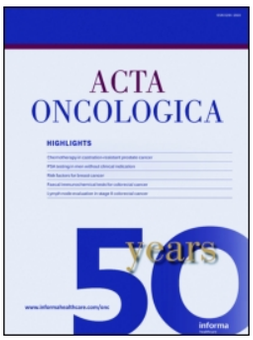

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LETTER TO THE EDITOR

Factors determining the effect of prophylactic cranial irradiation (PCI) in patients with stage-III nonsmall cell lung cancer: exploratory subgroup analyses of the NVALT-11/DLCRG-02 phase-III study

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Introduction

One-third of all patients who develop nonsmall cell lung cancer (NSCLC) are diagnosed with locally advanced (stage III) disease [1]. NSCLC patients frequently develop (symptomatic) brain metastases (BM), and the more advanced the disease is, the more frequent BM occur. Patients with stage-III NSCLC have a BM incidence of approximately 30% [2].

The effectiveness of prophylactic cranial irradiation (PCI) to reduce BM has been investigated in several randomized controlled trials (RCTs) [3–10]. The NVALT-11/DLCRG-02 trial [11] showed that two years after PCI, the proportion of patients with symptomatic BM was significantly lower in the PCI arm, compared to the observation arm (7.0% vs. 27.2%, hazard ratio (HR) 0.23, 95% confidence interval (95% CI) (0.09-0.56), $p \leq .001$). Additional analyses to assess the impact of PCI on symptomatic BM in predefined subgroups did not show statistically significant differences between both arms.

Literature suggests that the BM risk increases when disease stage advances and that patients with non-squamous histology have a higher risk of developing BM than patients with squamous histology [12,13]. Furthermore, evidence from the literature showed that the type of (multi)modality therapy may also influence the risk of developing BM [12,14]. Therefore, to obtain maximum information from the NVALT-11/DLCRG-02 trial on top of the stratification factors, we aimed to identify subsets of patients that may be more likely to benefit from PCI. Specifically, we performed additional exploratory subgroup analyses to examine the risk of developing symptomatic BM and PCI interaction effects for age (>61 years vs. ≤61 years), sex (males vs. females), disease stage (stage IIIb vs. stage IIIa) and prior treatment (total concurrent chemo-radiotherapy (RT) time (>64 days vs. ≤64 days), number of chemotherapy cycles (>3 cycles vs. ≤3 cycles) and thoracic RT dose (>60 Gy vs. ≤60 Gy)).

Material and methods

Study

The Dutch NVALT-11/DLCRG-02 randomized phase-III trial has been reported previously [11]. In short, after treatment with curative intent (mostly concurrent chemo-RT) patients with stage-III NSCLC were stratified according to histology, WHO performance score (0-1 vs. 2) and prior surgery and were subsequently randomized between PCI and observation. The primary endpoint of the study was the proportion of patients developing symptomatic BM within 24 months from randomization, defined as a combination of key symptoms suggesting BM (e.g., signs of increased intracranial pressure, headache, cognitive or affective disturbances) and MRI or CT proving evidence of BM. Follow-up assessments took place 4 weeks, 3, 6, 12, 24 and 36 months after completion of treatment, or earlier when symptoms of BM occurred. Both physician and patient reported measures were included in these assessments. Brain imaging was performed only after patients reported symptoms suggestive of BM or at the discretion of the treating physician.

Statistical analysis

In addition to the predefined subgroup analyses previously published [11], *post hoc* subgroup analyses were performed for subgroups based on age (>61 years vs. ≤61 years), sex

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Supplemental data for this article can be accessed here.

(males vs. females), disease stage (stage IIIb vs. stage IIIa) and prior treatment (total concurrent chemo-RT time (>64 days vs. ≤64 days), number of chemotherapy cycles (>3 cycles vs. ≤3 cycles) and thoracic RT dose (>60 Gy vs. ≤60 Gy)). For continuous variables, the median was calculated and used as a cut-off value.

Competing risk regression (based on Fine and Gray's proportional sub hazards model), including death of any cause as competing risk, was used to estimate HRs, 95% CIs and corresponding cumulative incidence plots for each subgroup. Furthermore, an interaction test was performed to test for a PCI treatment interaction effect across each subgroup (i.e., to test whether the effect of PCI was significantly different across levels of each subgroup). In order to reduce the chance of false-positive results, all statistical comparisons were considered statistically significant using an alpha of 0.01 (two-sided). All statistical analyses were run with Stata/SE 14.2 software.

Results

In total, 174 patients were analyzed, with a median follow-up of 48.5 months (95% CI 39–54 months). Patients were mostly male (65.5%), had non-squamous histology (64.2%), no prior surgery (89.0%) and a good performance status (0 or 1: 94.8%) (Table 1).

Regardless of treatment allocation, results of the competing risk regression analyses showed that older (>61 years) patients had a statistically significantly lower risk of developing symptomatic BM compared to younger (≤61 years) patients (HR 0.25, 95% CI 0.10–0.60) (Figure 1). No statistically significant difference in the risk of developing symptomatic BM was observed for the other subgroups (Table 1).

Results of the competing risk regression analyses assessing the impact of PCI within each level of the subgroups showed that the risk of developing symptomatic BM for patients in the PCI arm was statistically significantly lower compared to patients in the observation arm for patients with non-squamous histology (HR 0.24, 95% CI 0.08–0.70, $p = .009$), without prior surgery (HR 0.23, 95% CI 0.09 – 0.62, $p = .003$,), who received less than three cycles of chemotherapy (HR 0.16, 95% CI 0.05–0.54, $p = .003$) and were younger than 61 years at the time of randomization (HR 0.18, 95% CI 0.06–0.53, $p = .002$) (Supplementary file Figures S1-S4). Nevertheless, across none of the subgroups a statistically significant treatment interaction effect was observed (Table 2).

Discussion

The primary results of the NVALT-11/DLCRG-02 study showed that PCI significantly decreased the cumulative symptomatic BM incidence at two years after randomization [11]. This exploratory analysis showed that, regardless of treatment, older patients (>61 years) had a lower risk of developing symptomatic BM than younger patients (≤61 years). This finding might be explained by the higher incidence of adenocarcinomas in younger patients in the NVALT-11/DLCRG-02 study (47.3% vs. 34.9%), a well-known risk factor for BM development [12,13,15]. Additionally, in none of the subgroups, a statistically significant treatment interaction effect was observed for PCI compared to observation.

Table 1. Results of the competing risk regression analyses to assess the risk of symptomatic BM in several subgroups.

Subgroups	*N* (%)	Hazard ratio	95% confidence interval	*p*-value (alpha level=.01)
Subgroups based on stratification factors				
Histology				
Non-squamous	111 (64.2)	Reference		
Squamous	62 (35.8)	0.76	0.34–1.66	.483
Surgery				
No prior surgery	154 (89.0)	Reference		
Prior surgery	19 (11.0)	1.21	0.45–3.29	.707
WHO performance status				
0	66 (38.4)	Reference		
1	97 (56.4)	0.86	0.41–1.83	.702
2	9 (5.2)	2.12	0.59–7.63	.251
Other subgroups				
Disease stage				
Stage IIIa	93 (53.8)	Reference		
Stage IIIb	80 (46.2)	0.97	0.47–1.98	.934
Number of cycles of chemotherapy				
≤3 cycles	130 (76.0)	Reference		
>3 cycles	41 (24.0)	0.97	0.42–2.22	.943
Thoracic RT dose				
≤60 Gy	89 (52.4)	Reference		
>60 Gy	81 (47.6)	1.15	0.57–2.36	.686
Total concurrent chemo-RT time				
≤64 days	87 (50.9)	Reference		
>64 days	84 (49.1)	1.43	0.70–2.94	.325
Age				
≤61 years	91 (52.3)	Reference		
>61 years	83 (47.7)	0.25	0.10–0.60	**.002**
Sex				
Males	114 (65.5)	Reference		
Females	60 (34.5)	1.73	0.85–3.53	.133

p-values mar ked in bold indicate numbers that are statistically significant on a 99% confidence limit.

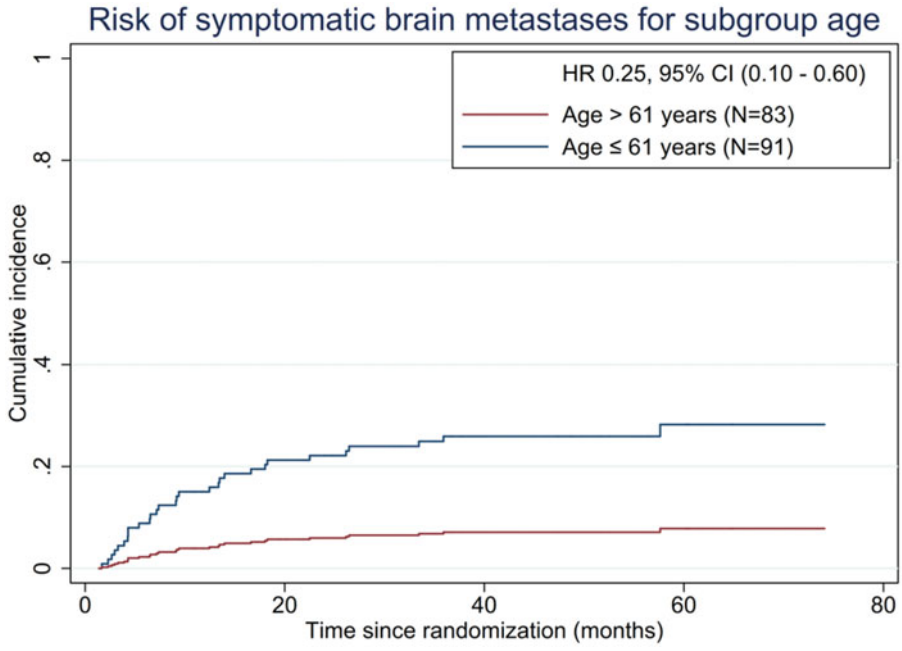

Figure 1. Cumulative incidence plot comparing the risk of developing symptomatic BM in patients > 61 years and patients ≤ 61 years of age.

Table 2. Results of the competing risk regression analyses to assess the impact of PCI on the risk of symptomatic BM within several subgroups.

	PCI vs. observation			
Subgroups	Hazard ratio	95% confidence interval	*p*-value (alpha level=.01)	*p*-value PCI treatment interaction effect (alpha level=.01)
Subgroups based on stratification factors				
Histology				
Squamous	0.23	0.05–1.11	.068	.965
Non-squamous	0.24	0.08–0.70	**.009**	
Surgery				
Prior surgery	0.21	0.02–1.89	.166	.976
No prior surgery	0.23	0.09–0.62	**.003**	
WHO performance status				
0	0.21	0.04–0.95	.043	.626
1	0.21	0.06–0.74	.015	
2	0.70	0.06–8.05	.775	
Other subgroups				
Disease stage				
Stage IIIa	0.27	0.08–0.95	.042	.818
Stage IIIb	0.20	0.06–0.71	.013	
Number of cycles of chemotherapy				
≤3 cycles	0.16	0.05–0.54	**.003**	.166
>3 cycles	0.59	0.14–2.55	.477	
Thoracic radiotherapy dose				
≤60 Gy	0.15	0.04–0.66	.012	.530
>60 Gy	0.29	0.09–0.92	.035	
Total concurrent chemo-radiotherapy time				
≤64 days	0.28	0.08–1.01	.051	.742
>64 days	0.21	0.06–0.72	.013	
Age				
≤61 years	0.18	0.06–0.53	**.002**	.361
>61 years	0.47	0.09–2.52	.376	
Sex				
Males	0.20	0.06–0.72	.013	.739
Females	0.27	0.08–0.95	.042	

p-values mar ked in bold indicate numbers that are statistically significant on a 99% confidence limit.

Previously published results from studies that investigated the risk of symptomatic BM across subgroups are in line with our findings. A recent update of the NRG Oncology/RTOG 0214 phase III trial [16] suggested that younger patients and patients with non-squamous histology were more likely to develop BM. Next to that, results of a retrospective study of Hendriks et al. [15] also reported associations between histological characteristics and age and the risk of developing symptomatic BM after concurrent chemo-RT for stage-III NSCLC.

This study has a number of limitations. Our subgroup analyses were not predefined and should thus be interpreted as hypothesis-generating. Furthermore, the main statistical limitation of performing exploratory subgroup analyses is that they are often underpowered, because the sample size of clinical trials is usually calculated to evaluate the primary objective of the study in the intention to treat population instead of in specific subsets of patients. Another statistical limitation of subgroup analyses is the inflated probability of getting a false-positive result when multiple comparisons are done. Therefore, to reduce the probability of false-positives in our analyses an alpha level of 0.01 was used to determine statistical significance.

In addition to PCI, adjuvant immune therapy could decrease the incidence of BM after chemo-RT. In the PACIFIC trial [17], the incidence of BM was approximately 50% lower with durvalumab compared to placebo (6% vs. 12%). There was, however, no standardized evaluation schedule for detecting BM in this trial. The incidence of BM in the control arm was much lower than in other prospective studies, including the NVALT-11/DLCRG-02 trial, in which the incidence was about 30%. Also in retrospective series, including the Dutch multi-centric series of Hendriks et al. [15], the incidence of BM (18%) was lower than in prospective studies, pointing to the importance of prospective evaluations.

Conclusion

NSCLC patients after concurrent chemo-RT with older age had a lower risk of developing symptomatic BM compared

to younger patients. Additionally, potentially due to a lack of power, no statistically significant interaction effect was observed, suggesting that none of the subgroups considered benefits more from PCI.

Disclosure statement

Willem J.A. Witlox
No relationship to disclose
Bram L.T. Ramaekers
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