	0.453
N-stage (N2-3 vs N0-1)	0.89 (0.37–2.11)	0.787
Treatment regimen (low dose cisplatin vs cyclic dose)	1.21 (0.70–2.09)	0.498
Histology (squamous vs adenocarcinoma)	0.25 (0.10–0.64)	**0.004**
Histology (NOS vs adenocarcinoma)	1.00 (0.55–1.80)	0.995

Abbreviations: N: number; OR: odds ratio; CI: confidence interval; T: tumor; N: node; NOS: not otherwise specified.
Bold values are the significant values.

were found for the specific chemotherapy regimens used in a cCRT regimen (data not shown). The finding that the chemotherapy regime does not influence brain metastases incidence is not entirely new. For example, the early RTOG 88-08/ECOG 4588 trial randomizing 490 stage III NSCLC patients between radical radiotherapy (standard or hyperfractionated) and sCRT revealed no difference in brain metastases incidence in the follow up (but significantly less distant metastases other than brain for sCRT compared to the radiotherapy alone arms ($p = 0.04$)) [16]. However, it is likely that due to inadequate brain imaging metastases at initial staging were missed. Indeed, in a recent study using brain MRI up to 16% had asymptomatic metastases at initial staging [5].

Strong points of this study are that it is a multi-center study including over 800 consecutive stage III NSCLC patients, all with up-to-date staging and all treated with CRT, which represents current practice. In order to exclude bias from suboptimal treatment only patients who completed treatment were included.

Limitations of our study are that within the cyclic dose doublet chemotherapy group different chemotherapy regimens were used, and that the number of patients per cyclic dose regimen was relatively small for comparing these regimens. However, when we compared the major subgroups of chemotherapy within the cCRT group no differences were found regarding symptomatic brain metastases development. Comparable results were found for daily low dose cisplatin versus cyclic dose taxane and non-taxane based regimens, respectively. Some patients did receive weekly platinum/docetaxel concurrent with radiotherapy (often preceded by full dose platinum based doubled chemotherapy) and these patients were grouped within the cyclic dose group. One can argue that this regimen has some low dose components. When we excluded these patients from our analyses, results did not change significantly (data not shown). In the present study we did not restrict development of symptomatic brain metastases to a certain time point after diagnosis of stage III NSCLC. One can argue that it is especially important to prevent development of symptomatic brain metastases in the first year after stage III diagnosis, as these patients did not have benefit from their intensive CRT treatment. However, results remained comparable when we restricted our analyses to development of brain metastases within one year of stage III NSCLC diagnosis (results not shown). Adenocarcinoma histology is a risk factor for brain metastases and it is possible that the chemotherapeutic regimens used have a different impact on adenocarcinoma histology compared to other histologies. When the analyses above were repeated with only adenocarcinoma patients, results did not change significantly (data not shown). Furthermore, it is a retrospective study and as such follow up was not standardized but according to local practice (*i.e.* PFS data difficult to compare). Only patients who completed their CRT treatment were included (no intention-to-treat-analysis) and patient selection for CRT eligibility was according to local protocols. This may have caused an imbalance in favor of the patients treated with sCRT regarding prognosis in the different subgroups. It is not common practice nor advised in guidelines to perform regular brain imaging in the follow-up of radically treated stage III NSCLC patients [3]. This results in underdiagnosis of asymptomatic brain metastases. One can argue the relevance of asymptomatic metastases when a patient dies of extracranial disease. Furthermore, bias regarding different regimes for cerebral metastases screening did not occur because brain imaging was only performed when a patient had symptoms indicative for brain metastases or when brain imaging was required for renewed staging. As it is not common practice to perform molecular screening in stage III NSCLC, molecular characteristics were mostly unknown. However, as especially patients with an *ALK*-rearrangement are prone to develop brain metastases and percentage of *ALK*-rearranged patients is low in the literature (±5%) it is unlikely that this has caused any bias [17]. Treatment factors that can reduce brain metastases development are important to identify, for these metastases are often associated with reduced QoL and poor prognosis [6,7]. Prophylactic cranial irradiation (PCI) to eradicate microscopic brain metastases is a possible treatment option. PCI is currently evaluated in the phase III randomized NVALT11/DLCRG 02 study (NCT01282437). It is closed for accrual and results are awaited.

5. Conclusion

The specific chemotherapy regimen used during CRT for stage III NSCLC has no impact on the subsequent development of clinically manifest brain metastases. It remains important to identify modifiable factors in order to reduce the development of brain metastases.

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Conflicts of interest

No conflict of interest for all other authors.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2016.09.008.

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